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IRIS Toxicological Review of Formaldehyde (Inhalation)

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ABBREVIATIONS

AC50	activity concentration at 50%
ACA	activated aerosol carbon
ADAF	age-dependent adjustment factor
ADH	alcohol dehydrogenase
ADME	absorption, distribution, metabolism, and excretion
AIC	Akaike's information criterion
ALDH	aldehyde dehydrogenase
ALM	anterior lateral meatus
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AOP	adverse outcome pathway
AST	aspartate aminotransferase
atm	atmosphere
ATS	American Thoracic Society
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
BAL	bronchoalveolar lavage
BBDR	biologically based dose-response
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMI	body mass index
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
$BW^{3/4}$	body weight scaling to the 3/4 power
CA	chromosomal aberration
CAA	Clean Air Act
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBMN	cytokinesis-block micronucleus assay
CD	cytokinesis-block micronucleus assay
CE	capillary electrophoresis
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
Cf	confounding
CHO	Chinese hamster ovary (cell line cells)
CI	confidence interval
CL	confidence limit
CML	chronic myeloid leukemia
CNS	central nervous system
COI	conflict of interest
CPAD	Chemical and Pollutant Assessment Division
CPHEA	Center for Public Health and Environmental Assessment
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DPX	DNA-protein cross-links
DSB	double-stand breaks
EA	ethyl acetate
ECHRS	European Community Respiratory Health Survey
EPA	Environmental Protection Agency
ER	extra risk
ETS	Environmental tobacco smoke
FA	formaldehyde
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
FSH	follicle stimulating hormone
FVC	forced vital capacity
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GLP	Good Laboratory Practice
GM	granulocyte macrophage
GSD	geometric standard deviation
GSH	glutathione
GST	glutathione-*S*-transferase
HAP	hazardous air pollutant
HAWC	Health Assessment Workspace Collaborative
Hb/g-A	animal blood:gas partition coefficient
Hb/g-H	human blood:gas partition coefficient
HBCD	hexabromocyclododecane
HEC	human equivalent concentration
HED	human equivalent dose
HERO	Health and Environmental Research Online
HPA	hypothalamus-pituitary-adrenal gland
HPG	hypothalamic-pituitary-gonadal
HSPCs	hematopoietic stem and progenitor cells
IB	information bias
i.p.	intraperitoneal
i.v.	intravenous
IAP	IRIS Assessment Plan
IARC	International Agency for Research on Cancer
ICD	International Classification of Disease

IRIS	Integrated Risk Information System
ISAAC	International Study of Arthritis and Allergies in Children
IUR	inhalation unit risk
JEM	job-exposure matrix
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LEC	lowest effective concentration
LHP	lymphohematopoietic
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
LRT	lower respiratory tract
MDA	malondialdehyde
MDS	myelodysplastic syndrome
MeSH	Medical Subject Headings
MLE	maximum likehood estimate
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MOR	mortality odds ratio
MTD	maximum tolerated dose
NA	not available
NALT	nasal-associated lymphoid tissue
NASEM	National Academies of Sciences, Engineering, and Medicine
NATA	National-Scale Air Toxic Assessment
NCI	National Cancer Institute
ND	not detected
NIOSH	National Institute for Occupational Safety and Health
NMD	normalized mean difference
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NPC	nasopharyngeal cancer
NR	not reported
NRC	National Research Council
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OAR	Office of Air and Radiation
OECD	Organisation for Economic Co-operation and Development
OHPC	oro/hypopharyngeal cancer
OLEM	Office of Land and Emergency Management
OR	odds ratio
ORD	Office of Research and Development
OSF	oral slope factor
OVA	ovalbumin
PBPK	physiologically based pharmacokinetic
PECO	populations, exposures, comparators, and outcomes
PEFR	peak expiratory flow rate
PK	pharmacokinetic
PMR	proportionate mortality ratio
PND	postnatal day
POD	point of departure
$POD_{[ADJ]}$	duration-adjusted POD
POE	portal of entry
QSAR	quantitative structure-activity relationship
RBC	red blood cells
RD	relative deviation
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
ROBINS I	Risk of Bias in Nonrandomized Studies of Interventions
RoC	Report on Carcinogens
RR	relative risk
SAR	structure-activity relationship
SB	selection bias
SCC	Squamous cell carcinoma
SCE	sister chromatid exchange
SCF	stem-cell factor
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SEM	systematic evidence map
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SMR	standardized mortality ratio
SNC	sinonasal cancer
SPIR	standardized proportional incidence ratio
TK	toxicokinetics
TRP	Transient Receptor Potential
TSCATS	Toxic Substances Control Act Test Submissions
TSCE	two-stage clonal expansion
TSFE	time since first exposure
TTP	time-to-pregnancy
TWA	time-weighted average
UCOD	underlying cause of death
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_D	database deficiencies uncertainty factor
UF_H	human variation uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
URT	upper respiratory tract
WBC	white blood cells
WOS	Web of Science
XRCC	X-ray repair cross-complementing gene

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The White House
- Office of Management and Budget (Step 3)

Department of Agriculture (Step 6)
Department of Defense (Step 3)
Small Business Administration (Step 3)
Department of Health and Human Services
- National Institute of Environmental Health Sciences (Step 3)
- Agency for Toxic Substances and Disease Registry (Step 3 and Step 6)
- National Institute of Occupational Safety and Health (Step 3 and Step 6)

This assessment was released for public comment on April 14, 2022, and comments were due on June 13, 2022. The public comments are available on Regulations.gov [docket: EPA-HQ-ORD-2010-0396]. A summary and EPA's disposition of the comments from the public is available in Appendix F.

This assessment was peer reviewed by independent, expert scientists external to EPA convened by the National Academies of Sciences, Engineering, and Medicine (NASEM). Peer-review meetings were held by NASEM (https://www.nationalacademies.org/our-work/review-of-epas-2022-draft-formaldehyde-assessment). The report of the review of the EPA's Draft Toxicological Review of Formaldehyde (Inhalation), dated 2023, is available on the NASEM website (https://nap.nationalacademies.org/catalog/27153/review-of-epas-2022-draft-formaldehyde-assessment) and the IRIS Website (https://iris.epa.gov/Document/&deid=248150). A summary and EPA's disposition of the comments received is included in Appendix F.

EXECUTIVE SUMMARY

ES.1 OVERALL SUMMARY

This IRIS health assessment presents a systematic review of the publicly available evidence relevant to inhalation exposure to formaldehyde and potential adverse health outcomes. The assessment specifically focuses on the following health effects: sensory irritation; pulmonary function; immune system effects, focusing on allergic conditions and asthma; respiratory tract pathology; nervous system effects; reproductive and developmental toxicity; and cancer. For cancer, the assessment focuses on cancers of the upper respiratory tract (including nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx/hypopharynx, and laryngeal cancer in humans) and of the lymphohematopoietic system (including Hodgkin lymphoma, multiple myeloma, myeloid leukemia, and lymphatic leukemia in humans). The evidence identification, evaluation, synthesis, and integration framework used to conduct the assessment is schematically depicted in Figure 2-1, with detailed methods provided in Section 2.

The main conclusions of the assessment are summarized below, with additional details in Tables ES-1 and ES-2 and the following sections.

- Inhaled formaldehyde can cause health effects in humans, most notably respiratory effects. Children and those with respiratory disease appear to be most susceptible.
- Formaldehyde is ***carcinogenic to humans*** by the inhalation route of exposure.
- The noncancer reference concentration (RfC) is 0.007 mg/m^3. Confidence in the RfC is **high**.
- The cancer inhalation unit risk (IUR) is 1.1×10^{-5} per μg/m^3 (1.1×10^{-2} per mg/m^3). Confidence in the IUR is **medium.**

Table ES-1. Evidence integration judgments for noncancer health effects and the reference concentration (RfC)

Noncancer health effect	Evidence integration judgment	POD basis	UFC	osRfC (mg/m^3)	Confidence in value [d]
Decreased pulmonary function	**evidence indicates [likely]** [c]	Human (children)	3	0.007	**High**
Allergic conditions	**evidence indicates [likely]**	Human (children)	3	0.008	**High-medium**
Prevalence of current asthma or degree of asthma control	**evidence indicates [likely]**	Human (children)	10 [c]	0.006 [c]	**Medium-high**
Sensory irritation	**evidence demonstrates**	Human (adults)	3	0.02	**Medium-low**
Female reproductive or developmental toxicity	**evidence indicates [likely]**	Human (adults)	10	0.01	**Low-medium**
Respiratory tract pathology	**evidence demonstrates**	Rat (adults)	30	0.003	**Medium-high**
Male reproductive toxicity	**evidence indicates [likely]**	Rat (adults)	1000	0.006	**Low**
Nervous system effects [a]	**evidence suggests**	Not Derived	-	-	
Reference Concentration (RfC) = 0.007 mg/m^3; confidence in the RfC is **high**					
Based on decreased pulmonary function, prevalence of current asthma or degree of asthma control, and allergic conditions [b]	**N/A**	Human	3 or 10	0.007	**High**

Abbreviations and definitions: RfC = reference concentration: An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure of a chemical to the human population (including sensitive subpopulations), that is likely to be without risk of deleterious noncancer effects during a lifetime. osRfC = organ- or system-specific RfC: an RfC based on the evidence for effects on that particular organ or system. UF_C = composite (total) uncertainty factor; POD = point of departure.

[a]For each of the three potential manifestations of nervous system effects evaluated in this review (i.e., amyotrophic lateral sclerosis incidence or mortality, developmental neurotoxicity, or behavioral toxicity), it was concluded that the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause these effects in humans.

[b]The RfC is supported by three osRfCs (shaded) from multiple *high* and *medium* confidence studies of residential or school-based formaldehyde exposure to children (Venn et al., 2003; Krzyzanowski et al., 1990; Annesi-Maesano et al., 2012). The RfC value is selected as the midpoint of the three osRfCs (i.e., 0.006, 0.007, and 0.008 mg/m^3) with the highest confidence and the lowest UF_C values (see Section 5.1.5).

[c]This osRfC is based on multiple studies and candidate values, sometimes with different UF_Cs applied. The UF_C value shown in this table and Figure 5-3 reflects the candidate value selected to represent this osRfC [i.e., the UF_C applied to the POD from Krzyzanowski et al. (1990)].

[d]For hyphenated confidence classifications, the first term reflects the confidence category, and the second term indicates whether the judgment is closer to a higher or lower confidence category (e.g., **High-medium** is a **High** confidence judgment that is close to a judgment of **Medium** confidence). See Section 2.7 for the methods for drawing these confidence judgments, and Section 5.1.5 for the supporting rationale for each judgment.

Table ES-2. Cancer evidence integration judgments, carcinogenicity descriptor, and inhalation unit risk (IUR) for cancer incidence

Cancer type investigated	Evidence integration judgment for cancer type risk	Unit risk estimate basis	Unadjusted unit risk estimate (per μg/m³)	Inhalation unit risk estimate (per μg/m³)[a] [ADAF-adjusted]	Confidence in the inhalation unit risk estimate
Nasopharyngeal cancer (or nasal cancer in animals)	**evidence demonstrates**[b]	Human	7.4×10^{-6}	**1.1×10^{-5}**	**Medium**
		Animal[c]	8.9×10^{-6} to 1.8×10^{-5}	NA[d]	NA[d]
Myeloid leukemia	**evidence demonstrates**[e]	Too uncertain[f]	-	-	
Sinonasal cancer	**evidence demonstrates**[g]	No usable data	-	-	
Oropharyngeal/Hypo-pharyngeal cancer	**evidence suggests**	Not derived	-	-	
Multiple myeloma	**evidence suggests**	Not derived	-	-	
Hodgkin lymphoma	**evidence suggests**	Not derived	-	-	
Laryngeal cancer	**evidence inadequate**	Not derived	-	-	
Lymphatic leukemia	**evidence inadequate**	Not derived	-	-	
Carcinogenicity Descriptor:	***Carcinogenic* to Humans**				
Total cancer risk (IUR)[h]:	**1.1×10^{-5} per μg/m³** (1.1×10^{-2} per mg/m³)**;** Confidence in the IUR is **Medium**				

Abbreviations and definitions: IUR = inhalation unit risk: the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg/m³ in air; ADAF = age-dependent adjustment factor.

[a]ADAF adjustments are recommended for cancers for which there is sufficient evidence that formaldehyde has, at least in part, a mutagenic MOA (see Section 5.2.4).

[b]The judgment of **evidence demonstrates** for NPC cancer is based on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels, and *robust* animal evidence of nasal cancers in rats and mice that exhibits steeply increasing incidence at high formaldehyde levels. Strong mechanistic support is provided across species (primarily rats, but also mice, monkeys, and humans), including genotoxicity, epithelial damage or remodeling, and cellular proliferation that are consistent with neoplastic development in a regional, temporal, and dose-related fashion.

[c]While the selected unit risk estimate for NPC is based on a cancer mortality study in humans, several estimates in general agreement with this value and each other were also derived based on animal nasal tumor incidence. The points of departure for these estimates were based on multiple mechanistic and statistical models, including biologically based dose-response (BBDR) modeling. Results for human extrapolation were based on internal dose metrics and BMRs ≤ 0.01 extra risk (see Section 5.2.1). In addition, an RfC for cytotoxicity-induced regenerative cell proliferation, one of the mechanisms contributing to nasal cancer development, was estimated to be between 0.006 and 0.018 mg/m³ (see Section 5.2.1).

[d]NA = not applicable; an ADAF-adjusted value was not calculated and a level of confidence was not assigned for the unit risk estimates based on the animal data on nasal cancer, as the human unit risk estimate for NPC was the selected estimate.

[e]The judgment of **evidence demonstrates** for myeloid leukemia is based on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels. Supporting mechanistic evidence consistent with leukemia development is

provided across numerous studies of peripheral blood isolated from exposed workers, including evidence of mutagenicity and other genotoxic damage in lymphocytes and myeloid progenitors, and perturbations to immune cell populations. The animal evidence is *indeterminate* and the findings to date suggest that there may be a lack of concordance across species for leukemia, as leukemia was not increased in two well-conducted chronic bioassays of rats or mice, and the available animal data provide weak mechanistic support for lymphohematopoietic (LHP) cancers. No MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia without systemic distribution (inhaled formaldehyde does not appear to be distributed to an appreciable extent beyond the respiratory tract to distal tissues).

[f]Although several attempts were made to derive a unit risk estimate for myeloid leukemia, it was ultimately concluded that these estimates were too uncertain. Thus, while the best estimate currently available (see Appendix D.2.3) may provide some perspective on the extent to which the IUR underestimates cancer risk (i.e., because estimates for myeloid leukemia and sinonasal cancer are not included), this estimate was not selected to represent a unit risk for myeloid leukemia or included in the IUR.

[g]The judgment of **evidence demonstrates** for sinonasal cancer is based primarily on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels. The strong animal and mechanistic evidence for nasal cancers across species is interpreted to provide *moderate* evidence supportive of sinonasal cancer (a judgment of *moderate* rather than *robust* reflects some uncertainty in interpreting the nasal cavity findings in animals as fully applicable to the specific human disease of sinonasal cancer; see Section 3.2.5).

[h]The full lifetime IUR estimate is based on the ADAF-adjusted estimate for nasopharyngeal cancer (which includes a mutagenic MOA; Section 3.2.5). Less-than-lifetime exposure scenarios with a very large fraction of exposure during adulthood may not warrant ADAF adjustment, and one may choose to use the unadjusted unit risk estimate of 7.4×10^{-6} per $\mu g/m^3$ or the adult-based estimate of 6.4×10^{-6} per $\mu g/m^3$. Otherwise, see Section 5.2.4 for how to apply the ADAFs to obtain total cancer risk estimates for less-than-lifetime exposure scenarios.

ES.2 NONCANCER HEALTH EFFECTS CONCLUSIONS AND QUANTITATIVE ESTIMATE

Overall, the integrated **evidence demonstrates** that inhalation of formaldehyde causes increased sensory irritation and respiratory tract pathology in humans (see Section 2.6 for a description of the bolded evidence integration judgments and their definitions), given sufficient exposure conditions[1]. Well-conducted studies in humans and animals support these hazard conclusions, and strong mechanistic evidence in animals provides plausible modes of action (MOAs) for the identified endpoints.

The available **evidence indicates** that formaldehyde inhalation likely causes decreased pulmonary function, an increased frequency of current asthma symptoms or difficulty controlling asthma, and increased allergic responses in humans, given sufficient exposure conditions. These conclusions were supported primarily by evidence in exposed humans, with supportive mechanistic evidence indicating that formaldehyde inhalation results in biological changes related to these outcomes in exposed animals. In addition, the **evidence indicates** that inhalation of formaldehyde likely causes female reproductive or developmental toxicity and reproductive toxicity in men, given sufficient exposure conditions. The conclusion for female reproductive or developmental toxicity is supported by evidence in humans, specifically increases in time-to-pregnancy (TTP) and spontaneous abortion risk; mechanistic evidence explaining such effects without systemic distribution of formaldehyde is lacking. The conclusion for male reproductive toxicity is supported primarily by coherent evidence of several alterations to the male reproductive

[1] Use of this phrase, "given sufficient exposure conditions", throughout the assessment highlights that, for those assessment-specific health effects identified as potential hazards, the exposure conditions associated with those health effects are defined (as are the uncertainties in the ability to define those conditions) during dose-response analysis.

system in animals exposed to very high levels of formaldehyde (> 6 mg/m^3), with some corroborative changes in an occupational epidemiological study; although no MOA is available, some relevant mechanistic changes have been observed in well-conducted studies of the male reproductive organs of exposed rodents.

Lastly, while a number of studies reported evidence of potential neurotoxic effects, including developmental neurotoxicity, behavioral toxicity, and an increased incidence of, or mortality from, the motor neuron disease amyotrophic lateral sclerosis (ALS), due to limitations in the database (e.g., poor methodology, lack of consistency), the integration of the evidence for each of these manifestations of potential neurotoxicity ultimately resulted in the determination that the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation may pose a human health hazard, and additional study is warranted. The available data on potential nervous system effects were considered insufficient for developing quantitative toxicity estimates.

ES.2.1. Inhalation Reference Concentration (RfC)

The reference concentration (the RfC) of 0.007 mg/m^3 formaldehyde is level of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

In this assessment, the RfC is based on several organ- or system-specific RfCs based on the evidence for effects on that particular organ or system (osRfCs), which are themselves based on candidate reference concentrations (cRfCs). The cRfCs are estimates for a specific endpoint based on a single, specific study within an organ- or system-specific hazard domain. The osRfCs differ from the associated cRfCs only when there are multiple cRfCs for the same organ system. The osRfCs were selected from those cRfCs that best represented the general population, including sensitive subgroups and which had a greater degree of certainty with regard to both reliability of study results and cRfC derivation (including POD selection). In addition, cRfCs with lower composite (total) uncertainty factors (UF_Cs) were preferred.

The osRfCs that were used to calculate the overall RfC in this assessment were all based on epidemiological studies of residential or school-based formaldehyde exposure to children that were interpreted with either **High** or **Medium** confidence and had the lowest composite uncertainty factor (UF_Cs) (see Table ES-1).

The selected RfC is the midpoint of three osRfCs (0.006, 0.007 0.008 mg/m^3) representing a group of respiratory system-related effects (i.e., pulmonary function, allergy-related conditions, and current asthma prevalence or degree of control) that were interpreted with the highest confidence and had the lowest UF_Cs. These health effects were observed in the range of typical formaldehyde exposures in population studies (effects were observed in the underlying studies at approximately ≥ 33 μg/m^3). The selected RfC is likely to be above outdoor formaldehyde levels in most locations, and levels in indoor air would be expected to exceed this concentration in many situations. However, as the RfC is interpreted to be without appreciable risk, even in sensitive subgroups, it is

important to note that the potential for health effects in individuals at concentrations between the RfC (0.007 mg/m^3) and levels at which health effects have been observed in the available population studies (~ ≥ 0.033 mg/m^3) is unknown.

Although the RfC is designed to apply to exposures over a lifetime, the relevant window of exposure for some of the effects observed in the contributing studies may be less than a lifetime. For example, the relevant window of exposure for effects on asthma outcomes is also less than lifetime, although the time frame for the control of asthma symptoms (i.e., a few weeks) is different than that for the prevalence of current asthma symptoms or a decrease in pulmonary function (i.e., the past 12 months).

Overall confidence in the RfC is **High.** There is **high** confidence in the composite set of studies used to derive the RfC, **high** or **medium** confidence in the derivation of the underlying cRfC numerical values, and **high** confidence in the completeness of the literature database supporting the judgment that formaldehyde causes the adverse noncancer health effects identified.

ES.3 HUMAN CARCINOGENICITY CONCLUSION AND QUANTITATIVE ESTIMATE

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), formaldehyde is ***Carcinogenic to Humans by the Inhalation Route of Exposure***. This conclusion is independently supported by three evidence integration judgments:

- The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer (NPC) in humans. This is based primarily on observations of increased risk of NPC in groups exposed to occupational formaldehyde levels and nasal cancers in mice and several strains of rats, with strong, reliable, and consistent mechanistic evidence in both animals and humans (i.e., *robust* evidence for both the human and animal evidence, and strong mechanistic support for the human relevance of the animal data). The nasopharynx, although not typically specified in animal studies, is the region adjacent to the nasal cavity, where the animal evidence was predominantly observed. In addition, the evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced nasopharyngeal carcinogenicity.

- The **evidence demonstrates** that formaldehyde inhalation causes sinonasal cancer (SNC) in humans. This is based primarily on observations of increased risk of SNC in groups exposed to occupational formaldehyde levels (i.e., *robust* human evidence) and supported by apical and mechanistic evidence for nasal cancers across multiple animal species. Some uncertainties remain in the interpretation of the animal nasal cavity data as wholly applicable to interpreting human sinonasal cancer (thus, the animal evidence is judged as *moderate*). In addition, while uncertainties remain, the evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced sinonasal carcinogenicity.

- The **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans. This is based primarily on observations of increased risk in groups exposed to occupational formaldehyde levels (i.e., *robust* human evidence). This evidence integration judgment is further supported by other studies of human occupational exposure that provide strong and coherent mechanistic evidence identifying clear associations with

additional endpoints relevant to lymphohematopoietic (LHP) cancers, including an increased prevalence of multiple markers of mutagenicity and other genotoxicity in peripheral blood cells of exposed workers, other perturbations to immune cell populations in blood (primarily from human studies), and evidence of other systemic effects (i.e., developmental or reproductive toxicity). Generally, evidence supporting the development of LHP cancers after formaldehyde inhalation has not been observed in experimental animals (i.e., rodents), including a well-conducted, chronic cancer bioassay in two species, a similar lack of increased leukemias in a second rat bioassay, and multiple mechanistic evaluations of relevant biological changes, including genotoxicity (i.e., *indeterminate* animal evidence). The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown.

ES 3.1. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK: INHALATION EXPOSURE

The inhalation unit risk (IUR) is 1.1×10^{-5} per $\mu g/m^3$, which is an upper-bound estimate of the increased lifetime risk of cancer from inhaling 1 $\mu g/m^3$ of formaldehyde for 70 years (see Table ES-2). The estimate is based on an estimate of increased risk for NPC, for which **evidence demonstrates** that formaldehyde inhalation causes this type of cancer in humans. The IUR does not incorporate a unit risk estimate for myeloid leukemia (also for which the **evidence demonstrates** that formaldehyde inhalation causes this type of cancer in humans) because the interpretation of the published exposure-response modelling results was deemed too uncertain (see Section 5.2.2). This estimate also does not incorporate risk from sinonasal cancer for which the **evidence demonstrates** that formaldehyde inhalation exposure causes this type of cancer in humans, as amenable data were unavailable. Thus, the IUR may underestimate actual cancer risk, to an unknown extent.

The IUR is based on the modeling results of the association of cumulative formaldehyde exposure with NPC mortality in an occupational cohort followed by the National Cancer Institute (Beane Freeman et al., 2013). The regression coefficient from the dose-response model (log-linear models) was applied to age-specific cancer incidence rates from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) database using life-table methods to estimate the upper bound on the extra risk[2] expected at a formaldehyde concentration of 0.1 ppm. The IUR is expressed as the upper-bound extra cancer risk estimated for a lifetime inhalation exposure to 1 $\mu g/m^3$. This estimate, based on a human study, was similar to what would be estimated using any of a tight range of values derived using experimental animal data. The analyses of the experimental data were based on multiple dose-metrics and included estimates derived using BBDR modeling approaches incorporating available mechanistic evidence (see Section 5.2.1). The unit risk estimate for NPC cancer prior to any age adjustments is 7.4×10^{-6} per $\mu g/m^3$ (see Table ES-2). EPA guidelines recommend that ADAFs be used when estimating the risk of NPC from childhood inhalation exposures to formaldehyde because the NPCs are judged to be due, at least in

[2] Extra risk is defined as $(R_x - R_o)/(1 - R_o)$, where R_x is the lifetime risk in the exposed population and Ro is the lifetime risk in an unexposed population; it is the added risk applied to the portion of the population that did not show background tumors.

part, to a mutagenic MOA. In the absence of information to support a chemical-specific age adjustment factor, EPA's default ADAFs are applied. Thus, the unit risk estimate was adjusted using age-dependent adjustment factors (ADAFs) to address expected increased susceptibility from early-life exposures (see Table ES-2).

Overall confidence in the IUR is **medium**. The availability of suitable human data from which to derive unit risk estimates eliminates one of the major sources of uncertainty inherent in most unit risk estimates—the uncertainty associated with interspecies extrapolation. The NCI longitudinal cohort study used as the basis for the inhalation unit risk is a well-conducted study for the purposes of deriving unit risk estimates and there is high confidence in the study's results. However, it was the only independent study with adequate exposure estimates for the derivation of unit risk estimates.

There are several uncertainties that, when considered together, are expected to result in an underestimation of the IUR. First, an important uncertainty is the inability to derive a unit risk estimate that incorporates risk for all three cancer types with conclusions of "**evidence demonstrates"** that formaldehyde inhalation exposure causes the cancer. Second, since industrial workers are healthier than the general population overall, the unit risk estimates derived from the NCI worker cohort data could underestimate the cancer risk for the general population to an unknown, but likely small, extent. Third, given the high survival rates for NPC, cancer incidence risk estimates were calculated using the dose-response relationships from the NCI mortality study to reduce the potential for underestimating the unit risk. However, the calculation required certain assumptions, thus, the estimates may under- or overpredict the true risk by an amount expected to be relatively small.

Because a mutagenic MOA was established for NPC (see Section 3.2.5 for details), the IUR was calculated using linear low-dose extrapolation from the 95% lower bound on the exposure level associated with the extra risk level serving as the benchmark response, which is considered to be a plausible upper bound on the risk at lower exposure levels. Use of the upper bound is a health-protective practice recommended in EPA guidelines (U.S. EPA, 2005a).

ES.4 SUSCEPTIBLE POPULATIONS AND LIFESTAGES

Overall, the most extensive research on the health effects of inhaled formaldehyde and susceptible groups indicates a greater susceptibility among children to formaldehyde's respiratory effects, manifested as reduced pulmonary function, increased prevalence of current asthma, and greater asthma severity (reduced asthma control). More research is needed to investigate the role of sex, race, nutrition, exercise, and coexposures that may modulate susceptibility to formaldehyde toxicity. Increased early-life susceptibility for cancer is assumed because of the mutagenic MOA for NPC carcinogenicity. Health status and disease, particularly related to the respiratory system, are likely to be modifying factors of formaldehyde toxicity. Studies suggest that asthmatics are more susceptible than nonasthmatics to declines in respiratory function following formaldehyde exposure. Based on multiple mechanistic studies of respiratory hypersensitivity, it also appears

likely that persons with preexisting respiratory allergies would be more sensitive to the respiratory health effects of formaldehyde exposure, although the data informing potential associations between more generalized atopy and respiratory effects in the available human studies were inconsistent. Experimental animal studies and occupational studies indicate that formaldehyde exposure-induced nasal lesions are more severe among individuals with prior nasal damage, which could result in heightened susceptibility to the development of nasal cancer following formaldehyde exposure.

In addition, epidemiological and toxicological studies identify female reproductive or developmental toxicity as a hazard of formaldehyde exposure. At this time, it is not clear whether increased time to pregnancy and spontaneous abortion rates seen in occupationally exposed women are due to reproductive system toxicity or to toxicity to the developing fetus. Finally, reproductive toxicity in males has been associated with formaldehyde inhalation, although this association has only been tested in well-conducted studies of rodents at very high formaldehyde concentrations.

1. BACKGROUND

1.1. INTRODUCTION

This Toxicological Review critically evaluates the publicly available studies on formaldehyde (inhalation) to identify its adverse health effects and to characterize exposure-response relationships. This assessment is prepared under the auspices of the U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) Program. IRIS assessments are not regulations, but they provide a critical part of the scientific foundation for decisions made in EPA program and regional offices to protect public health.

Assessment development was based on EPA guidelines as well as standard IRIS procedures (U.S. EPA, 2020) that were reviewed by the National Academy of Sciences, Engineering, and Medicine (NASEM) (NASEM, 2021). In 1990 and 1991, an oral reference dose (RfD) (reference value for ingested formaldehyde) and an inhalation unit risk (IUR) value for cancer, respectively, were developed for formaldehyde. A previous draft of the inhalation assessment was developed between 1998 and 2010. That document was reviewed by an external peer-review panel convened by the National Research Council (NRC) between June 2010 and April 2011 (NRC, 2011). The newly developed, current assessment addresses the comments from the NRC panel on that prior draft (see Appendix D of the external review draft [https://iris.epa.gov/document/&deid=248150]), as well as comments provided during review of this document (see Appendix F).

For additional information about this assessment or for general questions regarding IRIS, please visit the IRIS website (www.epa.gov/iris).

1.2. OVERVIEW OF BACKGROUND INFORMATION ON FORMALDEHYDE

The brief overview below (and the corresponding information in Appendix A) is provided to introduce potentially useful context for this assessment. These summaries do not provide comprehensive descriptions of the available information on these topics and are not intended for use in decision purposes. Readers are encouraged to refer to source materials cited below, more recent publications on these topics, and specific assessments on these topic areas.

1.2.1. Summary of Chemical Properties and Uses

Formaldehyde (CASRN 50-00-0) is an aliphatic aldehyde noted for its reactivity and versatility as a chemical intermediate. At room temperature, pure formaldehyde is a colorless gas with a strong, pungent, and irritating odor. Formaldehyde is readily soluble in water, alcohols, ether, and other polar solvents. Due to its chemical properties (see Appendix A.1 for additional details), formaldehyde is widely used in both commercial and industrial settings. Based on EPA's

Chemical Data Reporting, the national production volume for formaldehyde was 3.9 billion lb/year in 2011 and between 1 and 5 billion lbs/year for 2012 through 2015 (https://chemview.epa.gov/chemview/#).

Products containing formaldehyde are widespread in industry and in the home (see Appendix A.2). Approximately 55% of the consumption of formaldehyde is in the production of industrial resins (NTP, 2010). Formaldehyde is used in plywood adhesives, surface coatings, molding compounds, laminates, phenolic thermosetting, resin curing agents, and other products (IPCS, 1989). Formaldehyde is used in smaller quantities for the preservation and embalming of biological specimens. It is also used as a germicide, an insecticide, and a fungicide in some products. Some industries with the greatest potential for exposure to the workforce include health services, business services, printing and publishing, chemical manufacturing, garment production, beauty salons, and furniture manufacturing (IARC, 1995).

1.2.2. Summary of Human Inhalation Exposure

Generally, formaldehyde levels are higher in the indoor environment than in ambient air. Indoor sources of formaldehyde in air include building materials and household products (e.g., volatilization from pressed wood products, carpets, fabrics, insulation, permanent-press clothing, latex paint), as well as household sources of combustion (e.g., gas burners, kerosene heaters, cigarettes) (WHO, 2010). Median indoor air concentrations in some European countries in both commercial and residential buildings ranged from 10 to 50 μg/m^3 (Sarigiannis et al., 2011; Salthammer et al., 2010). Indoor average formaldehyde concentrations reported since 2000 in U.S. and Canadian conventional homes ranged from 12 to 39 μg/m^3 (see Appendix A.3). For example, a large study of 398 homes in Los Angeles, CA, Houston, TX, and Elizabeth, NJ, between 1999 and 2001 reported mean (±SD) formaldehyde levels of 22 ± 7.1 μg/m^3 (Weisel et al., 2005). Higher levels are found in mobile homes and trailers.

In 2018, annual site averages of formaldehyde concentrations outdoors ranged from 0.25 – 11.06 μg/m^3 (0.20–9.01 ppb), with an overall annual site average concentration of 2.97 μg/m^3 (2.42 ppb) (EPA's Ambient Monitoring Archive for HAPs, which includes data from the Air Quality System database and other data sources at https://www.epa.gov/amtic/amtic-air-toxics-data-ambient-monitoring-archive). Under the National-Scale Air Toxics Assessment (NATA) program, EPA has conducted an emissions inventory for a variety of hazardous air pollutants (HAPs), including formaldehyde. NATA uses the emissions inventory data to model nationwide air concentrations/exposures (https://www.epa.gov/national-air-toxics-assessment). The most recent NATA data are for 2014. The results of the 2014 ambient air concentration modeling for formaldehyde suggest that county mean air levels range from 0.1 to 2.78 μg/m^3 with a national mean of 1.3 μg/m^3 [personal communication to EPA (Palma, 2018)].

Although not final, a March 15, 2024, public draft TSCA risk evaluation includes formaldehyde exposure assessments (note: IRIS assessments do not include exposure assessments). While preliminary, the draft TSCA risk evaluation cites studies supporting estimates

similar to those described above. Namely, the draft estimates that the median formaldehyde concentration in U.S. homes is approximately 20 μg/m^3 and, using monitoring data from 2023, U.S. formaldehyde concentrations in outdoor air are estimated to have a median formaldehyde concentration of 1.88 μg/m^3. Please consult the EPA website for updates and release of the finalized TSCA risk evaluation (https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-formaldehyde).

2. ASSESSMENT METHODS

This chapter describes the underlying framework, organization, and methods used to conduct the systematic reviews included in this assessment. The evaluation of formaldehyde's toxicity was informed by what is known about the toxicokinetics of inhaled formaldehyde (see Section 3.1 and Appendix C.1), and this knowledge is reflected in the organization of the Hazard Identification section. These Assessment Methods outline the approaches implemented throughout different stages in the assessment development, which can be grouped into those used to (1) identify and evaluate individual studies (Sections 2.2 and 2.3); (2) summarize, synthesize and integrate the evidence, including interpreting the support for particular human health effects across different streams of evidence (i.e., human, animal, and mechanistic studies) and developing summary conclusions (Sections 2.4, 2.5 and 2.6); and (3) select and analyze studies and data to derive quantitative (dose-response) values (Section 2.7). The process for hazard identification, which involves hazard-specific literature searches, outcome/endpoint-specific evaluation of study methods, synthesis of information within each stream of evidence, and integration across streams of evidence, is displayed in Figure 2-1. The process involves a successive focusing on the more informative outcomes/endpoints within each hazard domain and the most methodologically sound studies.

The methods applied are described here, while the documentation (e.g., the results of literature search and screening and study evaluations) is provided in the Appendices. Literature search and screening and study evaluations are documented in Appendix B.2 and B.3, respectively.

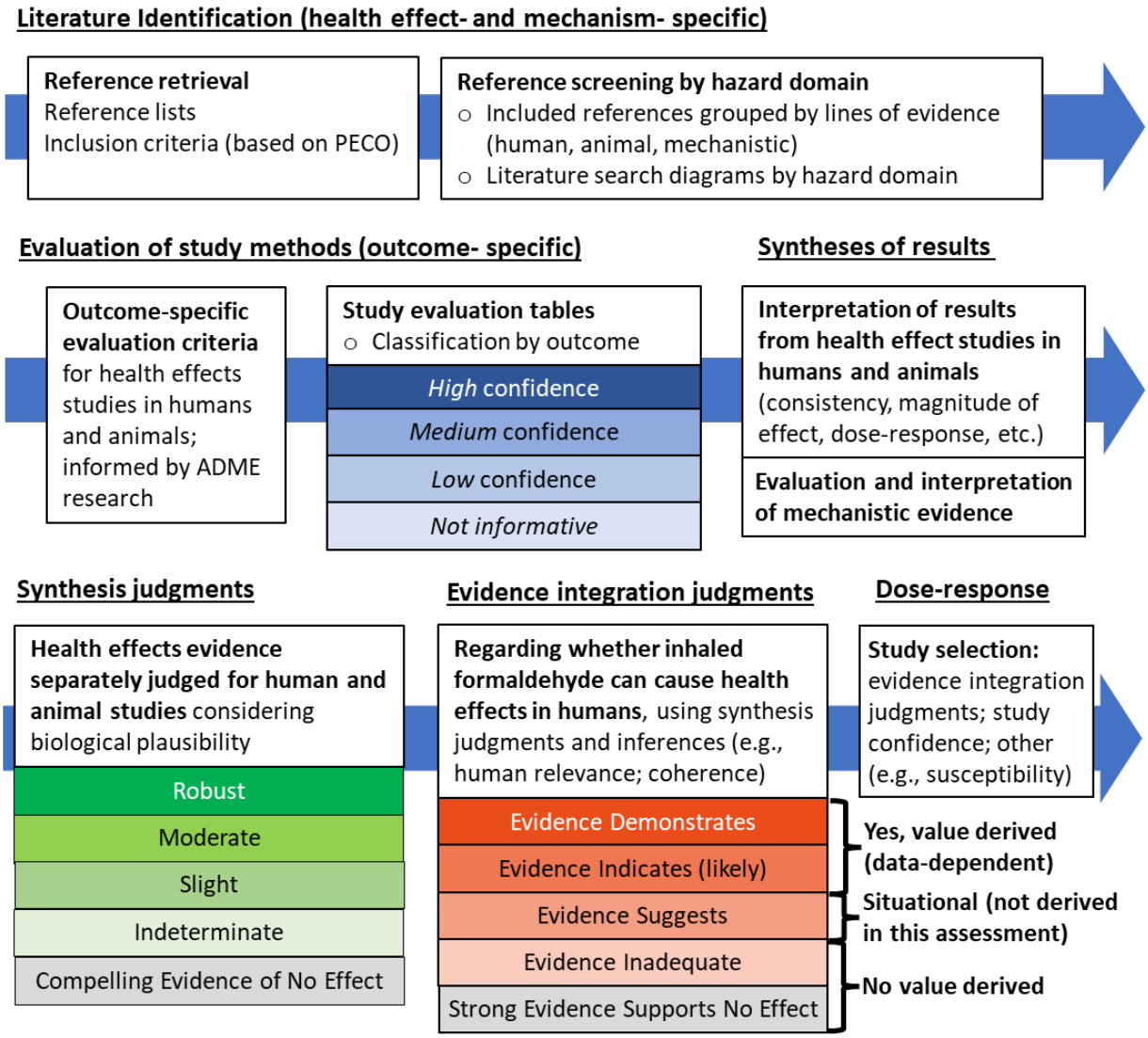


Figure 2-1. Overview of assessment methods for hazard identification.

This figure illustrates the flow of evidence through the assessment, sequentially focusing on the most useful information, as well as the decision-making processes for arriving at evidence judgments regarding the potential for noncancer health effects and for specific types of cancer. Mechanistic inference considered during evidence integration included biological plausibility or relevance of animal study results to humans and identification of susceptible groups. Notes: Given this assessment's framing around prior reviews of formaldehyde's potential toxicity (i.e., health effect-specific searches guide this review), for this assessment, the synthesis judgment of "compelling evidence of no effect" and the integration judgment of "strong evidence of no effect" were not reached for any of the evaluations; as such, criteria for these categories are not applied in this assessment. Importantly, hazard identification for carcinogenicity includes an additional step of assigning a descriptor regarding the potential for formaldehyde to cause cancer (this step is not shown but is discussed in this section below). Abbreviations: HERO = Health and Environmental Research Online; PECO = Populations, Exposures, Comparators, Outcomes; ADME = absorption, distribution, metabolism, excretion; MOA = mode of action.

2.1. ASSESSMENT ORGANIZATION AND DOCUMENT MAP

The Toxicological Review critically reviews the publicly available studies relevant to human health hazards that may result from formaldehyde inhalation and describes the level of certainty in the supporting evidence. When there was sufficient certainty in the evidence supporting a hazard and appropriate studies and data were available, toxicity values were derived using either analyses of dose-response or selected no-observed-adverse-effect levels or lowest-observed-adverse-effect levels (NOAELs or LOAELs). Although this review focused on exposure through inhalation, general population exposure to formaldehyde can occur via inhalation, ingestion, and dermal contact.

The Toxicological Review is organized into the following sections: Executive Summary, Background (Section 1); Assessment Methods (Section 2); Evidence Synthesis and Integration for Hazard Identification (Section 3); Summary of Hazard Identification Conclusions (Section 4); and Dose-Response Analysis (Section 5). Supplemental Information to the Toxicological Review is provided in a separate document, Supplemental Information to the Toxicological Review of Formaldehyde—Inhalation, containing appendices that support hazard identification and dose-response evaluation. The appendices include a brief description of the chemical properties and uses of formaldehyde; information specifically addressing exposure, toxicokinetics, and genotoxicity; supporting information for health hazard conclusions in the Toxicological Review (e,g., documentation of literature searches and study evaluations; additional analyses); dose-response modeling; a list of previous legislation and assessments by other agencies; and responses to external peer-review and public comments received on this IRIS assessment. Additional documents produced during assessment development are available on the IRIS website (http://www.epa.gov/iris).

In this assessment, potential human health hazards from formaldehyde exposure were identified and evaluated. These include sensory irritation; decreased pulmonary function; immune-mediated conditions, focusing on allergies and asthma; respiratory tract pathology; nervous system effects; reproductive and developmental toxicity; and carcinogenicity. These health outcomes were identified based on NRC recommendations on the 2010 draft IRIS assessment (NRC, 2011) and previous reviews of formaldehyde toxicity and health assessments by other agencies, including the International Agency for Research on Cancer (IARC), Agency for Toxic Substances and Disease Registry (ATSDR), and the National Toxicology Program (NTP) (NTP, 2014; IARC, 2012; ATSDR, 1999, 2010). For each health hazard, the literature regarding specific health effects was synthesized within each of the human, animal, and mechanistic streams of evidence and then integrated across the streams of evidence. The evidence integration includes a narrative summary of the key evidence and a corresponding level of evidence judgment (i.e., **evidence demonstrates**, **evidence indicates** [likely], **evidence suggests**, **evidence inadequate**, or **strong evidence supports no effect**) as to whether formaldehyde inhalation exposure may pose a human hazard for specific types of cancer or individual noncancer health effects, given sufficient exposure conditions. The assessment provides evidence integration judgments for each unit of analysis that can be reasonably supported

by the available health effect-specific evidence base. A unit of analysis is an outcome or group of related outcomes within a health effect category considered together during evidence synthesis. A given health hazard may have a single judgment or multiple judgments at more granular outcome groupings. The evidence integration for cancer concludes with a descriptor summarizing the weight of evidence for cancer according to EPA's cancer guidelines (U.S. EPA, 2005a). In this assessment, for both noncancer and cancer effects, those with evidence integration judgments of **evidence demonstrates** or **evidence indicates** [likely] (see methods in Section 2.6) are advanced for dose-response analysis in Section 5, including the derivation of toxicity values (see methods in Section 2.7).

The Toxicological Review includes an inhalation reference concentration (RfC) value for lifetime exposure. The inhalation RfC (expressed in units of μg of substance/m^3 air) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous daily exposure of formaldehyde to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. A carcinogenicity assessment was also performed, including derivation of an inhalation unit risk value (IUR), which is an upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg/m^3 in air. In addition, organ/system-specific RfCs (osRfCs) were derived for various noncancer health endpoints, when supported by the available evidence. These may be useful when considering cumulative risk scenarios. Multiple candidate RfCs (cRfCs) were sometimes compared before choosing a representative osRfC for a specific organ or system. An osRfC was typically selected from cRfCs based on use of higher confidence studies, and higher confidence in the cRfC derivation (including point-of-departure [POD] selection). Where relevant, mechanistic understanding regarding the development of specific health effects (e.g., temporal progression, potential thresholds in dose-response), as well as knowledge of susceptibility, was used to inform approaches to derive points of departure (PODs), uncertainty factors, or confidence levels for the quantitative estimates (e.g., osRfCs, RfC, IUR). Where possible, the assessment attempts to describe the level of response observed across different exposure levels within the range of the data, and to discuss transparently the uncertainties and assumptions when deriving toxicity value estimates (e.g., cRfCs, IUR). In addition, as the temporal window of exposure relevant to certain outcomes may vary, the window of exposure expected to be most relevant to each toxicity value is discussed in Section 5, Dose-Response Analysis, when applicable.

A confidence level of **high**, **medium**, or **low** was assigned to each cRfC, osRfC, and the overall RfC based on the reliability of the associated evidence and POD calculation(s). Confidence decisions included considerations of the quality, timing, and variability of the exposure estimates in an epidemiological study or the exposure protocols in an animal study. Moreover, higher confidence was placed in the toxicity value when the POD was identified close to the range of the observed data. Finally, confidence in the coverage and quality of the database of studies that informed the hazard conclusion for that organ/system was assigned. The evidence base for

different health outcomes varies in size, coverage of critical endpoints, and quality of the studies; this confidence level reflects database completeness for each of the organ systems.

Overviews of the methods used for the Literature Search and Screening (Section 2.2), Study Evaluation (Section 2.3), Data Extraction (Section 2.4), Evidence Synthesis (Section 2.5), Evidence Integration (Section 2.6), and Dose-Response Modeling (Section 2.7) are presented. The Document Map (Table 2-1) provides information on where to find the results and additional documentation for each of these steps for each health effect included in this Toxicological Review.

Table 2-1. Document map for each health topic and assessment development stage (Sections at the top indicate the location of the methods or relevant results; Appendices at the bottom indicate the location of supporting documentation)

Health effect or mechanisms searches	Evidence identification	Study evaluation	Evidence synthesis and integration	Dose-response analysis
Sensory Irritation	Section 2.2.2 Appendix B.2.2	Section 2.3.2 Appendix B.3.2	Section 3.2.1 Appendix C.2 (reflex bradypnea)	Section 5.1 Appendix D.1.1
Pulmonary Function	Section 2.2.3 Appendix B.2.3	Section 2.3.3 Appendix B.3.3	Section 3.2.2 Appendix C.5 (acute or short-term studies)	Section 5.1 Appendix D.1.2
Allergies and Asthma	Section 2.2.4 Appendix B.2.4	Section 2.3.4 Appendix B.3.4	Section 3.2.3 [see also Appendix C.7]	Section 5.1 Appendix D.1.3
Respiratory Tract Pathology	Section 2.2.5 Appendix B.2.5	Section 2.3.5 Appendix B.3.5	Section 3.2.4 Appendix C.6 (short-term animal studies) [see also Appendix C.7]	Section 5.1 Appendix D.1.4
Noncancer Respiratory Mechanistic Evidence	Section 2.2.6 Appendix B.2.6	Section 2.3.6 Appendix B.3.6	Sections 3.2.1—3.2.5 Appendix C.7	N/A
Nervous System Effects	Section 2.2.7 Appendix B.2.7	Section 2.3.7 Appendix B.3.7	Section 3.3.1 No appendix materials	N/A
Developmental or Reproductive Effects	Section 2.2.8 Appendix B.2.8	Section 2.3.8 Appendix B.3.8	Section 3.3.2 No appendix materials	Section 5.1 Appendix D.1.5
Respiratory Tract Cancers	Section 2.2.9 Appendix B.2.9	Section 2.3.9 Appendix B.3.9	Section 3.2.5 No appendix materials	Section 5.2.1 Appendix D.2.1 (human data) and D.2.2 (animal data)
LHP Cancers			Section 3.3.3 No appendix materials	Section 5.2.2 Appendix D.2.3
Other cancers		N/A	Appendix C.8	N/A
Cancer Mechanistic Evidence	Section 2.2.10 Appendix B.2.10	Section 2.3.10 Appendix B.3.10	Sections 3.2.5 and 3.3.3 Appendix C.3 (Genotoxicity)	N/A

Note: evidence on the toxicokinetics of inhaled and endogenous formaldehyde is summarized in Section 3.1 and Appendix C.1 and D.2.4, with discussions related to the implications of these data throughout Sections 3.2, 3.3, and 5.

2.2. LITERATURE SEARCH AND SCREENING METHODS

2.2.1. Overview of Approach

Literature Search Strategy

A separate search strategy was developed for each health hazard considered in the assessment (Table 2-2). Generally, health outcomes and search terms were selected after reviewing the draft Toxicological Review for Formaldehyde (2010) and other relevant health assessments or reviews of formaldehyde toxicity.

The primary literature search strategies involved keyword-based queries of PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (https://apps.webofknowledge.com/), with many of the health effect-specific searches including additional queries of Toxline (https://toxnet.nlm.nih.gov/newtoxnet/toxline.htm) and/or DART (https://toxnet.nlm.nih.gov/newtoxnet/dart.htm). Initial searches were conducted in 2012 (an exception being the search for mechanisms related to respiratory health effects, which was initially conducted in 2014) and updates were performed annually (i.e., in either September or October) through 2016 in support of development of a 2017 Step 1 draft IRIS formaldehyde-inhalation assessment, which was suspended in 2017 and re-started in 2021 (discussed more below). All search strings were submitted as keyword searches, which in the case of PubMed includes MeSH terms by default, except as specified with tags like [majr] which limited the search to only when the term (and any selected subheadings) are indexed as a major topic heading (not all MeSH terms); as defined by PubMed, a MeSH Major Topic is one of the main topics discussed in an article. The search results were augmented by secondary search approaches, including "forward searching" of key references, review of topic-specific meeting abstracts (e.g., from Society of Toxicology and International Society of Environmental Epidemiology annual meetings), and curation of reference lists in the identified studies, published reviews, meta-analyses, and national or international health assessments of formaldehyde, and Review of abstracts (initial title search for formaldehyde, then abstract review) from 2005–2014 presented at International Society of Environmental Epidemiology annual meetings.

The completed draft 2017 IRIS assessment was suspended by EPA (https://www.epa.gov/sites/default/files/2019-4/documents/iris_program_outlook_apr2019.pdf) However, in 2021, development of the IRIS assessment was unsuspended (https://www.epa.gov/sites/default/files/2021-03/documents/iris_program_outlook_mar2021.pdf). At the time of re-start, a separate systematic evidence map (SEM) was developed to identify the relevant literature published since the suspension of the 2017 draft (i.e., from January 2016 to May 2021, intentionally overlapping with the prior searches). The primary focus of the SEM was to identify studies with the potential to impact hazard or toxicity value conclusions. This SEM applied literature search strategies nearly identical to those used to develop the 2017 draft IRIS assessment. However, while earlier literature

updates included a search strategy on exposure to formaldehyde and a search specific to hypersensitivity in animals, these research categories were not updated for this search as exposure is not a review topic for the IRIS assessment and the respiratory mechanisms search encompasses hypersensitivity studies. In addition, the SEM update did not include ToxNet, which was migrated to PubMed in 2019.

Table 2-2. General approach to literature search strategies

Databases[a]	Health effect searches[b]	Additional mechanistic searches[d]
PubMed Web of Science ToxNet (for some effects) TSCATS2 (for some effects)	(formaldehyde, formalin, paraformaldehyde, OR CASN 50-00-0) AND: • Sensory Irritation[c] • Pulmonary Function[c] • Immune-Mediated Conditions, focusing on Allergies and Asthma • Respiratory Tract Pathology • Developmental and Reproductive Toxicity • Nervous System Effects • Site-specific cancer in Humans • Upper Respiratory Tract Cancer in Animals • Lymphohematopoietic Cancer in Animals	(formaldehyde, formalin, paraformaldehyde, OR CASN 50-00-0) AND: • Toxicokinetics • Inflammation and Immune-related mechanisms • Mechanistic Studies of Upper Respiratory Tract Cancer, focusing on Genotoxicity[e] • Mechanistic Studies of Lymphohematopoietic Cancer, focusing on Genotoxicity[e]

CASN, Chemical Abstracts Service Number; TSCATS, Toxic Substances Control Act Test Submissions.

[a]PubMed: http://www.ncbi.nlm.nih.gov/pubmed/, Web of Science: http://apps.webofknowledge.com/WOS_GeneralSearch_input.do?product=WOS&search_mode=. ToxNet: toxicology information previously contained in ToxNet were integrated into other NLM products in 2019 (see https://www.nlm.nih.gov/toxnet/index.html for where to access).

[b]Specific parameters and keywords for each hazard-specific database search strategy are included in Appendix B.2.

[c]A systematic search strategy was not applied to the database of animal studies on this health outcome. Sensory irritation in animals is a well described phenomenon. For pulmonary function, there was an extensive set of research studies on humans, and therefore, the few studies on this endpoint in animals were not reviewed.

[d]Separate, systematic literature searches were performed to augment the analyses of mechanisms relevant to health effect-specific searches.

[e] Search strategy developed for the SEM.

Literature Screening

Studies were screened for relevance for a specific health effect based on inclusion and exclusion criteria organized according to PECO (Populations, Exposures, Comparators, and Outcomes) category[3]. References that had potential relevance to more than one health effect were identified and screened within each category. The exposure criteria were of particular importance, and inclusion was limited to studies with direct measurement or reconstruction (e.g., use of a job-

[3] For screening of studies on a few topics (i.e., formaldehyde exposure; toxicokinetics; mechanisms of carcinogenesis), a PECO-based screening approach was not systematically applied or documented for searches through 2016, consistent with the state of practice at that time.

exposure matrix applied to indirect formaldehyde measurements) of formaldehyde exposure rather than reliance on proxies such as construction materials or age of a house. PECOs tailored to mechanistic studies were also used. Other exclusions were based on specific criteria relating to each health hazard, which are summarized in each of the respective health hazard sections below.

From 2012–2016, this screening was performed using title and abstract information or hand curation of the full text articles (when screening decisions could not be made based on the abstract) in Endnote libraries. Studies identified in the 2021 SEM database searches were imported into DistillerSR software (https://www.evidencepartners.com/products/distillersr-systematic-review-software/) for screening. Both title/abstract (TIAB) and full-text screening were conducted by two independent reviewers and any screening conflicts were resolved by discussion between the primary screeners with consultation by a third reviewer if needed. For citations with no abstract, articles were initially screened based on title relevance and page numbers (articles two pages in length or less are assumed to be conference reports or editorials). Eligibility status of non-English studies was assessed using the same approach with online translation tools or engagement with a native speaker used to facilitate screening. Access to the example screening form in DistillerSR is available upon request for users who have DistillerSR access. See Sections 2.2.2–2.2.10 for PECO criteria for specific health effects and types of mechanisms.

This assessment focuses on studies of inhalation exposure to formaldehyde in indoor air. Ambient levels of formaldehyde in outdoor air are significantly lower than those measured in the indoor air of workplaces or residences, and the exposure range was narrow in epidemiological studies of ambient exposure (<0.005 mg/m^3), limiting their sensitivity to find any associations with health outcomes even if they existed. Temporal (seasonal and diurnal) and spatial variation in formaldehyde concentration is strongly influenced by photochemical interactions and traffic emissions (Luecken et al., 2012). Consequently, the potential for exposure misclassification for estimates of individual exposure using mean formaldehyde concentrations from central outside monitors is greater than from indoor formaldehyde measurements. Therefore, the few studies examining health effects in relation to outdoor formaldehyde concentrations were excluded. In addition, although some uncertainties remain, the organization and analyses in the assessment assume that inhaled formaldehyde is not distributed to an appreciable extent beyond the upper respiratory tract to distal tissues; thus, it is assumed that inhaled formaldehyde is not directly interacting with tissues distal to the portal of entry (POE) to elicit systemic effects. Therefore, as a deviation from the literature screening approach applied to develop the 2017 draft, studies of exposure routes not involving inhalation, including in vitro studies involving cells from distal tissues, were not considered to be PECO relevant for the 2021 SEM literature update and were excluded; an exception to this was applied for studies of genotoxicity. Similarly, it is assumed that formaldehyde does not cause appreciable changes in normal metabolic processes associated with formaldehyde in distal tissues. Thus, studies examining potential associations between levels of formaldehyde or its metabolites in tissues distal to the POE (e.g., formate in blood or urine, brain

formaldehyde levels) were excluded for most health outcomes, particularly effects on systemic tissues such as the nervous system and reproductive and developmental effects. However, studies of endogenous formaldehyde and mechanisms with potential relevance to circulating hematopoietic precursor cells and lymphohematopoietic cancers were considered.

Study Inclusion from the 2021 SEM

For the 2021 SEM literature update, after screening the studies for PECO relevance, only those studies meeting the PECO criteria and judged as *possibly impactful* (i.e., likely, based on the study design and tested exposure levels, to have a potential impact on the hazard conclusions or toxicity values) are synthesized in this assessment. This process relied on information collected into a literature inventory and expert judgment by two reviewers. The literature inventory (see Appendix B.2) included the following:

- For animal studies, the following information was captured: formaldehyde source, study type (e.g., acute, chronic, developmental), duration of treatment, route, species, strain, sex, exposure levels tested, exposure units, and endpoints assessed.
- For epidemiological studies, the following information was summarized: population type (e.g., residential/school based, occupational, other), study design (e.g., cross-sectional, cohort, case-control, ecological, case-report, controlled trial), study location, lifestage (adults, children/infants), exposure measurement (air sampling, occupational history, other), and endpoints assessed.
- For mechanistic studies, the information gathered was dependent on the study type: human in vivo, animal in vivo, in vitro/ex vivo, or dosimetry/pharmacokinetic modeling. For dosimetry/pharmacokinetic modeling references, a summary from the paper's abstract was excerpted. For all types of mechanistic studies, study details and exposure metrics were summarized along with the endpoints assessed.

General considerations for designating studies as *possibly impactful* are included below, with the specific rationales documented in the SEM study summary tables:

- Studies with chronic or subchronic exposure durations or including exposure during reproduction or development, were considered more impactful than studies with acute or shorter-term exposure durations (e.g., <4 weeks in rodent studies).

- Animal studies with multiple dose groups covering a broad range of dose levels, and specifically including lower exposure levels, were considered more impactful than single-dose studies.

- Animal studies employing exposure to formaldehyde without methanol co-exposure (e.g., generated from paraformaldehyde) and with adequate inhalation exposure administration methods were considered more impactful. Methanol, present in aqueous formaldehyde solutions to inhibit polymerization, is a potential confounder of associations between observed health outcomes and formaldehyde exposure via formalin. The test article used to

generate the formaldehyde atmosphere and controls in experimental studies was an important consideration, particularly for non-respiratory health effects.

- More apical endpoints and those most directly related to the mechanistic uncertainties identified as most relevant to drawing hazard or dose-response judgments were considered more impactful. The specifics of this consideration vary depending on the health outcome(s) of interest. In some cases, this relevance determination relates to the potential human relevance of the endpoints, while in others this relates to an ability to infer adversity.

- For human studies, prioritization considerations depended on the health effect category, formaldehyde exposure levels, and the extent of the evidence base supporting the hazard conclusions. Studies of noncancer respiratory outcomes identified in the PECOs among residential populations or school-aged children were prioritized over occupational studies, which typically involve higher formaldehyde concentrations. Any study of reproductive or developmental outcomes that conducted an exposure assessment (qualitative or quantitative) for formaldehyde was considered *possibly impactful*. In addition, with some exceptions documented in the inventory tables, studies of ALS, genotoxicity endpoints, or PECO identified cancer outcomes that conducted an exposure assessment (qualitative or quantitative) for formaldehyde were generally considered *possibly impactful*.

Studies meeting PECO criteria that were judged to have no impact on assessment conclusions or toxicity values are summarized in Appendix B.2, along with explanations for these decisions. These latter studies are not further discussed or synthesized in the assessment.

Documentation

Evidence identification decisions are documented in Appendix B.2 and the formaldehyde page of the U.S. EPA's Health Effects and Research Online (HERO) database (https://hero.epa.gov/hero/) and they are summarized in Table 2-3 below. The formaldehyde HERO page (https://heronet.epa.gov/heronet/index.cfm/project/page/project_id/4051) was developed to present a consolidated view of the search and screening decisions for this assessment for the literature identified through 2016 and in the subsequent 2021 SEM. Tags for literature searching (under "literature identification") indicate from which electronic database each study was identified, noting that some studies were identified in duplicate across databases, or if considered studies were identified through other mechanisms (lists of reference from other or older formaldehyde assessments; lists of references from review articles screened for health effect-specific PECO studies; guidelines or methodological instructions; and other studies not otherwise tagged to a specific electronic database during import). Also tracked, for each health effect-specific series of literature searches including the 2021 SEM, are the screened studies, namely those identified as supplemental (e.g., a review; non-inhalation routes of exposure for some searches), those not meeting the PECO criteria that were excluded, and those identified as meeting the PECO criteria, with the latter bin including an additional tag for being identified as possibly impactful or not in the 2021 SEM. Thus, this HERO page can be used to easily navigate through the higher-level screening decisions for each health effect-specific search.

Table 2-3. Summary of literature search and screening

Health effect and mechanisms searches[a]	Identified studies[b]	Excluded studies[b]	Supplemental studies[b]	Met PECO[b]	Met PECO SEM decisions	
					Possibly impactful[c]	Not impactful[c]
Noncancer						
Sensory Irritation in Human Studies	979	820	97	62	1	4
Pulmonary Function in Human Studies	353	262	30	61	1	5
Immune-Mediated Conditions in Human Studies, Including Asthma and Allergy	6,206	5,649	499	58	11	5
Respiratory Tract Pathology in Human Studies	1,598	1,577	7	14	0	1
Respiratory Tract Pathology in Animal Studies	2,049	1,814	174	61	1	9
Mechanistic Studies Related to Noncancer Respiratory Effects, Including Immune Changes and Inflammation	9,894	8,729	966	199	8	48
Nervous System Effects	9,435	9,252	91	92	2	12
Reproductive and Developmental Effects	11,040	10,647	326	67	5	4
Cancer						
Cancer in Human Studies	2,552	2,419	76	67	3	3
Respiratory Tract (Nasal) Cancer in Animal Studies	945	893	27	25	1	1
Mechanistic Studies of Respiratory Tract Cancer, Genotoxicity Focus	744	417	101	225	8	19
Lymphohematopoietic (LHP) Cancer in Animal Studies	117	81	28	8	1	1
Mechanistic Studies of LHP Cancer, Genotoxicity Focus	3,307	3,019	150	138	14	11

[a]These counts reflect the summary decisions documented in the Formaldehyde HERO page (https://heronet.epa.gov/heronet/index.cfm/project/page/project_id/4051). Note that numbers of studies in each bin in

HERO can differ from the numbers of studies elsewhere, including in literature flow diagrams presented in the Appendix (e.g., HERO tracks as separate articles the parent articles and their translations, unpublished reports of published data, supplemental materials to published articles, and erratum).

[b]Studies identified in 2012–2016 annual searches and the 2021 SEM.

[c]SEM-related *possibly impactful* and *not impactful* judgments for studies meeting PECO in the SEM (see below for health effect-specific details).

2.2.2. Sensory Irritation PECO Criteria and Search Summary

The sensory irritation review focused on symptoms of irritation in humans, primarily ocular, nasal, and throat symptoms. Epidemiological and controlled exposure studies describing reports of sensory irritation based on questionnaire responses or objective measures, such as eye blink frequency or conjunctival redness, were included while other epidemiological study designs were excluded. There is an extensive database of research studies on relevant apical endpoints in humans after formaldehyde exposure. Systematic searches for studies of sensory irritation in experimental animals were not conducted. However, mechanistic data informing this health effect were identified and evaluated as part of the overarching review of mechanistic data relevant to potential respiratory health effects (see Appendix B.2.6, B.3.6, and C.7 for details).

PECO category inclusion and exclusion criteria used in the screening step are described in Table 2-4. The bibliographic databases, search terms, and specific strategies used to search them, as well as literature flow diagrams and other screening documentation, are provided in Appendix B.2.2.

Table 2-4. PECO inclusion and exclusion criteria for studies of sensory irritation in humans

PECO Category	Included	Excluded[a]
Population	• Human	• Animals (note: already well-established; see Appendix C.2)
Exposure	• Indoor exposure via inhalation to formaldehyde • Measurements of formaldehyde concentration in air	• Not formaldehyde • Dermal[b] • Exposure defined using job title/industry • Outdoor exposure
Comparison	• Evaluated risk in relation to variation in exposure based on level, duration, or other parameter.	• Case reports • Surveillance analysis /Illness investigation (no comparison)
Outcome	• Ocular, nasal and throat symptoms	• Exposure studies/no outcome evaluated • Studies evaluating other health outcomes

PECO Category	Included	Excluded[a]
		• Properties, uses

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).
[b]Dermal irritant effects result from direct dermal, not inhalation, exposure, and thus were excluded.

From the 979 studies identified by the searches, 58 studies identified through 2016 met PECO criteria; 38 were observational epidemiology studies and 20 were controlled exposure studies in human volunteers. Five additional studies from the 2021 SEM met PECO criteria; one study was deemed to be *possibly impactful* but already had been identified and incorporated by 2017. Thus, zero (0) additional studies from the SEM update were included for the sensory irritation review (see Appendix B.2.2 for details).

Overall, 58 human studies on sensory irritation were evaluated (see Section 2.3.2) for consideration in the Toxicological Review.

2.2.3. Pulmonary Function PECO Criteria and Search Summary

The pulmonary function review focused on standard quantitative measures of pulmonary function including spirometric measures, FEV_1, FVC, and FEF_{25-75}, as well as PEF measured using a flowmeter. Studies that evaluated both short-term as well as long-term exposure to formaldehyde were included. Observational studies of human populations evaluated exposures in residential communities, school classrooms and university lab courses, and industrial and other workplace settings. Controlled human exposure studies, which exposed subjects for minutes or hours, also were included. Although corresponding quantitative pulmonary function measures can be measured in animals, given the availability of well-conducted human studies and the challenges with conducting (e.g., due to the small size of rodent airways) and interpreting (e.g., the more precise and reliable measures require more invasive techniques) these endpoints (Bates and Irvin, 2003), as well as the sparsity of such studies with formaldehyde (based on prior reviews), systematic searches for studies of pulmonary function in experimental animals were not conducted. The mechanistic evidence informing this health effect was identified and evaluated as part of the overarching review of mechanistic data relevant to potential respiratory health effects (see Appendix B.2.6, B.3.6 and C.7 for details). The PECO category inclusion and exclusion criteria used in the screening step are described in Table 2-5. The bibliographic databases, search terms, and specific strategies used to search them, as well as literature flow diagrams and other screening documentation, are provided in Appendix B.2.3.

Table 2-5. PECO inclusion and exclusion criteria for studies of pulmonary function in humans

PECO Category	Included	Excluded[a]
Population	• Human	• Animals
Exposure	• Indoor exposure via inhalation to formaldehyde • Measurements of formaldehyde concentration in air, or exposure during dissection or embalming	• No formaldehyde specific analyses • Job title/industry-based analysis • Dermal • Outdoor exposure
Comparison	• Evaluated risk in relation to exposure based on level, duration, or other parameter.	• Case reports • Surveillance analysis /Illness investigation (no comparison)
Outcome	• Reported measure of FVC, FEV, FEF or PEF based on spirometry or flowmeter	• Pulmonary function among asthmatic subjects in controlled human exposure studies (there were evaluated in the section on other respiratory conditions including asthma • Exposure studies/no outcome evaluated • Studies of other outcomes

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

From the 353 studies identified by the searches, 53 studies identified through 2016 met PECO criteria; 42 were observational epidemiology studies and 11 were controlled exposure studies in human volunteers. Five additional studies from the 2021 SEM met PECO criteria; one study was deemed to be *possibly impactful* but already had been identified and incorporated by 2017. Thus, zero (0) additional studies from the SEM update were included for the pulmonary function review (see Appendix B.2.3 for details).

Overall, 53 human studies on pulmonary function were evaluated (see Section 2.3.3) for consideration in the Toxicological Review.

2.2.4. Immune-Mediated Conditions (Focusing on Allergies and Asthma) PECO Criteria and Search Summary

The immune-mediated conditions review focused on hypersensitivity (allergy) and on asthma, reflecting the question of whether formaldehyde exposure influences the sensitization response to respiratory allergens; these are well-developed areas of research with respect to immune-related effects of inhalation exposure to formaldehyde. This included the identification of

studies of specific health outcomes and particular exposure scenarios in studies of exposed humans (Appendix B.2.4) and relevant mechanistic data identified and evaluated as part of the overarching review of mechanistic data relevant to potential respiratory health effects, the latter of which included studies on hypersensitivity in animals (see Appendix B.2.6, B.3.6 and C.7 for details).

For the human health effect studies, several exposure settings and scenarios were included that encompassed different exposure durations and time windows. These included controlled human exposure studies among asthmatics, residential and school settings, as well as occupational studies. Controlled human exposure studies of pulmonary function change among asthmatic volunteers, including two studies that assessed whether formaldehyde exposure changed the response to an allergen challenge, are summarized in this section, but their results are most informative to the pulmonary function outcome and are included in the integration of evidence in that section (see Section 3.2.2). Specific types of outcome measures within the category of allergic conditions include questionnaire-based ascertainment of history of rhinitis, rhinoconjunctivitis, hay fever, pet allergy, eczema, or dermatitis; physician documentation of a specific diagnosis (e.g., atopic dermatitis); and allergic sensitization based on skin prick tests. Allergic conditions were grouped by site (nose, eyes, skin). Eczema is not a contact allergy but can be triggered by reactions to respiratory and other types of allergens (as well as by other factors). Unlike eczema, which can be triggered by reactions to respiratory and other types of allergens (as well as other factors), food allergies do not result from exposure to respiratory allergens or other inhaled substances. Because this assessment focuses on inhalation exposures only, food allergies are excluded from the literature search strategy. Measures of asthma include questionnaire-based ascertainment of prevalence of current asthma (e.g., within past 12 months), incidence of asthma, and measures of asthma control (based on symptom frequency and medication use in the past 2–4 weeks). EPA considered "ever had asthma" to be of limited use in this review, as the formaldehyde measures available do not reflect cumulative exposures that could be related to cumulative risk, and thus EPA did not include studies limited to "ever had asthma."

In addition, separate from asthma, EPA also considered studies of wheeze episodes, with or without lower respiratory infection, in infants and young children (≤ 3 years). The studies of wheezing episodes in infants were not classified as studies of asthma *per se* but could be indicatives of respiratory effects with implications for subsequent risk. These studies were evaluated as a separate health endpoint.

Given the frequency and general transiency of upper respiratory infections such as the common cold in human populations (which may complicate epidemiological evaluations), as well as their generally benign nature, this endpoint is not discussed in detail in this assessment, although several studies on this topic were identified and evaluated in the wider context of potential mechanisms for respiratory health hazards (see Appendix B.2.6, B.3.6 and C.7).

One potential mechanism for inducing hypersensitivity is the potential to elicit a formaldehyde-specific antibody response, specifically IgE. The presence of formaldehyde-specific

IgE in workers occupationally exposed to formaldehyde was described in case reports (Vandenplas et al., 2004; Kim et al., 2001), but larger studies in exposed populations or in asthma patients indicate this is a relatively uncommon occurrence, seen in no or only a few individuals (Wantke et al., 1996b; Thrasher et al., 1990; Krakowiak et al., 1998; Hisamitsu et al., 2011; Grammer et al., 1990; Doi et al., 2003). Formaldehyde-specific IgE was not included as an outcome for analysis in this section. However, a broader consideration of antibody responses following formaldehyde exposure is considered in the mechanistic evaluation of potential respiratory effects (see Appendix B.2.6, B.3.6 and C.7).

Based on the ultimate conclusion that the toxicity studies in animals were most appropriately reviewed as mechanistic information (see explanation in Section 3.2.3 of the Toxicological Review), the experimental studies identified as a result of this literature search are evaluated and described as mechanistic studies related to noncancer respiratory health effects (see Appendix B.2.6, B.3.6 and C.7). As noted previously, this search for animal hypersensitivity studies was not conducted for the 2021 SEM. In regard to the experimental studies identified by this literature search, particular emphasis was placed on the identification of studies examining the following endpoints:

- Airway inflammatory responses to sensitizing antigens, such as bronchoconstriction and airway hyperresponsiveness. (Studies describing the development of immunological or allergy animal models were not included, however.)

- Biomarkers relating to potential mechanisms in animal toxicology studies, such as eosinophil infiltration, immunoglobulins (e.g., total, or anti-allergen specific IgE or IgG), and cytokines pertinent to hypersensitivity responses, and neurogenic mechanisms of airway inflammation.

PECO category inclusion and exclusion criteria for selection of studies are summarized in Table 2-6 and Table 2-7, respectively, for human and experimental animal studies. The bibliographic databases, search terms, and specific strategies used to search them, as well as literature flow diagrams and other screening documentation, are provided in Appendix B.2.4.

Table 2-6. PECO inclusion and exclusion criteria for studies of allergy and asthma studies in humans

PECO Category	Included	Excluded[a]
Population	• Human	• Animals
Exposure	• Indoor exposure via inhalation to formaldehyde • Measurements of formaldehyde concentration in air	• Not formaldehyde • Outdoor formaldehyde exposure • Dental-related exposures or cosmetic and other dermal-related exposures

PECO Category	Included	Excluded[a]
		• Exposure via dialysis • Formaldehyde as fixative
Comparison	• Evaluate risk in relation to exposure based on level, duration, or other parameter.	• Case reports (selected references used for illustration) • Limited exposure range
Outcome	• Allergy symptoms[b] • Skin prick tests • Incidence of specific allergies • Prevalence of current asthma[a] • Incidence of asthma • Asthma control or severity • Wheezing symptoms and other lower respiratory tract conditions in infants and children < 5 years. • Controlled exposure pulmonary function studies in people with asthma	• Sick building syndrome, sick building symptoms, chemical sensitivity studies • Contact dermatitis, eczema, or urticaria in studies of worker populations with likely dermal exposure[c] • Formaldehyde-specific antibodies (FA-Ig) • Pulmonary function in controlled exposure studies in people without asthma [these studies are included in Section A.5.3. Pulmonary Function] • Lifetime prevalence of asthma ("Ever had asthma" or "ever had wheezing episode")

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

[b]Based on the methods used in the American Thoracic Society questionnaire (Ferris, 1978) or subsequent instruments that built upon this work, such as the International Study of Arthritis and Allergies in Children (ISAAC) and European Community Respiratory Health Survey (ECHRS) questionnaires.

[c] Contact dermatitis is a well-established effect from dermal exposure and the effects of dermal exposure are not a focus of this review; thus, studies of contact dermatitis from dermal exposures are excluded.

Table 2-7. PECO inclusion and exclusion criteria for studies of hypersensitivity in experimental animals

PECO Category	Included	Excluded[a]
Population	• Mammals (rodents, rabbits, nonhuman primates, pigs, dogs, and sheep have been used in hypersensitivity studies)	• Humans • Non-mammalian Species
Exposure	• Inhalation route, formaldehyde	• Not formaldehyde • Oral or dermal exposure protocol

PECO Category	Included	Excluded[a]
		• In vitro exposure
Comparison	• One or more exposure group compared to control	• No control group
Outcome	• Bronchoconstriction or airway hyperresponsiveness measures • Total or anti-allergen-specific IgE or IgG • Eosinophil infiltration in lung • Th2 cytokines (e.g., IL-4, IL-5)	• General chronic bioassay measures (e.g., organ weight, tumor incidence) • Host resistance assays. • Antibody responses not involving respiratory sensitizers (e.g., sheep red blood cells, tetanus toxoid) • Dermal sensitization measures • In vitro studies, measures of inflammation and irritation (e.g., TNF-a, ROS), and formaldehyde-specific antibody studies were identified using a more specific search string in Section A.5.6.

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

From the 6,204 studies identified by the searches, 36 studies identified through 2016 met PECO criteria; 27 were observational epidemiology studies and 9 were controlled exposure studies in human volunteers. Sixteen additional studies from the 2021 SEM met PECO criteria; 11 studies were deemed to be *possibly impactful* and thus were included in the allergy and asthma review (see Appendix B.2.4 for details).

Overall, 47 human studies were evaluated (see Section 2.3.4) for consideration in the Toxicological Review.

An additional 16 mechanistic studies in exposed animals were identified and considered as part of the literature on mechanisms related to noncancer respiratory effects; see Section 2.2.6).

2.2.5. Respiratory Tract Pathology PECO Criteria and Search Summary

The respiratory tract pathology review focused on histopathological endpoints and signs of pathology in nasal and respiratory tissues. Reports from observational epidemiology studies of effects in more distal respiratory tissues in humans are not common in the literature since measurements of those endpoints are highly invasive; thus, these endpoints were not a focus of the

human evidence synthesis.[4] Similarly, although included in the search strings to ensure capture of all potentially relevant studies, signs such as changes in mucous flow rate and rhinitis were tracked as supplemental and included in the discussion of mechanisms of respiratory inflammation and immune system-related responses rather than as an outcome included in the human or animal respiratory tract pathology evidence syntheses.

Systematic literature searches were conducted separately to identify health effect studies in humans and in experimental animals. The focus of the searches was on primary studies involving subchronic or chronic exposure durations using measurements of formaldehyde in workplace air and histopathological endpoints in nasal tissue in humans and measures of respiratory pathology in animal species, primarily rodents and nonhuman primates. The mechanistic evidence informing this health effect was identified and evaluated as part of the overarching review of mechanistic data relevant to potential respiratory health effects (see Appendix B.2.6, B.3.6, and C.7 for details). PECO category inclusion and exclusion criteria used in the screening step are described in Table 2-8 for humans, and 2-9 for animals. The bibliographic databases, search terms, and specific strategies used to search them, as well as literature flow diagrams and other screening documentation, are provided in Appendix B.2.5.

Table 2-8. PECO inclusion and exclusion criteria for studies of respiratory pathology in humans

PECO Category	Included	Excluded[a]
Population	• Humans	• Animals
Exposure	• Indoor exposure via inhalation to formaldehyde • Measurements of formaldehyde concentration in air	• Not about formaldehyde • Not inhalation (e.g., dermal exposure)
Comparison	• Evaluated risk in relation to variation in exposure based on level, duration, or other parameter	• Case reports • Surveillance analysis/Illness investigation (no comparison)
Outcome	• Histopathology and signs of pathology in nasal tissues	• Other health endpoints • Nasal symptoms (e.g., rhinitis; mucous flow rate); studies of these outcomes were considered as part of the immune-

[4]Bronchoalveolar lavage (BAL) is a less invasive procedure to evaluate pathology in the lungs. Studies that reported endpoints of injury using BAL were identified and are discussed in the section on mechanisms related to inflammation and immune responses (Section 2.2.6).

PECO Category	Included	Excluded[a]
		mediated conditions or MOA analyses (see Sections 2.2.4 and 2.2.6, respectively) • Not a health study • Exposure studies/no outcomes evaluated

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

Table 2-9. PECO inclusion and exclusion criteria for studies of respiratory pathology in animals

PECO Category	Included	Excluded[a]
Population	• Experimental animals (rodents, nonhuman primates, etc.)	• Humans • nonmammalian species (note: nonmammalian species tagged to the respiratory mechanistic search for this effect)
Exposure	• Inhalation exposure, formaldehyde or test article generating formaldehyde	• Not formaldehyde (or formaldehyde exposure not quantified) • Dermal or oral exposure or other noninhalation exposure • Endogenous properties
Comparison	• One or more exposure group compared to control	• No control group
Outcome	• Respiratory tract pathology • MOA for pathology (note: these are evaluated and discussed in the overarching MOA section; see Appendix B.2.6, B.3.6 and C.7)	• Assessment of formaldehyde exposure • Chemical properties • Formaldehyde use in methodology or treatment • Not related to respiratory tract pathology

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

From the 1,598 human studies and 2,049 animal studies identified by the searches, 12 human (observational epidemiology) and 41 animal studies identified through 2016 met PECO criteria. One additional human and 10 animal studies from the 2021 SEM met PECO criteria but was not considered to be potentially impactful; one of the animal studies was deemed to be *possibly impactful* but had already been identified and incorporated by 2017. Thus zero (0) additional

studies form the SEM update were included for the respiratory pathology review (see Appendix B.2.5 for details).

Overall, 53 studies (12 human studies, 41 animal studies) were evaluated (see Section 2.3.5) for consideration in the Toxicological Review.

An additional 35 studies potentially related to the MOA for respiratory tract pathology and other respiratory effects, including studies of cell proliferation and mucociliary function, were considered as part of the literature on mechanisms related to noncancer respiratory effects (see Section 2.2.6).

2.2.6. PECO Criteria and Search Summary for Mechanistic Information Related to Noncancer Respiratory Effects, including Inflammation and Immune Changes

This review of mechanistic information related to noncancer respiratory system effects included a specific focus on studies relevant to potential inflammation- and immune-related changes. This effort was undertaken to identify mechanistic information related to changes in the respiratory tract, blood, and lymphoid tissues that might not have been captured by health effect-specific systematic searches, including studies of cell proliferation and mucociliary function (note: this gap-filling search strategy was initiated in 2014). Given the breadth of this topic, this section uses a hierarchical approach to screen, sort, and distill information from over 10,000 references identified across multiple searches. Thus, additional steps were taken to focus this analysis on the most influential information. In addition to criteria identifying studies as relevant to assessing potential respiratory system changes, studies that failed to report a specific estimate of formaldehyde exposure (e.g., concentration, duration) were not considered. Nonmammalian models and tissue systems other than those that might be related to formaldehyde-induced respiratory effects (i.e., other than studies of the respiratory tract, or circulatory or immune-related effects) were excluded. Also, studies of in vitro exposure to formaldehyde in solution and of exposure routes other than inhalation, which may inform mechanistic understanding, were initially kept for possible further review or qualitative support of POE-related findings. However, given the large number of studies reporting results from inhalation exposure in vivo or gaseous exposure of airway cells, and considering the uncertainties associated with the toxicokinetics of noninhalation exposures, these comparably far less influential mechanistic data were ultimately not included in the final analysis described herein. PECO category inclusion and exclusion criteria used in the screening step are described in Table 2-10. The bibliographic databases, search terms, and specific strategies used to search them, as well as literature flow diagrams and other screening documentation, are provided in Appendix B.2.6.

Table 2-10. PECO inclusion and exclusion criteria for mechanistic information relevant to noncancer respiratory effects, including inflammation and immune changes

PECO Category	Included	Excluded[a]
Population	• Experimental animals • Humans	• Irrelevant species or matrix, including nonanimal species (e.g., bacteria) and studies of inorganic products
Exposure	• Quantified (e.g., levels; duration) exposure to formaldehyde in indoor air	• Not specific to formaldehyde (e.g., other chemicals) • No specific comparison to formaldehyde exposure alone (e.g., formaldehyde levels, duration, or similar in a study of exposure to a mixture)—NOTE: full text screening only • Nonrelevant exposure paradigm (e.g., use as a pain inducer in nociception studies) • Outdoor air exposure
Comparison	• Inclusion of a comparison group (e.g., pre- or postexposure; no exposure; lower formaldehyde exposure level)	• Case reports (selected references used for illustration)
Outcome	• Examining mechanistic endpoints relevant to interpretations of potential respiratory health effects	• Not relevant endpoints for section, including carcinogenicity studies and endpoints related to contact dermatitis • Exposure or dosimetry studies • Use of formaldehyde in methods (e.g., for fixation) • Processes related to endogenous formaldehyde • Related to hazard endpoints only (including genotoxicity; see those hazard sections)—NOTE: full text screening only

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

From the 9,824 studies identified by the searches, 140 studies identified through 2016 met PECO criteria; 56 additional studies from the 2021 SEM met PECO criteria. Of these newer studies, 8 were deemed to be *possibly impactful* and thus were included in the inflammation and immune-mediated mechanisms review (see Appendix B.2.6 for details).

Overall, 148 studies related to potential mechanisms informing noncancer respiratory effects were evaluated (see Section 2.3.6) for consideration in the Toxicological Review.

2.2.7. Nervous System Effects PECO Criteria and Search Summary for Nervous System Effects

The review of potential nervous system effects focused on inhalation exposure studies in humans or animals that examined objective, apical effects on the nervous system, including structural, behavioral, chemical, and electrophysiological changes, as well as mechanistic studies informing potential biological associations between formaldehyde exposure and nervous system effects. Human (observational epidemiology or controlled exposure) studies of neurobehavioral tests or specific neurological diseases were included.

Studies of symptoms that may be associated with nervous system effects (e.g., headache, fatigue) were excluded. These endpoints are highly subjective as compared to the other available data as these measures were primarily based on self-administered questionnaires that varied in type and specificity and were often conducted due to complaints about symptoms attributed to chemicals in the air. In addition, the symptoms were not rated by severity, were typically grouped with non-nervous system-specific complaints (e.g., related to irritation, such as dry eyes) and at best can only be indirectly related to specific nervous system perturbations. Thus, more objective, and direct nervous system measures were prioritized for review.

In vivo inhalation animal exposure studies were included, but in vitro studies and studies of other exposure routes (e.g., oral, injection), including a multitude of studies using formaldehyde exposure (typically hind paw or forepaw injections) as a model to study nociceptive (pain) behaviors in rodents, were not included. These experiments are considered unlikely to reproduce or reflect (for in vitro studies) the distribution of formaldehyde and its metabolites following inhalation exposures (see Section 3.1) and most are confounded by methanol in the aqueous formaldehyde formulations, reducing the ability of these experiments to attribute any observed effects to formaldehyde. Unlike formaldehyde, methanol, a known neurotoxicant, is transported in the blood to nervous system tissues. In addition, studies examining nervous system effects (e.g., memory loss; neurodegeneration) associated with increases in endogenous formaldehyde levels in the brain were identified by the literature search but excluded because formaldehyde inhalation does not appear to cause appreciable changes in formaldehyde levels in nonrespiratory tissues and no hypothesis currently exists to explain how inhaled formaldehyde would affect endogenous formaldehyde levels in the CNS[5].

PECO category inclusion and exclusion criteria used in the screening step are described in Table 2-11 for humans, and Table 2-12 for animals. The bibliographic databases, search terms, and specific strategies used to search them, as well as literature flow diagrams and other screening documentation, are provided in Appendix B.2.7.

[5] Studies suggesting that health effects might result from reduced function of enzymes responsible for clearing formaldehyde from relevant tissues (e.g., downregulated ALDH2 in the brain (Tan et al., 2018; Ai L, 2019)), highlight an area of interest for future studies on potential susceptibility to inhaled formaldehyde.

Table 2-11. PECO inclusion and exclusion criteria for studies of nervous system effects in humans

PECO Category	Included	Excluded[a]
Population	• Humans	• Animals
Exposure	• Indoor exposure via inhalation to formaldehyde • Measurements of formaldehyde concentration in air, or exposure during dissection or embalming	• No formaldehyde specific analyses • Job title/industry-based analysis • Dermal • Outdoor exposure
Comparison	• Evaluated risk in relation to exposure based on level, duration, or other parameter	• Case reports • Surveillance analysis /Illness investigation (no comparison)
Outcome	• Objective measures of nervous system effects, including behavior • Nervous system disease	• Subjective symptoms, including headache, fatigue, etc.

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language **(**e.g., after review of title and abstract, if available, or consultation with native speaker).

Table 2-12. PECO inclusion and exclusion criteria for studies of nervous system effects in animals

PECO Category	Included	Excluded[a]
Population	• Experimental animals	• Nonmammalian and nonanimal species (e.g., bacteria), and studies of inorganic products
Exposure	• Quantified (e.g., levels; duration) exposure to inhaled formaldehyde in indoor air	• Not specific to formaldehyde (e.g., other chemicals) • Nonrelevant exposure paradigm (e.g., use as a pain inducer in nociception studies) • In vitro or non-inhalation studies (note: these studies were initially screened as included prior to 2017 but were ultimately concluded not to inform hazard or dose-

PECO Category	Included	Excluded[a]
		response decisions for this outcome based on toxicokinetic understanding and were later excluded)
Comparison	• One or more exposure group compared to control	• No control group • Comparisons to (endogenous) formaldehyde measures in CNS tissues
Outcome	• Nervous system effects that could indicate a hazard (e.g., behavioral, chemical, structural, or physiological) • Mechanistic studies examining aspects of nervous system function	• Subjective symptoms, including headache, fatigue, etc. • Effects other than noncancer nervous system effects • Exposure or dosimetry studies • Use of formaldehyde in methods* (e.g., for fixation) • Processes related to endogenous formaldehyde

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

From the 9,435 studies identified by the searches, 147 studies identified through 2016 met PECO criteria. Based on the toxicokinetics conclusions, the 47 in vitro and non-inhalation exposure studies on this health outcome were ultimately excluded from consideration, leaving 100 included studies; 40 were observational studies in humans, 42 were animal health effects studies and 18 were animal inhalation studies specifically informing potential mechanisms. Fourteen additional studies from the 2021 SEM met PECO criteria; of these 14 studies, two human studies were deemed to be *possibly impactful*, but one had already been identified and incorporated by 2017. Thus, one additional study from the SEM update was included for the nervous system effects review (see Appendix B.2.7 for details).

Overall, 101 studies (41 human studies, 42 experimental animal studies, and 18 mechanistic studies) were evaluated (see Section 2.3.7) for consideration in the Toxicological Review.

2.2.8. Developmental and Reproductive Toxicity PECO Criteria and Search Summary

The developmental and reproductive toxicity review of the available human evidence focused on studies of inhalation exposure and time-to-pregnancy (TTP) as a measure of fecundability,[6] reproductive parameters in males (e.g., semen parameters), spontaneous abortion, and birth outcomes (e.g., birthweight, malformations). Outcomes assessed in animal toxicology studies included developmental toxicity (prenatal survival, fetal and postnatal growth, and structural alterations and malformations), male reproductive toxicity (sperm count and

[6]A couple's probability of conception in one menstrual cycle.

morphology, testes and epididymal weight and histopathology, and functional measures), and female reproductive toxicity (hormone levels, ovarian and uterine weight and histopathology, and early embryo loss). Functional developmental outcomes (i.e., developmental neurotoxicity) were addressed in the sections on potential nervous system effects. The considerations related to non-inhalation exposure paradigms (including in vitro exposure) and measurements of (endogenous) formaldehyde in systemic tissues relevant to reproduction and development were the same as those applied for potential nervous system effects (see Section 2.2.7).

PECO category inclusion and exclusion criteria used in the screening step are described in Table 2-13 and Table 2-14, respectively, for human and animal studies. The bibliographic databases, search terms, and specific strategies used to search them, as well as literature flow diagrams and other screening documentation, are provided in Appendix B.2.8.

Table 2-13. PECO inclusion and exclusion criteria for studies of reproductive and developmental effects in humans

PECO Category	Included	Excluded[a]
Population	• Humans	• Animals
Exposure	• Indoor exposure via inhalation to formaldehyde • Measurements of formaldehyde concentration in air • Formaldehyde-specific assessments in studies with exposure defined by occupation (wood workers, nurses, pathologists, cosmetologists)	• Not formaldehyde • Outdoor formaldehyde exposure • Mixtures or industry/job title analyses • Not inhalation
Comparison	• Evaluated risk in relation to variation in exposure based on level, duration, or other parameter	• Case reports
Outcome	• Reproductive toxicity (sperm measures) • Time-to-pregnancy (fecundity) • Spontaneous abortion • Birth outcomes	• Exposure studies/no outcomes evaluated • Other health outcomes not related to reproduction or development

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

Table 2-14. PECO inclusion and exclusion criteria for studies of reproductive and developmental effects in animals

PECO Category	Included	Excluded[a]
Population	• Experimental animals • Nonmammalian test species or test paradigms that are relevant for evaluation of developmental or reproductive hazard	• Humans • Irrelevant species (i.e., non-mammalian species, although established models of reproduction and development, such as chick embryo assays, tagged as potentially relevant supplemental information) or test paradigms
Exposure	• Inhalation route, formaldehyde	• Not formaldehyde • Noninhalation routes of exposure • Mixture studies • Ecological studies
Comparison	• Inclusion of a comparison group (e.g., pre- or postexposure, no exposure, vehicle exposure, lower formaldehyde exposure level)	• No comparison group • Comparison to (endogenous) formaldehyde measures in systemic tissues relevant to reproduction (e.g., testes)
Outcome	• Pre- and postnatal offspring biomarkers of: o Survival (e.g., resorptions, death) o Growth (e.g., body weight) o Structural anomalies (e.g., external, skeletal, or soft tissue malformations or variations) o Functional deficits • Adult biomarkers of reproductive toxicity, including: o Gonadotropic hormone measures o Reproductive organ weight o Reproductive organ macro- and microscopic pathology o Sperm measures (count, motility, morphology) o Reproductive function (e.g., mating, fertility, parturition, gestation, lactation) o Mechanistic data relevant to developmental or reproductive outcomes	• No health outcomes evaluated • Health outcomes not related to developmental or reproductive toxicity • Mechanistic data irrelevant to developmental or reproductive outcomes

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

From the 11,037 studies identified by the searches, 55 studies identified through 2016 met PECO criteria; 20 were observational studies in humans, and 35 were animal inhalation studies. Nine additional studies from the 2021 SEM met PECO criteria; four human and one animal study

were deemed to be *possibly impactful*. One of these human studies already had been identified and incorporated by 2017 and thus only four additional studies (three in humans and one in animals) from the SEM update were included for the developmental and reproductive toxicity review (see Appendix B.2.8 for details).

Overall, 59 studies (23 human studies and 36 experimental animal studies) were evaluated (see Section 2.3.8) for consideration in the Toxicological Review.

2.2.9. Carcinogenicity PECO Criteria and Search Summary

Systematic identification and evaluation of the literature database on studies examining the potential for carcinogenicity following formaldehyde exposure was performed separately for the following: (1) human studies of respiratory tract, lymphohematopoietic, or other cancers (including brain, lung, pancreatic, etc.); (2) experimental animal studies of respiratory tract (e.g., nasal) cancers; and (3) experimental animal studies of LHP cancers. Separate descriptions for the human and animal searches are provided below. PECO category inclusion and exclusion criteria used in the screening step for human studies, animal studies of respiratory tract cancer, and animal studies of LHP cancer are described in Tables 2-15, 2-16, and 2-17, respectively. The bibliographic databases, search terms, and specific strategies used to search them, as well as literature flow diagrams and other screening documentation, are provided in Appendix B.2.9.

Cancer Studies in Humans

Multiple review articles and meta-analyses have examined the epidemiologic evidence informing potential associations between formaldehyde and cancer endpoints (Zhang et al., 2009; Ojajärvi et al., 2000; Collins et al., 1997; Collins et al., 2001; Collins and Lineker, 2004; Bosetti et al., 2008; Blair et al., 1990; Bachand et al., 2010). The vast majority of studies focused on cancers of the upper respiratory tract (URT) and LHP system. Other cancer endpoints reported in the literature include cancers of the bladder, brain, colon, lung, pancreas, prostate, and skin. However, aside from cancer of the brain and lung, few studies showed any evidence of increased risks. Given the large number of studies available on URT and LHP cancers, the other endpoints were not included in the hazard evaluation. As numerous studies reported data on cancers of the brain or lung, a summary of the available studies for each of these endpoints is provided in Appendix C.8.1 for information; however, a limited review of the available studies did not suggest any consistent association with formaldehyde exposure and, as such, these endpoints were also not formally reviewed.

For the hazard evaluation, the URT cancer endpoints were restricted to specific cancers (i.e., nasopharyngeal cancer, sinonasal cancer, cancers of the oro- and hypopharynx, and laryngeal cancer). The occurrences of URT cancers in humans have been described and grouped according to the International Classification of Disease (ICD) coding rubrics. Rarely, cancers of the buccal cavity as a whole are reported, but as this grouping includes lip, tongue, salivary glands, gums, and the floor of the mouth, which combine cancers of potentially different etiology and cell origin, the collection of cancers of the buccal cavity are not reviewed here. The specific LHP cancers that were

formally reviewed were Hodgkin lymphoma, multiple myeloma, myeloid leukemia, lymphatic leukemia. Non-Hodgkin lymphoma is a nonspecific grouping of dozens of different lymphomas and classification systems for specific subtypes have changed over time, complicating the synthesis of study results for this cancer type. If formaldehyde is associated with particular non-Hodgkin lymphoma subtypes, then these studies might be not sensitive enough to detect an association. As review articles and an initial review of the available literature did not suggest an association between formaldehyde exposure and non-Hodgkin lymphoma, this endpoint was not formally reviewed.

Table 2-15. PECO inclusion and exclusion criteria for evaluation of studies of cancer in humans

PECO Category	Included	Excluded[a]
Population	• Human	• Animals
Exposure	• Exposure assessment for formaldehyde • Industries or occupations known to involve exposure to formaldehyde	• Not formaldehyde • Outdoor formaldehyde exposure
Comparison	• Evaluated risk in relation to variation in exposure based on level, duration, or other parameters	• Case reports
Outcome	• Nasopharyngeal cancer • Sinonasal cancer • Cancers of the oro- and hypopharynx • Laryngeal • Specific lymphohematopoietic cancers (i.e., Hodgkin lymphoma, multiple myeloma, myeloid leukemia, lymphatic leukemia	• Bladder, colon, pancreas, prostate, and skin • Brain and lung cancer studies were initially included but were subsequently excluded from the systematic review (tracked as supplemental) • "Buccal cavity" • Non-Hodgkin lymphoma

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents, secondary analyses), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker). Note that some cancer studies were initially categorized as meeting PECO before it was understood that some of those represented additional follow-ups of cohort studies of secondary analyses.

[b]For cohort studies with more than one follow-up paper, earlier studies without unique data are tracked as 'Met PECO', but only the most recent follow up was included in the evidence syntheses.

From the 2,551 human cancer studies identified by the searches, 63 studies identified through 2016 met PECO criteria. Six additional studies from the 2021 SEM met PECO criteria; three were deemed to be *possibly impactful*. One of these human studies already had been identified and

incorporated by 2017 and the other two studies were reanalysis of studies in the assessment prior to 2017; the two new reanalyses were included in the review of human cancer studies (see Appendix B.2.9 for details).

Overall, 67 human studies were evaluated (see Section 2.3.9) for consideration in the Toxicological Review.

Cancer Studies in Animals

Similar to the evidence in humans described above, the animal evidence for cancers other than those of the respiratory tract and the LHP system were not systematically identified or reviewed; rather, any such observations (e.g., if identified through other, health effect-specific searches) are summarily described but not considered in hazard identification or dose-response analyses. The considerations related to non-inhalation exposure paradigms (including in vitro exposure) and measurements of (endogenous) formaldehyde in systemic tissues relevant to LHP cancers were the same as those applied for potential nervous system effects (see Section 2.2.7) and reproductive or developmental effects (see Section 2.2.8). The cancer evidence included from animal experiments included both precancerous lesions (i.e., dysplasia) and neoplasms (tumors).

Table 2-16. PECO inclusion and exclusion criteria for studies of respiratory tract cancers in animals

	Included	Excluded
Population	• Experimental mammals	• Nonmammalian species and other test paradigms
Exposure	• Exposure to formaldehyde for an exposure duration longer than short term	• Not related to formaldehyde (e.g., other chemicals) • Mixture studies • Short study duration
Comparison	• Inclusion of a comparison group (e.g., pre- or postexposure, no exposure, vehicle exposure, lower formaldehyde exposure level)	• No comparison group
Outcome	• Endpoint evaluation included nasal cancers or other respiratory tract cancers, and dysplasia	• Exposure or dosimetry studies • Related to formaldehyde use in methodology • Endpoint not respiratory tract cancer

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

Table 2-17. PECO inclusion and exclusion criteria for studies of LHP cancers in animals

PECO Category	Included	Excluded
Population	• Experimental mammals	• Irrelevant species or matrix, including nonanimal and nonmammalian species
Exposure	• Exposure to formaldehyde	• Not related to formaldehyde (e.g., other chemicals)
Comparison	• Inclusion of a comparison group (e.g., pre- or postexposure, no exposure, vehicle exposure, lower formaldehyde exposure level)	• No comparison group • Comparison to (endogenous) formaldehyde measures in systemic tissues relevant to LHP cancers (e.g., bone marrow)
Outcome	• Endpoint evaluation included LHP cancers and dysplasia	• Exposure or dosimetry studies • Related to formaldehyde use in methodology • Endpoint unrelated to LHP cancer

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

From the 945 animal studies identified by the searches on respiratory cancers and the 117 studies identified by the searches on LHP cancers, 19 studies on respiratory (including nasal) cancers and 4 LHP cancer studies identified through 2016 met PECO criteria. Two additional analyses for nasal and two for LHP cancers identified from the 2021 SEM met PECO criteria. Of these newer analyses meeting the PECO criteria, one study was deemed to be *possibly impactful* for both cancer types; however, this study already had been identified and incorporated by 2017 and thus zero (0) newer animal studies were considered in the review of animal cancer studies (see Appendix B.2.9 for details).

Overall, 23 animal studies (19 on respiratory tract cancers and 4 on LHP cancers) were evaluated (see Section 2.3.9) for consideration in the Toxicological Review.

2.2.10. PECO Criteria and Search Summary for Mechanistic Information Related to Cancer, Focusing on Genotoxicity

Consolidated systematic approaches to identifying the literature examining mechanistic effects relevant to interpreting the potential for formaldehyde to cause either upper respiratory tract (URT) or lymphohematopoietic (LHP) cancers were not performed. Rather, these sections consider studies identified through other health effect-specific literature searches in the context of the specific cancer etiology being evaluated. Supplemental literature relevant to interpreting the biological relevance of some mechanistic data was also identified from review articles and other national-level health assessments. Thus, these sections rely heavily on searches and evaluations

performed in the following sections: genotoxicity[7], respiratory tract pathology, and mechanistic information related to noncancer respiratory effects, including inflammation and immune changes. For the 2021 SEM, supplementing the other health effect- and mechanisms-specific searches, broad and straightforward PECO criteria were used to ensure capture of newer literature (e.g., published after the available national-level health assessments) during screening in Distiller SR for mechanistic information on respiratory tract cancers (Table 2-18) and LHP cancers (Table 2-19). The PECO criteria were based on an assumption of potential direct cellular and molecular interactions with formaldehyde for respiratory cancers but not for LHP cancers.

Table 2-18. PECO inclusion and exclusion criteria for mechanistic studies relevant to respiratory tract cancers, focusing on genotoxicity

PECO Category	Included	Excluded
Population	• Human: Any population and lifestage (occupational or general population, including children and other sensitive populations). • Animal: Nonhuman mammalian animal species (whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages). • Other: Ex vivo and in vitro studies of genotoxicity or other mechanistic endpoints (including direct interaction with formaldehyde in respiratory and non-respiratory cells)	• Irrelevant species or matrix, including nonanimal species (e.g. bacteria) unless an established model of genotoxicity (e.g., Ames test)
Exposure	• Human: Indoor exposure via inhalation to formaldehyde and including measurements of formaldehyde concentration in air or with quantified exposure defined by occupation (wood workers, nurses, pathologists, cosmetologists) • Animal or Other Experimental: Quantified formaldehyde exposure levels (by any route or in vitro)	• Not formaldehyde • Human: Outdoor or non-inhalation formaldehyde exposure, or industry/job title analyses • Animal or Other: Non-experimental dosing regimen or Nonrelevant exposure paradigm (e.g., forepaw injection)
Comparison	• Human: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of formaldehyde, or exposure to formaldehyde for shorter periods of time.	• Human case reports • No specific comparison to formaldehyde exposure (e.g. formaldehyde levels, duration)

[7] For genotoxicity, a consistent set of search terms was applied within electronic databases (i.e., PubMed and Web of Science) as outlined in Section 2.2.1. These terms (see Appendix B.2.10) were developed considering the broader topic of mode of action for either respiratory tract or LHP cancers and the retrieved citations were screened for studies on genotoxic endpoints. Like other searches, this was augmented by review of references in prior draft and final national and international health assessments of formaldehyde.

PECO Category	Included	Excluded
	• Animal or Other Experimental: A concurrent control group exposed to vehicle only treatment and/or untreated control (control could be a baseline measurement).	• No comparison to controls in animal or other experimental studies • Mixtures-only comparisons
Outcome	• Mechanistic information relevant to respiratory cancers, including genotoxicity endpoints	• Exposure studies/no outcomes evaluated • Studies of cancer or tumor incidence or mortality only, including carcinogenicity studies

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

Table 2-19. PECO inclusion and exclusion criteria for mechanistic studies relevant to LHP cancers, focusing on genotoxicity

PECO Category	Included	Excluded
Population	• Human: Any population and lifestage (occupational or general population, including children and other sensitive populations). • Animal: Nonhuman mammalian animal species (whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).	• Irrelevant species or matrix, including nonanimal species (e.g. bacteria) unless an established model of genotoxicity (e.g., Ames test) • Ex vivo and in vitro studies that model direct molecular or cellular interaction with inhaled formaldehyde
Exposure	• Human: Indoor exposure via inhalation to formaldehyde and including measurements of formaldehyde concentration in air or with quantified exposure defined by occupation (wood workers, nurses, pathologists, cosmetologists) • Animal or Other Experimental: Quantified formaldehyde exposure levels (by inhalation exposure)	• Not formaldehyde • Human: Outdoor or non-inhalation formaldehyde exposure, or industry/job title analyses • Animal or Other: Non-experimental dosing regimen or Nonrelevant exposure paradigm (e.g., forepaw injection); non-inhalation exposure tracked as supplemental
Comparison	• Human: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of formaldehyde, or exposure to formaldehyde for shorter periods of time.	• Human case reports • No specific comparison to formaldehyde exposure (e.g. formaldehyde levels, duration)

PECO Category	Included	Excluded
	• Animal or Other Experimental: A concurrent control group exposed to vehicle only treatment and/or untreated control (control could be a baseline measurement).	• No comparison to controls in animal or other experimental studies • Mixtures-only comparisons
Outcome	• Mechanistic information relevant to LHP cancers, including genotoxicity endpoints	• Exposure studies/no outcomes evaluated • Studies of cancer or tumor incidence or mortality only, including carcinogenicity studies

[a]Additional reasons for not meeting PECO (includes supplemental): Not primary research (e.g., reviews, reports, commentaries, policy documents), meeting abstract, no abstract, methodology paper, nonessential article in a foreign language (e.g., after review of title and abstract, if available, or consultation with native speaker).

From the 744 studies identified through searches on mechanisms relevant to respiratory tract cancer focusing on genotoxicity, 225 studies with relevant primary data (including 8 studies identified as *possibly impactful* from the 2021 SEM) were considered in the Toxicological Review, with an additional 101 studies tagged as supplemental information (e.g., not primary research articles; primary research articles with little direct relevance to these cancers, such as non-inhalation or in vitro studies of non-respiratory tissues).

From the 3,307 studies identified through searches on mechanisms relevant to LHP cancers focusing on genotoxicity, 138 studies with relevant primary data (including 14 studies that were identified as *possibly impactful* from the 2021 SEM) were considered in the Toxicological Review, with an additional 150 studies tagged as supplemental information (e.g., not primary research articles; primary research articles with little direct relevance to these cancers, such as non-inhalation or in vitro studies of non-respiratory tissues).

The general approach to evaluating the mechanistic evidence is described in Section 2.3.10.

2.3. STUDY EVALUATION METHODS

2.3.1. Overview of Approach and Evaluation Criteria

All human and experimental animal health effect studies identified in the search and screening processes described in Section 2.2, without regard to magnitude or direction of study results, were considered for use in assessing the evidence for health effects associated with inhalation exposure to formaldehyde. In addition to the evaluations of the individual health effect studies, systematic evaluations of individual mechanistic studies were conducted in relation to several important health domains when this information could contribute to judgments about the human and animal evidence or hazard conclusions (discussed below). Individual study evaluations for literature on exposure, toxicokinetics, and some types of mechanistic data (e.g., in vitro studies)

were not systematically conducted and documented. The study evaluations were used to inform the interpreted reliability of the study findings and whether those findings are likely to be caused by formaldehyde exposure alone.

Study methods were evaluated to assign a level of confidence in the results of the study with respect to the hazard question under consideration. The study confidence levels were *high*, *medium*, and *low* confidence, and *not informative*, and are presented as italicized text in the body of the assessment (Table 2-20). These evaluations were performed on a health outcome-specific basis, rather than a study-specific basis; thus, a single study was sometimes evaluated multiple times for different endpoints, using endpoint-specific considerations. *High* confidence studies generally had no notable methodological limitations for an outcome, while *medium* confidence studies were considered well conducted but had specific issues that might introduce a minor amount of uncertainty about attribution of the results solely to formaldehyde exposure. Methodological limitations of *low* confidence studies are considered to be significant, but the outcome-specific results might still be of limited use (e.g., as support for observations from other studies; to identify potential data gaps).

Table 2-20. Confidence classification definitions

Confidence Classification	Definition
High Confidence *(highly informative, with no notable limitations)*	• No notable concern for bias, *AND* • No notable methodological limitations, *AND* • Study design is highly informative[a] for the outcome in question, *AND* • Analyses were appropriate and robust (observational studies)
Medium Confidence *(informative, with minor limitations[b])*	• Minor uncertainty regarding bias or methodological limitations *AND* • Study design and analyses were informative for the outcome in question
Low Confidence *(minimally informative, with major limitations)*	• Methodological uncertainties or limitations are significant, but the study results might still be of limited use (e.g., as support for observations from other studies; to identify potential data gaps) *OR* • Bias is apparent or other study aspects reduced sensitivity
Not Informative *(not used, critically deficient)*	• Major concerns exist regarding methodological limitations that are expected to be a driver of study results or cause an unacceptably increased risk of bias, *OR* • Description of methods, exposure levels or range, and/ or results were not adequate to enable a complete evaluation (observational studies), OR

Confidence Classification	Definition
	• Experimental design is noninformative for the outcome in question (experimental studies)

[a]For experimental animal studies, considerations for whether the experimental design is informative include the sensitivity and specificity of the methodological approaches for informing the outcome in question, based on known or expected biology and common practice. These considerations include, but are not limited to: appropriateness and sufficiency of exposure timing and/or duration to allow for the outcome to be affected; sensitivity and specificity of the endpoint assays regarding their ability to detect subtle changes in the outcome; and how well the tested animals (e.g., based on what is known about insensitive species, strains, or sexes) are able to reveal the outcome (note: the human relevance of the response is not considered at this point).

[b]As the expectation is that experimental studies should attempt to control all variables, any study limitation capable of influencing the data was considered to have negatively affected the reliability of the results. Studies were categorized as *medium* confidence if they had specific issues which introduce a limited amount of uncertainty regarding the interpretation of the results as solely attributable to formaldehyde inhalation exposure.

The evaluations for studies identified as *not informative* are documented in Appendix B.3, but these data have no influence on assessment decisions and are not discussed in any detail in the Toxicological Review. In general, if a study or individual analysis (e.g., when multiple health outcomes or cohorts were assessed) was judged to have multiple severe limitations, or if reporting deficiencies precluded the ability to conduct an evaluation, it was concluded to be *not informative*. When potential limitations were identified, the evaluations considered the anticipated direction (i.e., bias toward or away from the null) and magnitude of the impact of the limitation(s) on the study results (when possible). Emphasis was placed on discerning limitations that would be expected to produce a substantive change in the results.

The evaluations used a domain-based approach focused on potential sources of bias or other limitations (including reduced sensitivity) that can affect the validity or interpretation of a study's results. Thus, the confidence conclusions for individual studies reflect an interpretation of the reliability of the study results for answering each hazard question. The general procedure involved evaluating specific methodological features within different domains (categories) defining the potential areas of concern (different types of risk of bias and areas of potential insensitivity), although the categories differed between observational epidemiological, animal toxicological, and human-controlled exposure studies (see subsections below for discussion by study design, noting that the approach for mechanistic studies differs). Specific criteria for each domain developed for each health effect category (see Sections 2.3.2–2.3.10) were evaluated by two or more reviewers

based on expert judgment of each study's details to agree on a rating of good[8], adequate, or deficient for each domain (see Table 2-21).

Table 2-21. Domain rating definitions

Domain Rating	Definition
Good	No notable uncertainties or limitations regarding study methodology
Adequate	Minor uncertainties or limitations interpreted as unlikely to have a notable impact on study results or their interpretability
Deficient	Serious uncertainties or limitations interpreted as likely to have a notable impact on the study results or their interpretability

Confidence classifications were determined for each study by integrating ratings of good, adequate, or deficient across domains. These determinations were not prescriptive, but rather were based on expert judgment. However, *high* confidence studies generally had good ratings for most or all domains with no deficient domain ratings; *medium* confidence studies generally had one or more adequate domain ratings interpreted to warrant reducing confidence, or a single deficient domain rating interpreted as unlikely to substantially affect results; *low* confidence studies typically had one or more deficient ratings interpreted as likely to affect the results or their interpretability; studies classified as *not informative* had one or more deficient ratings of notable concern, or multiple deficient ratings of lesser concern, which were judged to make the study results unusable.

Appendix B.3 contains summary evaluation tables developed for studies in each health effect category, which provide the relevant study characteristics and other information relating to evaluation of each domain, and overall confidence classification, with justifications as described for each study type (e.g., epidemiology; experimental animal) in the Appendix. In some situations, in which key study details or results were not presented, the study author(s) were contacted to obtain this information. Any additional study details obtained from the authors are noted in the evaluation summary tables and evidence tables.

The confidence classifications and primary drivers of those classifications are presented for the studies discussed in the evidence synthesis sections in the tables summarizing the evidence for each health effect. The evidence syntheses (Section 3; see methods in Section 2.5) and assessment conclusions (i.e., for hazard identification and dose-response analysis) focus on *high* and *medium*

[8] The evaluation of each study involved an initial review by a primary topic-specific expert and a secondary review by a second expert who also reviewed the extracted domain-specific details for accuracy (i.e., the secondary reviewer was not blinded to the primary review). Disagreements across the two reviewers were addressed through discussion, with a third reviewer added to address any disagreements that could not be resolved. Only the final domain judgments and classifications were documented. In addition, the discipline-specific experts (e.g., epidemiologists) conducting the evaluations met to discuss judgments on studies across health effects to ensure consistency in the judgments.

confidence studies, if available. *Low* confidence studies are less impactful to the evidence syntheses (and thus their discussion is minimized when higher confidence studies are available) and studies that are *not informative* are not impactful to any assessment decisions, and thus are not discussed in any detail.

Observational Epidemiology Studies: Evaluation Criteria and Classification Scheme

For each type of health outcome examined, the epidemiological studies were evaluated for information relevant to internal validity (bias) that could lead to an under- or overestimate of risk and to other features that could affect the interpretation of the results or limit the ability to detect a true association (e.g., narrow exposure range). The potential for selection bias, information bias (relating to exposure measurement and levels, and outcome ascertainment), confounding, and other details of the analysis and presentation of results were evaluated, alongside the application of considerations related to study sensitivity, and an overall confidence classification was developed for each study (or for a specific analysis within a study). For each evaluation domain, Table 2-22 describes the preferred study characteristics (i.e., supporting a "good" rating for that domain). The outcome-specific evaluations consider the methodological conduct of each study against these general preferences, also considering the health effect-specific considerations for evaluating each domain (see Sections 2.3.2–2.3.10), to rate each domain based upon the number and severity of the uncertainties and limitations identified, as previously described. For the documentation of the epidemiology study evaluations in Appendix B.3, domains with uncertainties or limitations leading to a *low* confidence classification are gray shaded; this shading is carried over to the evidence syntheses.

Table 2-22. Evaluation domains for epidemiology study evaluation

Evaluation domain	Preferred study characteristics (i.e., "Good" rating)
Population Selection	Recruitment, selection into study, and participation independent of exposure status and reported in sufficient detail to understand how subjects were identified and selected; recruitment or selection process unlikely to lead to inflated or attenuated effect estimate.
Information Bias: Exposure	Exposure assessment methods allow characterization of exposure within the etiologically relevant period for the outcome under study. See detailed description of exposure considerations below.
Information Bias: Outcome	Validated instrument for data collection; validation described, or citation provided; sensitive and specific outcome assessment. Ascertainment conducted without knowledge of exposure status.
Potential for Confounding	Important potential confounders addressed in study design or analysis. Potential confounding by relevant co-exposures addressed.
Analysis	Appropriateness of analytic approach given design and data collected; consideration of alternate explanations for findings; presentation of quantitative results.

Evaluation domain	Preferred study characteristics (i.e., "Good" rating)
Other Sensitivity Considerations	Sensitivity of study (exposure levels and contrast, duration of follow-up, sample size or number of cases[a].

[a]Sample size alone is not used to judge a study as *not informative.*

Like all other studies, the synthesis of evidence from epidemiology studies focuses on the *high* and *medium* confidence studies, if available, taking into account differences in populations and settings (e.g., children and adults; occupational, residential, or in schools), exposure levels, and other aspects of the studies.

All residential or school-based studies with measures of formaldehyde exposure were included in the hazard identification evaluation. Because the database of studies with direct measurements is relatively large, residential studies with indirect measures of formaldehyde exposure (e.g., based on age of building or presence of plywood) were not included. Most of the included studies attempted to estimate average formaldehyde levels using area samples placed in one or more locations, with measurement periods ranging from 30 minutes to > 2 months. A few studies included more than one sampling period (i.e., sampling on multiple days in different seasons over the course of a year). Studies in adults and in children indicate that area-based (e.g., residential or school) samples are highly correlated with personal samples (Lazenby et al., 2012; Gustafson et al., 2005); therefore, the use of measures based on residential (e.g., bedroom) samples rather than personal samples was not considered to be a limitation when evaluating a study. Formaldehyde concentrations have been found to be uniform throughout the home in both standing housing stock and mobile homes (Stock, 1987; Sexton et al., 1989; Quackenboss et al., 1989c; Dally et al., 1981; Clarisse et al., 2003). Therefore, associations have generally been analyzed using a specific room measurement or household average concentrations.

The focus of the evaluation of exposure assessment was to determine the confidence that the methods used characterized exposure that occurred during the etiologically relevant period for the health outcome being reviewed. The validity of the measurement of average formaldehyde concentration was assessed by reviewing the description of sampling methods provided in each study. Indoor average formaldehyde measurements may be influenced by humidity and temperature, season, number of rooms sampled, sample placement, ventilation, and specific sources of formaldehyde in the building (Salthammer et al., 2010; Dannemiller et al., 2013). For chronic health outcomes, longer sampling periods (e.g., 1- to 2-weeks duration) were considered to be reflective of usual average exposure levels experienced by occupants. Studies have shown that formaldehyde levels remain relatively stable over a series of days or weeks (Stock, 1987; Quackenboss et al., 1989c; Hodgson et al., 2000; Gustafson et al., 2005), and reasonably represent longer term ongoing exposures. Concentrations are also correlated with season, which reflects the influence of temperature and humidity (Jarnstrom et al., 2006; Dannemiller et al., 2013; Clarisse et al., 2003). Within-person variability increases with shorter sampling durations (Gustafson et al.,

2005). However, indoor formaldehyde concentrations have not been found to be associated with indoor combustion sources, such as active smoking or ETS exposure, or cooking with gas stoves or wood burning (Stock, 1987; Mullen et al., 2015; Hanrahan et al., 1984; Gustafson et al., 2005; Dannemiller et al., 2013; Dally et al., 1981; Clarisse et al., 2003).

Study evaluations looked for information regarding factors that influence formaldehyde levels as well as quality control measures and/or citations for exposure protocols. The following characteristics were examined to assess the potential bias and informativeness of the exposure measures in the observational epidemiology studies of formaldehyde in residences and schools:

- Duration of exposure measurement period and number of sampling occasions.
- Consideration of temperature, relative humidity, and a discussion of quality control.
- For shorter exposure periods (< 1 day), details regarding measurement protocol (e.g., shutting windows).
- Limit of detection (LOD) and percent <LOD.
- Ability to examine variability in risk in relation to variability in exposures above 0.010 mg/m^3; the ability is based on the distribution of exposure, specifically the upper portion of the distribution (e.g., 75th percentile) or the range of exposure encompassed within the study population (e.g., the degree of contrast between "high" and "low" exposure). A study that does not include values above 0.010 mg/m^3 would not be able to detect variation in risk in relation to variation in exposure typically seen in indoor settings.[9]
- Information about the distribution of formaldehyde encompassed by the study (at least one descriptive statistic, preferably denoting a point on the upper part of the distribution such as the 75th or 95th percentile). EPA's analysis is based on a comparison across studies of results, taking into account exposure levels; thus, it is not possible to interpret the results of a study that does not indicate the exposure levels that are being studied.
- The study design per se does not in itself determine the validity of the exposure assessment. That is, retrospective, concurrent (i.e., cross-sectional), or prospective designs can produce either *high* confidence or *low* confidence results, depending on the exposure measure and outcome under study. Even in cross-sectional designs, although exposure and outcome measurement may occur during the same time period, the exposure assessment can be retrospective, i.e., representing exposures that occurred prior to the change in health status. EPA carefully considered the etiologically relevant exposure period where exposure to formaldehyde could result in changes in health status for each outcome under review. For example, average levels of formaldehyde in a home or classroom during the previous several weeks and months was concluded to be the etiologically relevant periods for measures of current pulmonary function status or asthma episodes in the past 12 months. Exposure assessment protocols that included measurements of 5–7 days or more were considered to be "good" estimates of average ongoing exposure for this period of time. The

[9]Note that this criterion applies specifically to formaldehyde and the conditions examined in this review; the relevant exposure range for other exposures or conditions could be very different.

residential exposure measurement protocol used in Krzyzanowski et al. (1990), consisting of two one-week samples, some taken in different seasons, in multiple locations in the home, used for assessment of current pulmonary function status as well as history of respiratory symptoms in the past 12 months, is an example of this category. In contrast, a 2-hour exposure measurement sample was considered "deficient" for outcomes with an etiologically relevant window measured in the past 12 months, concurrently, or in the subsequent 12 months. The 2-hour residential (bedroom) exposure measurement protocol used in the Norback et al. (1995) study of asthma and pulmonary function is an example of the "deficient" exposure measurement category.

A primary consideration in the evaluation of the occupational studies is the ability of the exposure assessment to reliably distinguish among levels of exposure within the study population, or between the study population and the referent population. A large variety of occupations are included within the studies; some represent work settings with a high likelihood of exposure to high levels of formaldehyde, and some represent work settings with variable exposures and in which the proportion of people exposed is quite small. In the latter case, the potential effect of formaldehyde would be "diluted" within the larger study population, limiting the sensitivity or informative nature of the study.

A variety of different approaches to the assessment of occupational exposure were used. These ranged from more specific, highly informative measures such as estimates of job-exposure matrix (JEM)-based TWA concentrations (based on job-specific formaldehyde measurements and the proportion of time spent at the job reported by participants) to measures subject to greater misclassification error, such as the self-reported use of specific products or chemicals, or assignment to exposures by supervisors.

Exposure assessments in some occupational studies involved one or more area samples in specific task areas, personal samples, or a combination of both. Sampling periods ranged from less than 1 hour to an entire work shift over 1 or more days. Concentrations were reported as an average over all samples for a particular location or as a time-weighted average (TWA) over the sampling period. Generally, a TWA concentration from a full shift measurement using personal sampling was considered a more precise estimate of exposure. Some occupational groups (e.g., carpenter, embalmer, pathologist) or industry (e.g., production or use of formaldehyde resins, wood-products, paper, textiles, foundries) were considered to be highly exposed to formaldehyde and were included despite the absence of sampling data.

Some studies may have documented formaldehyde exposures using exposure monitors or quantified the absolute or relative exposure for different tasks, which may be matched to individual occupational patterns using "job exposure matrices" or JEMs. The following characteristics were examined to assess the potential bias and informativeness of the exposure measures in studies based on occupational history:

- Consideration of long-term and short-term job history with industry, occupation, and task details.

- Use of formaldehyde monitoring data to allow assessment of intensity and frequency of exposure.

- Completeness of occupational history for the relevant time period for a given outcome (e.g., 20+ years preceding diagnosis for cancer and ALS; pre-conception and during pregnancy for studies of spontaneous abortion; recent job history prior to neurobehavioral testing).

- Validation of JEM using formaldehyde measurements and industry, occupation, and task details specific to the study location.

As previously indicated; studies that evaluated more than one outcome might be classified differently for each outcome. The classification of a study could also vary among different analytical groups or analytic strategies within a study (e.g., studies of children and adults, with separate analyses for each group), depending on the information presented for the different analyses. In addition, and primarily for *low* confidence studies, when sufficient information was available, the potential direction of bias (i.e., a *low* confidence study with a likely over-estimation of the effect estimates) is documented and discussed.

Experimental Studies in Animals: Evaluation Criteria and Classification Scheme

Toxicological studies in animals differ systematically from observational epidemiological studies because the former seek to control both the exposure and nonexposure conditions of an experiment. This leads to some differences in approach and interpretation. In general, however, toxicological study evaluations in animals considered similar categories to the epidemiological studies. In addition to exposure quality, the categories were based on the design of a toxicological study, including test animals, experimental design (e.g., duration of exposure, timing of endpoint evaluations, allocation procedures), exposure conduct, endpoint evaluation procedures, and data presentation and analysis. The specifics of the considerations applied within each evaluation domain were different for each type of health outcome examined. As the expectation is that experimental studies should attempt to control all variables, any study limitation interpreted as capable of influencing the data was considered to have negatively affected the quality (e.g., validity, accuracy) of the results. Thus, potential "confounders" in experimental studies (i.e., any uncontrolled variable capable of influencing the results) differ fundamentally from what would be deemed a potential "confounder" in epidemiological studies (the latter of which must be associated with both the exposure and the outcome).

For each evaluation domain, Table 2-23 describes the preferred study characteristics (i.e., supporting a "good" rating for that domain). The outcome-specific evaluations consider the methodological conduct of each study against these general preferences, also considering the health effect-specific considerations for evaluating each domain (see Sections 2.3.2–2.3.10), to rate each domain based upon the number and severity of the uncertainties and limitations identified, as previously described. These evaluations were conducted for each independent "experiment" (i.e., a cohort of exposed animals assessed for an endpoint or set or related endpoints). The

documentation of the animal study evaluations uses symbols and shading to present the domain specific ratings in Appendix B.3 (i.e., Good = ++; Adequate = +; Deficient = gray shading); this shading is carried over to the evidence syntheses (i.e., gray shading reflects a classification of *low* confidence). Additional considerations that might influence the interpretation of the usefulness of the studies during the hazard synthesis are noted in the Appendix study documentation tables and evidence synthesis. Depending on the specified health effect-specific study evaluation criteria, factors falling outside the specified scope of review could include limitations such as a short exposure duration or the use of only one test concentration or concentration that are all too high or too low to provide a spectrum of the possible effects, as well as study strengths such as very large sample sizes, use of good laboratory practices (GLP), or particularly robust endpoint protocols; however, this information generally did not affect the study confidence classifications themselves.

Table 2-23. Evaluation domains for experimental animal study evaluation

Evaluation domain	Preferred study characteristics (i.e., "Good" rating)
Exposure Quality	Studies should apply and document appropriate methods for the seven elements of inhalation exposure quality (the most notable elements for this assessment are: test article characterization, controls, and chamber type)
Test Subjects	The species, strain, sex, and age are appropriate and sensitive for the endpoint(s) of interest; no overt systemic toxicity is noted or expected; and allocations can be inferred as appropriate, considering matching across groups at onset of experiment; the sample size provides reasonable power to assess endpoint(s) in question[a].
Study Design	The design of the experiment is appropriate, reproducible, and sensitive for the endpoint(s) of interest, including a sufficient exposure duration and appropriate timing of endpoint evaluations; lack of additional variables introduced over the course of the study that would be expected to modify the results (no "confounding factors" introduced).
Endpoint Evaluation	The methods used to assess the outcome are sensitive, complete, discriminating (specific), and biologically sound (reliable); experimenter bias is minimized.
Data considerations and statistics	The statistical methods are reported[b], group comparisons and data (including variability) presentation are appropriate and discerning; results for all endpoints evaluated in the study are presented (lack of selective reporting)

[a]Sample size alone is not used to judge a study as *not informative.*

[b]During study evaluation, the focus for reviewing statistical methods is on transparent reporting as EPA may decide to conduct additional or alternative statistical analyses as part of data extraction or evidence synthesis.

Overall, as in observational studies in humans, considerations related to the quality of the exposure paradigms used in experimental studies typically had the strongest influence on study confidence determinations. As experimental studies should aim to control all variables other than the exposure or manipulations of interest, coexposure to methanol introduces uncertainty that the effects were caused by formaldehyde alone. Inhaled methanol could affect health endpoints or introduce quantitative uncertainty. Highly reactive formaldehyde is mostly captured in the nose,

the main site of formaldehyde-induced lesions, and very little enters the blood stream. Conversely, methanol mostly bypasses the nose but is readily absorbed in the lungs and then distributed to distal sites, including the blood and other nonrespiratory tissues, where it can be metabolized to formaldehyde. Since inhaled methanol can be distributed to different locations than inhaled formaldehyde, it could either directly cause effects or, theoretically, be metabolized to formaldehyde and cause effects in tissues that are not a target of inhaled formaldehyde. In addition, because methanol is metabolized to formaldehyde in vivo, substantial coexposure to methanol could result in differences in tissue-specific formaldehyde levels at identical external formaldehyde exposure levels when different test articles are used. This limitation is expected to introduce a bias toward an effect and is of particular concern in studies evaluating non-portal-of-entry effects. Thus, conclusions about the level of uncertainty introduced by this coexposure varied by health outcome, with a far greater level of concern for potential impacts on nonrespiratory health effects (Section 3.3), as compared to respiratory health effects (Section 3.2). This disproportionate level of concern is primarily based on two factors: (1) as compared to formaldehyde, which does not appear to be distributed to distal sites in appreciable amounts, inhaled methanol would be readily transported beyond the portal of entry (POE) and could elicit direct effects at distal target tissues, and (2) certain systemic effects evaluated in this assessment (i.e., reproductive and developmental toxicity, nervous system effects) are health outcomes known to be a target of methanol toxicity, while other health outcomes, although generally less well studied, have not been clearly associated with methanol exposure (U.S. EPA, 2013). These issues are discussed further in each major endpoint discussion in Section 3.

For certain health outcomes, the irritant and odorant nature of formaldehyde gas and the inescapable nature of these exposures (animals cannot terminate exposure at irritating levels), can complicate interpretations of causality. In addition, reflex bradypnea is an irritant response that exists in rodents, typically at formaldehyde concentrations exceeding 1 mg/m^3 (see Appendix C.2), but not humans, and can cause large variations between the administered and internal exposures. Although the understanding of irritation-related responses, including reflex bradypnea in rodents, is incomplete (e.g., responses following repeated and prolonged exposure are not well studied), it is generally assumed that irritation- and odorant-specific changes are either short lived or markedly reduced shortly after formaldehyde exposure is removed. In light of these considerations, care was taken to consider in detail the specifics of the study protocols related to formaldehyde exposure (e.g., determining whether a sufficient duration was allotted between exposure and testing, evaluating whether the exposure levels tested were capable of introducing variables such as reflex bradypnea) for certain health outcomes, particularly for the evidence syntheses of potential nervous system effects (Section 3.3.1) and developmental and reproductive toxicity (Section 3.3.2).

Inhalation toxicity studies are particularly challenging because of the inherent complexity of generating and characterizing consistent chamber atmospheres. Poor study design, human error, and problems with mechanical and electronic equipment can impair an inhalation exposure and

undermine the validity of a study. In experimental studies, there is an expectation that test subjects in an inhalation chamber study will be exposed solely to a well-characterized test article under conditions that are carefully regulated, frequently measured, and clearly reported. When a chamber study is conducted under GLP standards, there is typically greater certainty that all aspects of that study were properly performed and documented.

Experimental inhalation studies were evaluated by two or more scientists familiar with inhalation chamber operations for seven key elements of exposure quality:

1) **Test Article Characterization:** The test article is the substance or mixture of substances to which humans or animals are exposed. Any substances used to generate the test article should be well characterized. For example, formaldehyde gas can be produced by heating paraformaldehyde, formalin, UFFI insulation, or Delrin plastic. The test article description should ideally include its physical nature (solid, liquid, gas, etc.), purity, CAS registry number (if known), and physicochemical properties (including isomerization and radiolabeling). Because inhaled methanol (but not formaldehyde) is systemically distributed and can cause neurological and developmental effects, a methanol control group is desirable for studies of commercial formalin, typically contains methanol as a stabilizer. Only 2 of 84 studies known or believed to have tested commercial formalin included methanol controls.

2) **Controls:** A concurrent negative (air) control group should be used in inhalation toxicity studies. The test chamber, itself, is considered an experimental variable that should be controlled.

3) **Generation Method:** The equipment and method used to generate a chamber atmosphere should be clearly described. If methods from another publication are cited, the methods in the secondary article were evaluated (if accessible). Given the simplicity of generating a test atmosphere of formaldehyde, a deficiency in this element was not considered to represent a notable limitation for this assessment. Greater weight was applied to the test article used to generate the atmosphere (above).

4) **Analytical Method:** The method used to measure test atmospheres should be clearly described and suitable for the test chemical. There are specific methods (e.g., direct sampling, adsorptive, or chemical reactive methods, and subsequent analytical characterization such as HPLC, gas chromatography, etc.) and nonspecific methods such as gravimetric filter analysis. In addition, a real-time monitoring device (e.g., an aerosol photometer for aerosols or a total hydrocarbon analyzer for gases or vapors) may be used to monitor the stability of chamber atmospheres.

5) **Analytical Concentrations:** Every chamber study should report three concentrations, which are listed in the order of their usefulness:

   - The analytical concentration is the analytically measured concentration of a substance to which test subjects are exposed in their breathing zone. Because analytical concentrations are recorded throughout the course of a chamber study, they can reveal generation problems, fluctuations in chamber levels, analytical problems, and missed exposures. If analytical concentrations are not reported for a study considered for use in quantitative analyses, an effort should be made to acquire them from the study authors,

as analytical concentrations are preferred when deriving an RfC. The use of target or nominal concentrations to derive an RfC should be cited as a study limitation, although nominal concentrations are considered accurate for gases (but not vapors).

- The nominal concentration is the mass of generated test article divided by the total volume of air passed through the chamber. Nominal and analytical concentrations for gases are usually quite close. Conversely, the nominal concentration for a vapor or aerosol is typically greater than the analytical concentration (sometimes orders of magnitude greater) due to test chemical clumping, precipitation, and/or deposition on chamber walls and plumbing.

- The target concentration is the concentration the study director hopes to achieve in a chamber study (e.g., 1, 3, and 10 mg/m^3). Because a target concentration is a goal—not a measurement—one should not assume that test subjects were actually exposed at the precise target concentrations.

- Some fluctuation in analytical chamber concentration is expected, but concentrations should deviate from the mean chamber concentration by no more than ±10% for gases or vapors or ±20% for liquid or solid aerosols (GD 39 (OECD, 2009)). Excessive atmosphere fluctuation is evidence of a test article generation problem.

- The lack of reporting of analytical concentrations alone (no other deficiencies) was considered a minor limitation (i.e., an adequate rating overall).

6) **Particle Size Characteristics:** Particle median diameter, density, and distribution (geometric standard deviation or σg) should be characterized whenever test subjects may be exposed to an aerosol or to a vapor that may condense into inhalable aerosol particles. Particle sizing is not necessary when testing a gas. The mass median aerodynamic diameter (MMAD) is often calculated, but metrics such as physical diameter, median particle number, or surface area may also be evaluated as the most relevant metric. This element was not important for formaldehyde.

7) **Chamber Type:** Inhalation chambers are either dynamic or static. Dynamic chambers, which include nose-only, head-only, and whole-body chambers, have a constant flow of filtered air and consistent test article concentrations, but static chambers do not. EPA and OECD inhalation test guidelines indicate use of a dynamic chamber. Static chamber studies are not preferred for longer term hazard identification or exposure response analyses in particular, as they can lead to a harmful buildup of by-products (e.g., CO_2). Consideration should also be given to whether the test article is best delivered by whole-body or nose-only chambers. Animals exposed to an aerosol in a whole-body chamber may receive a significant oral exposure due to preening of particles deposited on their fur. To prevent this, nose-only chambers are recommended when testing aerosols and vapors that may precipitate into particles.

The documentation of the exposure quality assessment for controlled exposure studies is included in Appendix B.3.1 (note: the evaluations of elements #1 and #2 are documented together) and then summarized as one (very influential) domain of the health effect-specific documentation of study evaluations by health effect in Appendix B.3 and the syntheses (Section 3).

Controlled Exposure Studies in Humans: Evaluation Criteria and Classification Scheme

A process incorporating aspects of the evaluation approaches used for epidemiological studies and experimental animal studies (see below) was used to evaluate controlled exposure studies in humans. Controlled human exposure studies were evaluated for important attributes of possible bias and the appropriateness of the study design for the outcome(s) of interest. For each evaluation domain, Table 2-24 describes the preferred study characteristics (i.e., supporting a "good" rating for that domain). The outcome-specific evaluations consider the methodological conduct of each study against these general preferences, considering also the health effect-specific considerations (see Sections 2.3.2–2.3.10), to rate each domain based upon the number and severity of the uncertainties and limitations identified, as previously described.

Table 2-24. Evaluation domains for controlled exposure studies in humans

Evaluation domain	Preferred study characteristics (i.e., "Good" rating)
Exposure Assessment	Domain considerations applied to experimental animal studies regarding the conduct of the inhalation exposures were applied, including inclusion of a clean air control exposure and other aspects of the exposure protocol. For example, a study was judged to be *low* confidence if the exposure generation method resulted in exposure to substances other than formaldehyde (e.g., emissions from pressed wood products).
Outcome Classification	Appropriateness of the timing and methods used to evaluate the outcome(s) of interest.
Consideration of Potential (Observer and Subject) Bias	Specifically, randomization and blinding of subjects and investigators. In general, low confidence was applied if allocation to the order of exposure categories was not random, or subjects were not blinded to their exposure order; however, when studies evaluated multiple dose levels, an important strength for the hazard assessment, they were judged as *medium* confidence when reporting detail was the only identified limitation (e.g., the authors did not describe the measures used to control bias).
Consideration of Likely Confounding	Important potential confounders addressed in study design or analysis; lack of additional variables introduced over the course of the study that would be expected to modify the results.
Results Presentation	The group comparisons and data (including variability) presentation are appropriate and discerning; results for all endpoints evaluated in the study are presented (lack of selective reporting).
Size	The evaluation of few individuals (generally $n \leq 10$, considering the endpoints evaluated) resulted in reduced confidence[a].

[a]Sample size alone is not used to judge a study as *not informative.*

Mechanistic Studies: Approach and Evaluation Criteria

For this assessment, in multiple instances where a reasonable number of studies were available, but the mechanistic interpretations were not well-established, the individual mechanistic studies were systematically evaluated. For evaluations of individual mechanistic studies in experimental animal studies or in vitro models of gaseous formaldehyde exposure (i.e., mechanistic

studies related to respiratory effects; mechanistic studies of formaldehyde inhalation related to nervous system effects and developmental and reproductive toxicity) the same general features evaluated for more apical measures of toxicity were considered (i.e., evaluations of exposure quality and study design were emphasized), although the specific criteria were simplified to accommodate the increased heterogeneity of the available mechanistic studies as compared to more traditional, apical measures of toxicity. Similarly, study evaluations of individual human studies (i.e., mechanistic studies related to respiratory effects; human studies of genotoxicity endpoints) emphasized consideration of exposure assessment, study design, outcome ascertainment, and comparison groups for potential sources of bias and their potential impact. While these individually evaluated studies represented the totality of the evaluated mechanistic information for some health effect-specific evaluations (most of the noncancer health effects), several other health effect-specific mechanistic analyses (e.g., respiratory tract pathology; cancer MOA) considered subsets of these individually evaluated studies alongside other information, including sets of studies that were not individually evaluated (e.g., while human genotoxicity studies were individually evaluated, the myriad animal and in vitro studies of genotoxic endpoints were not). In these latter cases, the body of evidentiary support (or lack thereof) for specific, influential mechanistic events (e.g., those known to be associated with the health outcome of interest; those previously implicated in authoritative reviews as relevant to interpreting formaldehyde exposure-induced health effects) were considered in totality, with judgments based on overarching interpretations across the different sets of inter-related studies. Additional details on these approaches are provided in Sections 2.3.6 and 2.3.10.

2.3.2. Sensory Irritation Study Evaluation Criteria

The literature search for sensory irritation focused on identifying relevant studies in humans (see Section 2.2.2). Evaluations of individual mechanistic studies conducted as part of the overarching review of mechanistic information related to noncancer respiratory effects emphasized consideration of issues related to exposure conduct, as described elsewhere (see Section 2.3.6 and Appendix B.3.6). All human studies identified by the literature search for sensory irritation that met the inclusion criteria as described in Section 2.2.2, were evaluated, and classified by confidence level. Tables that document the evaluation of human studies are found in Appendix B.3.2, including both the identified observational epidemiology studies and the studies of controlled human exposure.

Human Observational Epidemiology Studies

Table 2-25 provides criteria used to evaluate the domains for each observational epidemiology study of sensory irritation.

Symptoms related to irritation of the eyes, nose, and throat were reported by most studies. Generally, symptoms were ascertained via self-report or through interviews, both using a standardized questionnaire (e.g., American Thoracic Society [ATS]). Self-reported symptoms may

be influenced to some degree by recall bias if exposure is known to the responder, although this is of less concern if an appropriate comparison is used. For some studies, there were more serious concerns about selection or information bias related to the participants' knowledge of their exposure or selection into a study based on presence of symptoms and concerns about exposure, which could produce spurious findings (Wei et al., 2007; Salonen et al., 2009; Ritchie and Lehnen, 1985, 1987; Norsted et al., 1985; Dally et al., 1981; Bracken et al., 1985). The studies of residential formaldehyde exposure included a wide range of ages (adults and children) and potentially susceptible individuals, some of whom had existing respiratory issues and other health conditions, and thus, in general, concerns regarding potential insensitivity of the study population did not apply.

The time frame of the exposure assessment relative to the assessment of symptoms was an important aspect of the evaluation of symptom prevalence. The relevant period for the assessment of irritant responses was considered to be concurrent with the time period of the exposure assessment because the symptoms associated with irritation occur immediately (Krakowiak et al., 1998; Andersen, 1979; Andersen and Molhave, 1983). Questions about symptom occurrence over an extended time period (weeks and months) that were separated in time from the exposure assessment period were considered to be more limited by recall bias. Some of the studies of anatomy students assessed symptoms of irritation that occurred during lab sessions several weeks or months previously, which increased concern regarding recall bias. The occupational studies generally ascertained the prevalence of symptoms while at work via interview using standardized questionnaires.

Table 2-25. Criteria for domain ratings in epidemiology studies of sensory irritation

Evaluation domain	Primary criteria for domain ratings		
	Good ('++')	Adequate ('+')	Deficient ('gray')
Population (SB)	**General population**: Participant selection based on population-based sampling frame with high participation rate. **Occupational settings**: High participation rate but potential for "healthy worker effect" to lead to attenuated effect estimate.	Uncertainty regarding participant recruitment process or participation rate.	**General population**: Participant selection based on exposure status. **Occupational settings**: Recruitment process or self-selection likely to lead to inflated effect estimate.
Exposure (IB)	**General population**: Exposure measurements designed to characterize average concentrations in a residence over a defined period with details regarding measurement protocol (e.g., shutting windows).	**General population**: Details regarding measurement protocol provided, but uncertainty regarding characterization of average residential concentrations corresponding to the period of outcome assessment.	**All settings**: Large percentage (e.g., 50% or higher) of measures < LOD, or other ways in which exposure range does not allow meaningful analysis of risks above 0.010 mg/m^3; small exposure contrast between exposure groups

Evaluation domain	Primary criteria for domain ratings		
	Good ('++')	**Adequate ('+')**	**Deficient ('gray')**
	Occupational settings: Ability to differentiate between exposed and unexposed, or between low and high exposure. **All settings**: Exposure window should reflect the same period as the characterization of symptoms.	**Occupational settings**: Referent group may be exposed to formaldehyde or to other exposures affecting respiratory conditions (potentially leading to attenuated risk estimates)	limits ability to detect differences.
Outcome (IB):	American Thoracic Society (ATS) questionnaire or other validated questionnaire for irritation symptoms. Symptoms reported without knowledge of exposure status.	Instrument or methods for data collection less well described. Symptoms reported without knowledge of exposure status, or knowledge unlikely in light of exposure levels or range.	Symptoms reported with knowledge of exposure status. Instrument or methods for data collection not described and uncertainty whether symptoms were reported without knowledge of exposure status.
Confounding (Cf)	Potential for confounding considered and addressed in design or analysis. Primary potential confounders were age, gender, smoking, and respiratory exposures associated with the outcomes that were correlated with formaldehyde.	Potential for confounding considered and addressed in design or analysis but some questions regarding degree of correlation between formaldehyde and other exposures associated with sensory irritation may remain.	Potential for confounding prevents differentiation of effect of formaldehyde from effect of other exposure(s).
Analysis and Other (Oth)	Analysis allows for examination of variation in effect in relation to variation in exposure level using analytic procedures that are suitable for the type of data. Data provided that allows characterization of the distribution of exposure, e.g., upper 75th percentile.	Sample size limited in stratified analyses.	Limited data analysis (or analysis that is not appropriate for the data) or small overall sample size increased potential for unreliable results.

Controlled Exposure Studies in Humans

Controlled human exposure studies were evaluated for important attributes of experimental studies, including randomization of exposure assignments, blinding of subjects and investigators, and inclusion of a clean air control exposure and other aspects of the exposure protocol. The evaluation of few individuals ($n \leq 10$) resulted in reduced confidence. Several studies did not describe the measures used to control bias, resulting in a lower level of confidence in study results. However, some of these studies evaluated multiple dose levels, an important strength for the hazard assessment. Therefore, these studies were included with *medium* confidence when reporting detail was the only identified limitation.

2.3.3. Pulmonary Function Study Evaluation Criteria

The literature search for pulmonary function focused on identifying relevant studies in humans (see Section 2.2.3). Controlled exposure studies in humans were evaluated as described for sensory irritation endpoints in Section 2.3.2. Likewise, evaluations of individual mechanistic studies conducted as part of the overarching review of mechanistic information related to noncancer respiratory effects emphasized consideration of issues related to exposure conduct, as described elsewhere (see Section 2.3.6 and Appendix B.3.6). Thus, the discussion and criteria discussed below relate primarily to the identified observational epidemiology studies. The individual study evaluation decisions are documented in Appendix B.3.3.

Pulmonary function is assessed using spirometry, which measures the volume and speed of air that is exhaled or inhaled. Several parameters can be measured during spirometric testing to characterize an individual's respiratory health (Table 2-26). The American Thoracic Society has published guidelines for equipment performance requirements, validation, quality control, test procedures, and reference equations for each type of spirometric measurement (Miller et al., 2005a; Miller et al., 2005b), as well as the interpretation of testing results (Pellegrino et al., 2005). Ratings in the outcome domain were highest when pulmonary function outcomes were measured using the guidelines published by the American Thoracic Society or providing a description of the protocols and reference equations that were used. In addition to the use of conventional spirometric equipment, peak expiratory flow has been measured in research settings using portable flow meters operated by study participants trained in their use. Although it requires careful training and monitoring, this method has the advantage that it can be used in large epidemiological studies and multiple measurements can be obtained over time (Tepper et al., 2012). Studies of residential exposure to formaldehyde were conducted in this way (Krzyzanowski et al., 1990; Kriebel et al., 2001).

Table 2-26. Common measures of pulmonary function reported in studies of formaldehyde inhalation

Measure	Definition
Vital Capacity (VC) (Liters at BTPS)	The volume of air between a full inspiration and maximal expiration (an unforced maneuver)
Forced Vital Capacity (FVC) (Liters at BTPS)	The maximum volume of air forcibly exhaled after a maximal inspiration
Forced Expiratory Volume, 1 second (FEV_1) (Liters at BTPS)	The volume of air that is exhaled with maximal force in the first second
Forced Expiratory Flow 25–75% (FEF_{25-75}) (L/sec)	The mean forced expiratory flow in the 25th and 75th percentiles of FVC (also called maximum mid-expiratory flow [MMEF, MEF])
Ratio of FEV_1 to FVC (FEV_1/FVC)	Proportion of vital capacity exhaled in the first second of forced expiration

Peak Expiratory Flow Rate (PEF or PEFR) (L/sec at BTPS or L/min)	The maximum flow obtained from a person's maximum forced expiration starting from the point of a maximal lung inflation

BTPS: Body temperature and ambient pressure saturated with water vapor.
Source: Miller et al. (2005a).

Pulmonary function varies by race or ethnic origin, gender, age, and height, and is best compared when normalized to the expected lung function based on these variables (Tepper et al., 2012; Pellegrino et al., 2005; Hankinson et al., 1999). Studies that did not adjust or otherwise account for these variables when comparing results between exposure groups were not considered. Pulmonary function also is associated with smoking status (Becklake and White, 1993), which was considered in the evaluation of potential confounding. FEV_1 and PEFR exhibit diurnal variation, and this complicates the interpretation of changes across a work shift or during a laboratory session if no comparisons were made with an unexposed group (Lebowitz et al., 1997; Chan-Yeung, 2000). Studies with no comparison group were given less weight in evaluating study results.

The healthy worker effect and survivor (lead time) bias was a concern for several cross-sectional occupational studies, some of which had no other major limitations. Removal of individuals more sensitive to the irritant effects of formaldehyde from jobs or tasks with formaldehyde exposure likely occurred in industries with high formaldehyde exposures, and this type of selection bias might result in an attenuation of risk estimates or a null finding if these individuals also experienced effects on pulmonary function. Table 2-27 provides criteria used to evaluate the domains for each observational study of pulmonary function.

Table 2-27. Criteria for domain ratings in epidemiology studies of pulmonary function

Evaluation domain	Primary criteria for domain ratings		
	Good ('++')	**Adequate ('+')**	**Deficient ('gray')**
Population (SB)	**General population**: Participant selection based on population-based sampling frame with high participation rate. **Occupational settings**: High participation rate but potential for "healthy worker effect" to lead to attenuated effect estimate.	Uncertainty regarding participant recruitment process or participation rate.	**General population**: Recruitment process or self-selection likely to lead to inflated effect estimate.
Exposure (IB)	**General population**: For inferences above 0.050 mg/m^3, exposure range includes large enough sample above 0.050 mg/m^3 to allow for meaningful analysis in this range. **Occupational settings**: Ability to differentiate between exposed and unexposed, or between low and high exposure.	**General population**: More limited exposure assessment than described in "Good" category (e.g., 1-5 days) with some details regarding measurement protocol. **Occupational settings**: Referent group may be exposed to formaldehyde or to other exposures affecting	**All settings**: Large percentage (e.g., 50% or higher) of measures < LOD, or other ways in which exposure range does not allow meaningful analysis of risks above 0.010 mg/m^3; small exposure contrast between exposure groups limits ability to detect differences.

Evaluation domain	Primary criteria for domain ratings		
	Good ('++')	**Adequate ('+')**	**Deficient ('gray')**
	All settings: Exposure measure must reflect the etiologically relevant time window. For measures of average pulmonary function, average ongoing exposure experienced during the past several weeks or months. Exposure measure based on at least 5-d sample, or if < 5 days, measures in more than one season. For measures of change, exposure assessment occurring concurrently or representing average conditions prior to change.	respiratory conditions (potentially leading to attenuated risk estimates). **All settings:** Uncertainty regarding correspondence between measured levels and levels in the etiologically relevant time window.	**General population**: Short (<1 d) exposure measurement period with no, or limited, discussion of protocol and quality control assessment. **All settings**: Large percentage (e.g., 50% or higher) of measures < LOD, or other ways in which exposure range does not allow meaningful analysis of risks above 0.010 mg/m^3; small exposure contrast between exposure groups limits ability to detect differences.
Outcome (IB)	Pulmonary function outcomes measured using American Thoracic Society guidelines or providing a description of the protocols and reference equations that were used. Methods described or reference provided for measures of peak expiratory flow. Outcome measurement conducted without knowledge of exposure status.	Instrument or methods for data collection less well described.	Instrument or methods for data collection not described. Symptoms reported with knowledge of exposure status.
Confounding (Cf)	Potential for confounding considered and addressed in design or analysis. Primary potential confounders were race, height, age, gender, smoking, and respiratory exposures associated with the outcomes that were correlated with formaldehyde.	Potential for confounding considered and addressed in design or analysis but some questions regarding degree of correlation between formaldehyde and other exposures associated with pulmonary function may remain.	Potential for confounding prevents differentiation of effect of formaldehyde from effect of other exposure(s).
Analysis and Other (Oth)	Analysis allows for examination of variation in effect in relation to variation in exposure level using analytic procedures that are suitable for the type of data. Data provided that allows characterization of the distribution of exposure, e.g., upper 75^{th} percentile.	Sample size limited in stratified analyses.	Limited data analysis (or analysis that is not appropriate for the data) or small overall sample size increased potential for unreliable results. <u>For changes across work shift or lab session:</u> No comparison to changes in an unexposed group during same time-period.

2.3.4. Immune-Mediated Conditions, Focusing on Allergies and Asthma, Study Evaluation Criteria

The literature search for immune-mediated conditions initially focused on identifying relevant studies in humans or animals (see Section 2.2.4), although the experimental animal studies were ultimately considered most appropriately analyzed as mechanistic evidence within the broader context of the review of mechanistic information for potential respiratory effects (see Section 2.3.6); thus, the documentation of the animal study evaluations is in Appendix B.3.6. The evaluation of observational epidemiology studies section is discussed below first, followed by a summary of the evaluation of controlled human acute exposure studies. Tables documenting the evaluation of each of the human studies in this section is found in Appendix B.3.4.

Observational Epidemiology Studies

EPA consulted with two panels of epidemiology experts to develop criteria to rate the confidence in the results for observational epidemiology studies of allergic response[10] and of asthma.[11] Each panel was given extracted information regarding case ascertainment or outcome classification from studies using questionnaire-based measures (or, for the allergy panel, skin prick tests). These studies were reflective of the most common study designs used, e.g., cross-sectional with concurrent assessment of exposure and of symptoms over a preceding period ranging from 4 weeks to 12 months. Descriptive information about the study population (e.g., size, age, country) was also provided but the material did not include any information regarding results for formaldehyde or other exposures.

The panels' discussions and the criteria relating to the evaluation of outcome assessment are described below.

Ascertainment of allergic sensitization and allergies

Questionnaire-based ascertainments of nasal and ocular symptoms have been developed and widely used, for example in the International Study of Arthritis and Allergies in Children (ISAAC) (Asher et al., 1995). The additional ascertainment of seasonality and triggers can be helpful in distinguishing between allergic and nonallergic basis of the symptoms. When comparing specific types of self-reported allergies to specific types of positive skin prick tests, specificity of self-report is relatively high (approximately 90% or higher), but sensitivity is lower (ranging from 30–70%) (see for example (Lakwijk et al., 1998; Dotterud et al., 1995; Braun-Fahrländer et al., 1997)).

[10]Dr. Hasan Arshad, University of Southampton, Southamptom, United Kingdom; Dr. Peter Gergen, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; Dr. Elizabeth Matsui, Johns Hopkins University, Baltimore, Maryland; Dr. Dan Norbäck, Uppsala University, Uppsala, Sweden; Dr. Matthew Perzanowski, Columbia University, New York City, NY.

[11]Dr. Lara Akinbami, U.S. Centers for Disease Control, Atlanta, Georgia; Dr. Peter Gergen, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; Dr. Christine Joseph, University of Michigan, Ann Arbor, Michigan; Dr. Felicia Rabito, Tulane University, New Orleans, Louisiana; Dr. Carl-Gustaf Bornehag, Karlstad University, Karlstad, Sweden.

Limiting case ascertainment to physician-diagnosed allergies increases specificity but is considered to have low sensitivity because self-treatment with nonprescription medications is common. Questionnaire-based ascertainments of atopic dermatitis or eczema have also been developed (Williams et al., 1996; Asher et al., 1995). These questionnaires focus on the extent, location, and itchiness of the rash and age at onset (typical onset before age 2 years). Specificity, compared to physician diagnosis, was high (>0.95) in school-age children (Williams et al., 1996) and in younger children (von Kobyletzki et al., 2013).

Based on advice from the expert panel, EPA considered cross-sectional designs using questionnaires for rhinitis or rhinoconjunctivitis to provide an adequate basis for case ascertainment in studies in Europe and the United States; in studies in other areas (i.e., areas that have not been included in ISAAC), specific mention of validation of the questionnaire was needed to receive a *high* confidence rating. Although the specificity of questions pertaining to rhinitis may be lower than the specificity of questions pertaining to rhinoconjunctivitis (Kim et al., 2012), based on the feedback received, this difference was interpreted by EPA as insufficient to conclude that the rhinitis questions should be viewed with lower confidence.

Ascertainment of asthma

Self- (or parent-) report of physician-diagnosed asthma can be reliably used in epidemiological studies of incidence of asthma, although this method can miss undiagnosed asthma. "Current" asthma, or prevalence of current asthma, is typically ascertained through a set of questions pertaining to symptoms or medication use over of period of time (e.g., last 12 months). A similar, but usually expanded, set of questions can be used to assess asthma control over a shorter period of time (e.g., 2–4 weeks). (Asthma control pertains to the extent to which symptoms can be reduced or eliminated with medication.) Asthma exacerbation is a term typically used in clinical trials and considers the need for using systemic corticosteroids.

Most of the studies identified in the formaldehyde literature are studies of prevalence of current asthma and used a classification scheme based on the American Thoracic Society (ATS) questionnaire (Ferris, 1978) or subsequent instruments that built upon this work, including the ISAAC and European Community Respiratory Health Survey (ECHRS) questionnaires. Based on consultation with the expert panel, these questionnaire-based approaches have been found to have an adequate level of specificity and positive predictive value for use in etiologic research (Ravault and Kauffmann, 2001; Jenkins et al., 1996; Burney et al., 1989) that focuses on the occurrence of episodes of asthma, as opposed to the first occurrence of asthma. The questionnaires typically use several questions to define current asthma based on symptoms relating to wheezing episodes or shortness of breath, reported history of asthma attacks, or use of asthma medication. As noted in the discussion of ascertainment of allergies, the questionnaires have been used in many studies but have not necessarily been validated in every population.

The age of study participants is an important consideration in the interpretation of various measures. Specificity of symptom questions is reduced in the very young (<5 years) because

wheezing can occur with respiratory infections in infants and young children, and specificity is reduced at older ages (e.g., >75 years) because of the similarities in symptoms and medication use for chronic obstructive pulmonary disease and asthma (Taffet et al., 2014; Abramson et al., 2014).

Asthma can be atopic (allergic) or nonatopic. In the United States 1988–1994 NHANES data, 56% of self-reported physician diagnosed asthma cases had at least one positive skin prick test (Arbes et al., 2005). Thus, the delineation of asthma into these different groups can reduce some of the heterogeneity, but exclusion of either group may significantly reduce the sensitivity of case ascertainment.

Considering the expert advice and the considerations above, the eligible population for asthma was defined for the purposes of this assessment as "humans, age > 4 years" because the respiratory disorder occurring in infants and toddlers may be related to, but is distinct from, asthma, which is more reliably diagnosed in school-aged children. Thus, five studies initially identified as asthma studies in the literature search are not classified as studies of asthma in the assessment, but rather as studies of "lower respiratory tract symptoms in infants and toddlers" Raaschou-Nielsen et al. (2010) Roda et al. (2011) Rumchev et al. (2002). Li et al. (2019) Yu et al. (2017). Studies of asthma or asthma symptoms that included ages 3–4 within a larger cohort of older children were included if the proportion of the study group in the age range was likely to be relatively small (e.g., if the mean age was > 5 years).

Summary of Evaluation Criteria

Table 2-28 describes the criteria used for the domain ratings informing the confidence classifications for epidemiological studies of immune-mediated conditions.

Table 2-28. Criteria for domain ratings in epidemiologic studies of allergies and asthma

Evaluation Domain	Primary criteria for domain ratings		
	Good ('++')	**Adequate ('+')**	**Deficient ('gray')**
Population (SB)	**General population:** Participant selection based on population-based sampling frame with high participation rate. **Occupational settings:** High participation rate but potential for "healthy worker effect" to lead to attenuated effect estimate.	Uncertainty regarding participant recruitment process or participation rate.	**General population:** Participant selection based on exposure status. **Occupational settings:** Recruitment process or self-selection likely to lead to inflated effect estimate. **Asthma:** Studies of infants and children < 5 years[a]
Exposure (IB)	**General population:** For inferences above 0.050 mg/m^3, exposure range includes large enough sample above 0.050 mg/m^3 to allow for meaningful analysis in this range. **Occupational settings:** Ability to differentiate between exposed and unexposed, or between low and high exposure.	**General population:** More limited exposure assessment than described in "Good" category (e.g., 1-5 d); some details regarding measurement protocol provided. **Occupational settings:** Referent group may be	**General population:** Short (<1 d) exposure measurement period; no or limited discussion of protocol - quality control assessment. **All settings:** Large percentage (e.g., 50% or higher) of measures < LOD, or other ways in which exposure range does not allow analysis of risks above 0.010 mg/m^3; small exposure

Evaluation Domain	Primary criteria for domain ratings		
	Good ('++')	**Adequate ('+')**	**Deficient ('gray')**
	All settings: Exposure measure should reflect etiologically relevant period. **Incidence of allergies (over subsequent 12 months) – or prevalence of allergy symptoms (in past 12 months or shorter period)** - Exposure measure based on at least 5-d sample measures or fewer days if sampled in more than one season. **Allergy sensitization** (skin prick tests) - exposure measure should reflect the period before or during which sensitization occurs. **Current asthma** (in past 12 mos or shorter time period) Exposure measure based on at least 5-d sample measures or fewer days if sampled in more than one season. **Asthma control** (symptoms and medication use over the past 2–4 weeks) - exposure measure concurrent with the outcome assessment. **Nighttime asthma symptoms,** exposure measures taken in the home.	exposed to formaldehyde or to other exposures affecting respiratory conditions (potentially leading to attenuated risk estimates) **All settings:** Uncertainty regarding correspondence between measured levels and levels in the etiologically relevant time window. For example, for studies of nighttime asthma symptoms, exposure measures taken at school or work.	contrast between exposure groups limits ability to detect differences.
Outcome (IB):	**Incidence or prevalence of allergy symptoms** - ISAAC questionnaires for rhinitis or rhinoconjunctivitis (in United States or Europe), or other validated questionnaire. **History of allergies –** self-report of specific allergies. For children, skin prick tests covering at least 5 allergens. **Contact atopic dermatitis or eczema -** validated questionnaire. **Current asthma** (in past 12 mos or shorter time period) - ISAAC or other ATS-related questionnaires (in United States or Europe), or other validated questionnaire with similar level of sensitivity and specificity.	**Prevalence of allergy symptoms -** ISAAC or other questionnaire in areas other than US or Europe, without validation. **History of allergies -**report of physician-diagnosed allergy (high specificity but low sensitivity). For adults - skin prick tests. **Atopic eczema. allergic rhinitis** (in the past year) - self-report of medical treatment (medication use), without clarifying the type of medication. **Current asthma:** ISAAC or other questionnaire in areas other than U.S. or Europe, without validation; self-report of medical treatment (medication use) for asthma in the past year.	**History of allergies** - self-report of allergies that includes food allergies.
Confounding (Cf)	Confounding considered and addressed in design or analysis. Primary potential confounders were age, gender, and respiratory exposures associated with the outcomes that were correlated with formaldehyde.	Confounding considered and addressed in design or analysis but some questions regarding degree of correlation between formaldehyde and other exposures associated with	High likelihood of confounding that makes it unable to differentiate effect of formaldehyde from effect of other exposure(s).

Evaluation Domain	Primary criteria for domain ratings		
	Good ('++')	**Adequate ('+')**	**Deficient ('gray')**
		allergies or asthma may remain.	
Analysis and Other (Oth)	Analysis allows for examination of variation in effect in relation to variation in exposure level using analytic procedures that are suitable for the type of data. Data provided that allows characterization of the distribution of exposure, e.g., upper 75th percentile.	Sample size limited in stratified analyses.	Limited data analysis (or analysis that is not appropriate for the data) or small overall sample size increased potential for unreliable results.

Abbreviations: SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis.
[a] These studies used in a separate evaluation of lower respiratory tract conditions in infants and children < 5 years.

Controlled Exposure Studies in Humans

The evaluation of controlled exposure studies examined four primary elements: the type of exposure (paraformaldehyde preferred over formalin or undefined test articles), use of randomization procedures to allocate exposure, blinding of the participant and of the assessor to exposure, and the details regarding the analysis and presentation of results (see Appendix B.3.4 for documentation of these study evaluations).

2.3.5. Respiratory Tract Pathology Study Evaluation Criteria

Studies in Humans

Considerations specific to the evaluation of the outcome assessment domain are described below; other evaluation domains pertaining to population (participant selection and comparability), exposure measurement, possibility of confounding, analysis and completeness of results, and study size, are discussed in Section 2.3.1. A table documenting the evaluation of each of the studies in this section is found in Appendix B.3.5.

For studies that evaluated histopathological lesions in nasal biopsies, EPA looked for either a detailed explanation of how tissues were evaluated and scored, or a citation for a standard method. Nasal biopsies were taken in four occupational studies; tissues were subsequently stained, and cell structure examined according to variations of the Torjussen et al. (1979) method. The original Torjussen method scored morphological characteristics of the nasal epithelium using a whole number between 0 and 8, with 0 indicating normal epithelium and 8 indicating carcinoma and the midpoint of four signifying stratified squamous epithelium with a horny layer. Despite the variations of this scale, in each study the lowest numbers (0 or 1) always indicated normal cell structure while increasingly higher numbers indicated more disruptive cellular changes. Although the focus of this section is nonneoplastic histopathologic lesions, the studies compared the means of the total score between exposed and referent groups. Therefore, the prevalence of dysplasia is presented in the evidence synthesis tables when it was reported.

The criteria relating to the evaluation of human respiratory tract pathology studies are outlined in Table 2-29.

Table 2-29. Criteria for domain ratings in epidemiology studies of respiratory pathology

Evaluation Domain	Primary criteria for domain ratings		
	Good	**Adequate**	**Deficient**
Population (SB)	**General population**: Participant selection based on population-based sampling frame with high participation rate. **Occupational settings**: High participation rate but potential for "healthy worker effect" to lead to attenuated effect estimate.	Uncertainty regarding participant recruitment process or participation rate.	**General population**: Participant selection based on exposure status. **Occupational settings**: Recruitment process or self-selection likely to lead to inflated effect estimate.
Exposure (IB)	**General population**: Exposure measure based on at least 3-d sample; measures in more than one season if time window covers 12 months or addressed season in the analysis. **Occupational settings**: Ability to differentiate between exposed and unexposed, or between low and high exposure. Relevant exposure period for nasal pathology is period prior to and during development of nasal lesions.	**General population**: More limited exposure assessment (e.g., < 1 d) with details regarding measurement protocol provided. **Occupational settings**: Referent group may be exposed to formaldehyde or to other exposures affecting respiratory conditions (potentially leading to attenuated risk estimates) **All settings**: Uncertainty regarding correspondence between measured levels and levels in the etiologically relevant time window.	**All settings**: Large percentage (e.g., 50% or higher) of measures < LOD, or other ways in which exposure range does not allow analysis of risks above 0.010 mg/m^3; small exposure contrast between exposure groups limits ability to detect differences. **General population**: Short (<1 d) exposure measurement period without discussion of protocol - quality control assessment.
Outcome (IB)	**Cytopathology in nasal tissues**: Detailed description of how tissues were evaluated and scored or citation to standard method. **Other endpoints**: Detailed description or citation to standard method.	Nonstandard methods but documentation provided.	Nonstandard methods and no documentation establishing validity.
Confounding (Cf)	Confounding considered and addressed in design or analysis. Primary potential confounders were age, smoking, and respiratory exposures associated with the outcomes that were correlated with formaldehyde.	Confounding considered and addressed in design or analysis but some questions regarding degree of correlation between formaldehyde and other exposures associated with	High likelihood of confounding that makes it unable to differentiate effect of formaldehyde from effect of other exposure(s),

Evaluation Domain	Primary criteria for domain ratings		
	Good	**Adequate**	**Deficient**
		respiratory tract pathology may remain.	
Analysis and Other (Oth)	Analysis allows for examination of variation in effect in relation to variation in exposure level using analytic procedures that are suitable for the type of data. Data provided that allows characterization of the distribution of exposure, e.g., upper 75th percentile.	Sample size limited in stratified analyses.	Limited data analysis (or analysis that is not appropriate for the data) or small overall sample size increased potential for unreliable results.

Studies in Animals

In addition to the general factors considered for all toxicology studies of formaldehyde inhalation exposure (see Appendix B.3.1), factors specific to the interpretation of respiratory tract pathology were considered when determining study confidence. These criteria reflect the large database of well-conducted studies, and include: the use of too few test subjects (i.e., a sample size of less than 10 was considered a significant limitation); a failure to report lesion incidence and/or severity; the lumping of multiple lesions (e.g., squamous metaplasia and hyperplasia) together; a failure to report quantitative incidences and/or statistical analyses; the use of insensitive sampling procedures (multiple sections across multiple levels of the respiratory tract were preferred); and use of an exposure duration or follow-up that is likely insensitive for detecting slow-developing lesions (a duration of ≥1 year was preferred).

Somewhat in contrast to the available experimental animal studies for other health effect sections, most studies of respiratory pathology used paraformaldehyde or freshly prepared formalin as the test article, although some studies tested commercial formalin. As noted previously, while co-exposure to methanol is a major confounding factor for systemic endpoints, it is less of a concern (i.e., an adequate domain rating ("+"); see below) when identifying effects of inhaled formaldehyde on respiratory pathology. Most inhaled methanol bypasses the nose but is readily absorbed in the lungs and distributed systemically. Inhalation studies of methanol suggest that URT effects occur at concentrations many times higher than estimates of methanol concentrations in air, at least those generated from spraying formalin solutions onto heated glass[12] (e.g., >650 mg/m^3 in methanol studies by Poon et al. (1995) and Andrews et al. (1987) versus 5.5 mg/m^3 methanol reported by Kamata et al. (1997) in a formalin study testing formaldehyde levels of 0 and 18.27 mg/m^3). Thus, in general, the levels of methanol in formalin studies are considered unlikely

[12]Even though methanol levels in the air using the generation methods in the other available formalin studies may be quite different, and possibly significantly higher, than the levels estimated by Kamata et al. (1997), given the relative insensitivity of the URT to methanol, these crude comparisons were considered sufficient for interpretations drawn in the context of these URT effects.

to cause substantial increases in URT lesion severity. However, it does introduce the possibility that effective respiratory tract tissue concentrations of formaldehyde might be slightly higher after inhalation of formalin (due to some methanol conversion to formaldehyde within the tissue) than after exposure to the same concentrations of formaldehyde from sources without methanol, which would result in an overestimate of the effect of formaldehyde exposure and thus can influence study selection for dose-response analysis (see methods in Section 2.7).

For assessing histopathological changes for the different regions of rodent nasal passages, standard cross-section levels (e.g., Levels I–V) have generally been adopted for consistent analysis across studies (Young, 1981; Mery et al., 1994). Although the number and naming of cross-section levels varied from study to study, the levels always progressed through the nasal cavity from the area posterior to the nostrils (e.g., Level I or A) to areas anterior to the nasopharynx. Two different examples of the cross-sectioning procedures in rats are illustrated in Figure 2-2, with other studies of rats and other rodents employing similar procedures; however, illustrations of the specific cross-section levels used in each individual study are not included in the evidence tables.

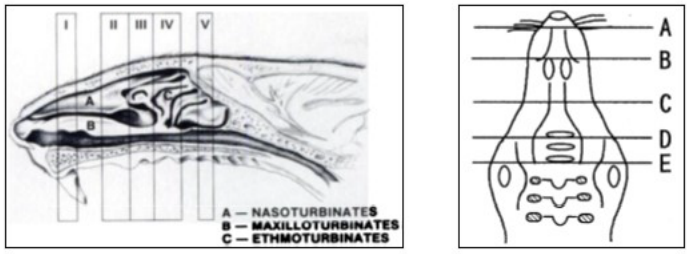


Figure 2-2. Example cross-section levels in rat nasal passages used for histopathological evaluations from Kerns et al. (1983) (left; Levels I-V) and Kamata et al. (1997) (right; Levels A-E).

For this assessment, it was preferred that studies assessed multiple tissue sections across multiple cross-section levels to allow for reasonable sampling of the nasal mucosa. Where applicable, histopathological findings in the nasal mucosa are discussed with reference to these sections, and the specific structures examined are stipulated in the evidence tables (e.g., nasoturbinates, maxilloturbinates, or ethmoid turbinates). When data were available, the type of epithelium affected (e.g., respiratory epithelium) was also noted. Only a few studies evaluated sections of the URT distal to the nasal cavity, and these evaluations were generally less rigorous (e.g., examining only a single tissue section) than evaluations of the nasal mucosa and tested much higher formaldehyde concentrations. Similarly, pathological findings in the LRT were generally not identified in studies with "good" or "adequate" exposure quality; thus, while these findings are briefly summarized in the evidence synthesis, separate criteria for outcome evaluation were not developed.

Table 2-30 describes the criteria used for the domain ratings informing the confidence classifications for animal studies of respiratory tract pathology.

Table 2-30. Criteria for domain ratings in animal studies of respiratory tract pathology

Evaluation domain	Overview of preferred study features	Primary criteria for domain ratings (Documentation shorthand used in Appendix B.3.5)		
		Good ('++')	Adequate ('+')	Deficient ('gray')
Exposure Quality	Well-characterized and appropriate inhalation exposure conditions (See methods in Section 2.3.1, applied consistently across experimental studies; see documentation in Appendix B.3.1)	• "Good" Exposure Quality [Note: for POE endpoints such as this, methanol co-exposure was not a major concern]	• "Adequate" Exposure Quality or "Deficient" Exposure Quality if the driver of the domain rating was use of formalin (i.e., this was not considered a critical deficiency for this POE effect)	• "Deficient" Exposure Quality not based on use of formalin as the test article [Note: interpretation of the exposure levels is discussed in the hazard synthesis and is not, on its own, a reason for deficient]
Test Subjects	Sample size provides reasonable power to assess endpoint(s) in question; species, strain, sex, and age relevant to endpoint; no overt systemic toxicity noted or expected; allocations can be inferred as appropriate	• Based on OECD TG 452 and TG 413, chronic study: N ≥ 20; subchronic: N ≥ 10 (note: for this outcome, testing only one sex not a limitation) • Details on test subjects reported • Randomization preferred (but not required)	• Small N (N= >3 to <10 in subchronic study; N= >3 to <20 in chronic study) • Individual less essential test subject details (e.g., sex) unclear	• Inadequate N (N ≤ 3) • Multiple less essential study details (e.g., sex, strain) unclear • Individual essential study detail (e.g., species) unclear
Study Design	The design of the experiment is appropriate, reproducible, and sensitive for the endpoints of interest	• Study design, including exposure duration and timing of exposure and endpoint evaluation, are considered informative, discerning, and appropriate.	• Components of the study protocol were unclear or insufficiently assessed. • Limited sensitivity of exposure timing or duration	• Study design could not be evaluated or had critical flaws (e.g., timing or duration or exposure likely to compromise the integrity of the findings)
Endpoint Evaluation	The protocols used to assess the outcome are sensitive, complete, discriminating (specific), and biologically sound (reliable); experimenter bias minimized	• Adequate use and reporting of discerning endpoint protocols, including blinding • No potential confounding identified	• Limitation in conduct of evaluations (e.g., no lesion severity; limited sampling; lack of blinding) • Other uncontrolled variables unrelated to exposure quality may affect results	• Uncontrolled variables are expected to confound the results • Lack of reporting lesion incidence and severity • Multiple additive limitations

Evaluation domain	Overview of preferred study features	Primary criteria for domain ratings (Documentation shorthand used in Appendix B.3.5)		
		Good ('++')	Adequate ('+')	Deficient ('gray')
Data considerations and statistics	Statistical methods are presented, group comparisons and data/variability presentation are appropriate and discerning	• Adequate reporting and presentation of results • No evidence of selective reporting • Statistical methods described	• Failure to report statistical analyses • Concern regarding selective reporting • Concern with presentation of results (e.g., pooling of lesions)	• Failure to report enough data to interpret reported findings • Multiple limitations

2.3.6. Study Evaluation Criteria for Mechanistic Information Related to Noncancer Respiratory Effects, Focusing on Inflammation and Immune Effects

Study Evaluations

Because many relevant articles (mostly experimental studies with multiple, relevant endpoints) were considered in this analysis, a method was developed to distinguish the experiments likely to provide the most useful information from those providing less informative data or a comparably negligible amount of information. Individual mechanistic studies were evaluated using basic screening-level criteria (see Table 2-31) for each relevant endpoint or group of related endpoints (e.g., hematological parameters) assessed by the study authors; thus, a study may be evaluated multiple times. Expert judgment of the totality of the potential limitations was used to determine a final level of confidence in the utility of the study results, with the reasoning documented. In some instances, notation is included regarding the sensitivity of the methods and whether they can provide information with direct relevance to interpreting cellular, structural, or functional changes related to potential respiratory system health effects. Although this information was not used in study evaluations, it was considered when developing the synthesis.

The study evaluation decision criteria were different for observational epidemiology studies and experimental studies, although all criteria emphasized exposure-related considerations. The intent of the criteria applied, and the purpose of this mechanistic evaluation, was to focus on potential mechanisms associated with constant, chronic inhalation exposure to formaldehyde. Some studies of other effects that might be related to respiratory health effects have been evaluated in other sections of the Appendix and support evaluations of potential respiratory hazards; these evaluations informed the interpretation of overlapping studies presented in this section, as well as in the MOA analyses presented in the toxicological review. Studies of cellular proliferation, mucociliary function, and genotoxicity were separately reviewed, with the relevant conclusions directly incorporated into the MOA analyses described in the Toxicological Review. The application of the decision criteria to the identified mechanistic studies is presented in Appendix B.3.6. Interpretations of the usefulness of the individual mechanistic studies for evaluating the effect(s) in question were drawn based on the results of applying the decision criteria. Specifically, regarding

the mechanistic studies related to potential noncancer respiratory effects (focusing on immune and inflammatory changes), given the large number of studies identified, individual experiments were characterized as *high or medium confidence*, *low confidence*, or *not informative*. These evaluations emphasized exposure-related considerations and were designed to identify the mechanistic data most likely to be associated with constant, chronic inhalation exposure to formaldehyde (see Appendix B.3.6 for additional details). These interpretations were *high or medium confidence*—experiments considered very useful for describing potential formaldehyde inhalation-induced effects (since both medium and high confidence studies were considered well conducted, additional criteria were not applied to distinguish one from the other). In contrast, *low confidence* experiments might provide useful information, but should be considered in the context of other available data. *Not informative* studies were interpreted as providing negligible information regarding the potential for formaldehyde inhalation to cause the effect(s) of interest and were ultimately not included in the mechanistic analyses, given the identified limitations and the large number of available studies. Note that studies evaluating tissues interpreted as unlikely to be contributing to respiratory health effects (e.g., liver) are included in Appendix B.3.6, but are not included in the MOA analyses presented in the Toxicological Review or the systematic evidence map; the relative importance and ultimate decision to not include such information in the mechanistic analyses may change if the conclusion regarding their lack of relevance to respiratory health effects were to change with additional, future research.

Table 2-31 describes the criteria used for the domain ratings informing the confidence classifications for mechanistic studies relevant to potential noncancer respiratory effects.

Table 2-31. Decision considerations for the evaluation of mechanistic studies relevant to potential noncancer respiratory effects

Observational studies preferences	Experimental studies (human or animal, controlled exposure) preferences
Generally, studies were considered *low* confidence if they had multiple (2 or more) unmet preferences and *not informative* if the majority of preferences were not met:	**Generally, studies were considered *low* confidence if they had multiple (2 or more) unmet preferences and *not informative* if the majority of preferences were not met:**
Exposure duration • duration ≥5 d (acute exposures noted) • daily exposures of several hours	*System* • in vivo with nose-only or whole-body inhalation exposure
Exposure levels • inhaled concentration accurately quantified in exposed group • use of an appropriate referent group • exposure contrast expected to allow for detection of differences across groups	*Test article* • explicit use of paraformaldehyde (PFA) or methanol-free preparations of formaldehyde; note: experiments of non-URT tissues/models (including lung) were automatically "low confidence" if this preference was not met)
Comparability	*Exposure paradigm* • duration of ≥5 d (acute exposures noted)

Observational studies preferences	Experimental studies (human or animal, controlled exposure) preferences
• endpoint result comparisons can discern effects of formaldehyde exposure alone (e.g., controlling for co-exposures, blinding)	• periodicity of ≥5 hrs/d and ≥5 d/week (if ≥1 d)
Sample size • >10 persons/ group to (theoretically) reduce variability	*Exposure levels* • inhaled concentration was quantified (as ppm, mg/L or mg/m^3) • at least one tested exposure level of ≤3 mg/m^3 (Note: studies only testing above 10 mg/m^3 were considered "excessive")
Reporting • clear description of methods • detailed, quantitative reporting of results	*Comparability* • endpoint result comparisons can discern effects of formaldehyde exposure alone (e.g., controlling for other experimental manipulations, including chamber air exposure).
	Sample size • >10 humans or >5 animals/ group to (theoretically) reduce variability
	Reporting • clear description of methods • detailed, quantitative reporting of results

Specific Evaluation and Summary of URT mucociliary function and cellular proliferation

Studies examining the potential effects of formaldehyde exposure on mucociliary function and cell proliferation were considered for use in identifying potential hazards associated with respiratory tract pathology effects but were ultimately determined to be most useful as mechanistic evidence describing the potential progression of effects on structures within the URT that might lead to more apical effects (e.g., squamous metaplasia). In contrast to the other mechanistic studies described in this section, these observational human studies and experimental animal studies were individually evaluated according to the criteria laid out for human and animal apical endpoint (i.e., hazard) studies described in Appendix B.3.6, noting that the decisions for the specific endpoints considered in this section can differ when interpretations of the reliability of the methods differed from those of the more apical endpoints. Thus, studies were judged as *high*, *medium*, or *low confidence*, or as "not informative" (i.e., not discussed).

2.3.7. Nervous System Effects Study Evaluation Criteria

The literature searches (see Section 2.2.7) identified observational epidemiology studies of neurobehavioral effects and of risk of amyotrophic lateral sclerosis (ALS), controlled human exposure studies of neurobehavioral effects, and experimental animal inhalation exposure studies examining a variety of endpoints (e.g., learning and memory; motor activity, habituation, and anxiety; neuropathology). The specific criteria for evaluation are described below.

Human Observational Epidemiology Studies

Amyotrophic lateral sclerosis is a rare neurodegenerative disorder of the motor neurons with an incidence in Western countries of 1–2 per 100,000 person-years (Ingre et al., 2015). Three of the studies of ALS evaluated ALS mortality; analysis of mortality rather than incidence was not considered to be a limitation. Because the 5-year survival rate is low, mortality studies of ALS provide a good estimate for incidence of this disease. Because the disease is rare, the precision of risk estimates reported by these studies is a major limitation; for most of the studies, the number of exposed cases for the case-control studies or total cases ascertained for the cohort studies was small. Established risk factors that should be considered as potential confounders are age, and sex. Smoking also has been associated with ALS in multiple studies. Family history is also a risk factor but would not likely be associated with formaldehyde exposure; therefore, controlling for family history was not considered essential. While potential misclassification of exposure was another limitation for all of the studies, this was a particular concern for the general population studies, which collected exposure information using questionnaires (Weisskopf et al., 2009; Fang et al., 2009) or job-exposure matrices based on industry or occupation (Seals et al., 2017; Roberts et al., 2015; Peters et al., 2017). Fang et al. (2009) used a more detailed evaluation of exposure level and duration based on a structured occupational questionnaire and classification by industrial hygienists. Peters et al. (2017) and Seals et al. (2017) assigned individuals to exposure categories using the Nordic Occupational Cancer Study job exposure matrix which contained formaldehyde concentration data specific to either Sweden or Denmark; data on occupations over time were obtained from national censuses in Sweden (Peters et al., 2017) or the National Pension Fund in Demark (Seals et al., 2017). Roberts et al. (2015) used data from the National Longitudinal Study in the United States, which obtained information via a survey on the most recent occupation at the time subjects were enrolled; information on later occupations during follow-up was not captured.

Table 2-32 describes the criteria used for the domain ratings informing the confidence classifications for epidemiology studies of nervous system effects.

Table 2-32. Criteria for rating domains in epidemiology studies of nervous system effects

Evaluation domain	Primary criteria for domain ratings		
	Good	**Adequate**	**Deficient**
Population (SB)	**General population:** Participant selection based on population-based sampling frame with high participation rate. **Case-control:** Selection from same source population **Occupational settings:** Cohort studies uncompromised by loss-to-follow up.	Uncertainty regarding participant recruitment process or participation rate.	**General population:** Participant selection based on exposure status. **Occupational settings:** Recruitment process or self-selection likely to lead to inflated effect estimate.

Evaluation domain	Primary criteria for domain ratings		
	Good	**Adequate**	**Deficient**
Exposure (IB)	**ALS Case-Control (occupational settings):** Long-term and short-term job history with industry, occupation and task details allowing for independent assessment of exposure potential. Use of a validated job-exposure matrix (JEM). **ALS Cohort studies**: Long-term and short-term job history with industry, occupation and task details allowing for independent assessment of exposure potential supported by formaldehyde monitoring data. **Etiologically relevant time window (ALS):** Previous 20 years prior to diagnosis and design that excludes prevalent cases. **Neurobehavior (occupational settings):** Ability to differentiate between exposed and unexposed, or between low and high exposure. Exposure assessment specific to formaldehyde exposures and using some concentration measurements; includes assessment of intensity and frequency (for example, job exposure matrix). **Relevant time window (neurobehavior):** Period prior to health assessment	**Cohort studies:** Job history with industry and occupation, although task-level details not available, and job histories may not be complete. Use of a validated JEM. **ALS Case-Control (occupational settings):** Job history with industry and occupation, although task-level details not available, and job histories may not be complete. Use of a validated JEM. **Neurobehavior (occupational settings):** Ability to differentiate between exposed and unexposed, or between low and high exposure but greater possibility of misclassification (e.g., exposure definition not informed by measurements or job exposure matrix not validated for population). Referent group may be exposed to formaldehyde or to other exposures affecting respiratory conditions (potentially leading to attenuated risk estimates)	**General population**: Short (<1 d) exposure measurement period without discussion of protocol - quality control assessment. **ALS Case-Control (occupational settings):** Exposure definition includes group with large variation in probability or intensity of exposure with likely attenuation of results; Exposure definition based only on industry/occupation codes or other exposure ascertainment with potential to include high numbers of nonexposed or inadequate sensitivity (e.g. "ever-never exposed; use of open-ended question regarding occupational exposures. **Neurobehavior (all settings):** Large percentage (e.g. 50% or higher) of measures < LOD, or other ways in which exposure range does not allow analysis of risks above 0.010 mg/m^3; small exposure contrast between exposure groups limits ability to detect differences.
Outcome (IB)	**ALS:** Incidence or mortality; ICD-7 356.1, ICD-8 348.0, ICD-9 335.2, ICD-10 G12.2. Source of cases from national registries or hospital-based diagnoses by specialists in motor neuron disease. Deaths from death certificates or National Death Index. **Neurobehavior:** Standardized neurobehavioral test battery administered by trained technician.	**ALS:** Outcome ascertainment same as for high. **Neurobehavior:** Incomplete test battery	**Neurobehavior:** Instrument or methods for data collection not described. Symptoms reported with knowledge of exposure status.

Evaluation domain	Primary criteria for domain ratings		
	Good	**Adequate**	**Deficient**
Confounding (Cf)	Confounding considered and addressed in design or analysis. Primary potential confounders for ALS were age, gender, smoking, and respiratory exposures associated with the outcomes that were correlated with formaldehyde. Primary potential confounders for neurobehavior outcomes were age, gender and education.	Confounding considered and addressed in design or analysis but some questions regarding degree of correlation between formaldehyde and other exposures associated with ALS or neurobehavior may remain.	High likelihood of confounding that makes it unable to differentiate effect of formaldehyde from effect of other exposure(s),
Analysis and Other	Analysis allows for examination of variation in effect in relation to variation in exposure level using analytic procedures that are suitable for the type of data.	Sample size limited in stratified analyses.	Limited data analysis (or analysis that is not appropriate for the data) or small overall sample size increased potential for unreliable results.

Controlled Exposure Studies in Humans

Controlled exposure studies in humans were evaluated as described for sensory irritation endpoints in Section 2.3.2. In addition to the general considerations for study evaluation, the controlled human exposure studies that assessed a battery of neurobehavioral tests were evaluated with respect to the completeness and appropriateness of the battery of tests used, and the timing of their administration with respect to exposure as noted for epidemiology studies except they included consideration of the potential for irritant responses to influence behaviors due to concurrent or near-concurrent exposures, as discussed for animal studies below.

Studies in Animals

Evaluations of animal studies of nervous system effects only encompass studies reporting results following in vivo inhalation exposures. Noninhalation exposures are expected to involve significant distribution of formaldehyde beyond the portal of entry (which is not observed to an appreciable extent following inhalation exposure), and thus were not considered to be informative to the evidence synthesis. In vitro studies were similarly excluded from this analysis.

In addition to the general criteria discussed in Section 2.3.1, considerations specific to the evaluation of potential nervous system effects were also evaluated. Due to the known neurotoxicity hazard of methanol, studies failing to use an appropriate test article were automatically assigned *low confidence* and, to avoid confusion with methanol's effects, if they evaluated high exposure levels (defined here as relying only on exposures > 10 mg/m^3) they were deemed to be *not informative*. Additional criteria included: consideration of the potential influence of irritation or changes in olfaction on behavioral measures (e.g., exposure during behavioral training was considered a limitation; a preference was given to behavioral studies with a period of latency between exposure and endpoint testing of 24 hours, or 2 hours at a minimum); blinding of the

outcome assessors was preferred for subjective measures (e.g., slide evaluation; behavioral observations; etc.), although this was not necessarily considered a limitation for automated measures; a sample size of n = 10/group was preferred; methods include a description of and a preference for endpoint evaluation procedures that are sensitive and specific for the detection of potential nervous system effects (see Table 2-33 for additional details). Although studies with a longer exposure duration were most relevant to interpreting the lifetime neurotoxicity hazard of inhaled formaldehyde, nervous system effects studies of short term or even acute duration were not automatically considered to be less informative (i.e., exposure duration < 28 days was indicated as a minor limitation). This is somewhat in contrast to the interpretation of animal studies in other sections (e.g., respiratory tract pathology), and this reflects an understanding that neurotoxic effects from very brief exposures can oftentimes represent important health concerns.

Table 2-33 describes the criteria used for the domain ratings informing the confidence classifications for animal studies of nervous system effects.

Table 2-33. Criteria for domain ratings in animal studies of nervous system effects

Evaluation domain	Overview of preferred study features	Primary criteria for domain ratings (Documentation shorthand used in Appendix B.3.7)		
		Good ('++')	Adequate ('+')	Deficient ('gray')
Exposure quality	Well-characterized and appropriate inhalation exposure conditions (See methods in Section 2.3.1, documentation in Appendix B.3.1)	• "Good" Exposure Quality [Note: for non-POE endpoints such as this, methanol co-exposure is a major concern]	• "Adequate" Exposure Quality	• "Deficient" Exposure Quality [Note: interpretation of the tested exposure levels is discussed in the hazard synthesis]
Test subjects	The species, sex, strain, and age are appropriate for the endpoint(s); sample size provides reasonable power to assess the endpoint(s); overt systemic toxicity is absent or not expected, or it is accounted for; group allocations can be inferred as appropriate	• Details on test subjects reported • No toxicity observed or expected • Randomization preferred (but not required) • N ≥ 10	• Small N (e.g., N= >3 to <10) • Individual less essential test subject details (e.g., sex) unclear • Examination of only one sex	• Inadequate N ≤ 3 • Multiple less essential study details (e.g., sex, strain) unclear • Individual essential study detail (e.g., species) unclear • Allocations viewed as inappropriate • Overt systemic toxicity
Study design	A study focus was nervous system effects; the exposure regimen is	• Study design, including exposure duration and timing of exposure	• Limited sensitivity of exposure timing or duration	• Behaviors tested during or shortly after exposure

Evaluation domain	Overview of preferred study features	Primary criteria for domain ratings (Documentation shorthand used in Appendix B.3.7)		
		Good ('++')	**Adequate ('+')**	**Deficient ('gray')**
	informative for the tested endpoint; latency from exposure to testing reduces the potential for irritation-driven responses Note: No guideline or GLP studies were identified	and endpoint evaluation, are considered informative, discerning, and appropriate.	• Unclear if potential confounding variables were introduced	(irritant effects likely) • Lack of control for litter effects in developmental study designs • Other confounding likely due to design
Endpoint evaluation	The protocols used to assess the nervous system effects are sensitive for detecting an effect, complete, discriminating (i.e., specific for the response in question), and biologically sound; experimenter and sampling bias minimized	• Adequate use and reporting of discerning endpoint protocols, including blinding	• Limited evaluations • Incomplete reporting of methods	• Lack of essential blinding • Only cursory observations • Multiple additive limitations • Critical methodological details missing
Data considerations and statistics	Statistical methods are reported, group comparisons and data presentation (including variability) are complete, appropriate, and discerning; selective reporting bias avoided	• Adequate reporting and presentation of results • No evidence of selective reporting • Statistical methods described	• Failure to report statistical analyses • Concern regarding selective reporting • Concern with presentation of results (e.g., no reporting of motor activity in learning and memory tests)	• Failure to report a sufficient amount of data to interpret reported findings • Multiple limitations

Studies Specific to Mechanistic Considerations Only

In vivo inhalation studies examining mechanistic events related to nervous system effects were systematically evaluated to inform biological plausibility. Although parallel criteria to those used to evaluate studies describing potential neurotoxicity health effects (see above) were used to judge the mechanistic studies, the stringency of some criteria were adapted to accommodate this type of information and additional leniency was applied for certain parameters (e.g., acute exposure was not considered a limitation).

2.3.8. Developmental and Reproductive Toxicity Study Evaluation Criteria

The literature searches (see Section 2.2.8) identified observational epidemiology and experimental animal studies relevant to developmental and reproductive toxicity. The specific criteria for evaluation are described below, with the documentation of the application of these criteria to individual studies provided in Appendix B.3.8.

Human Studies

Participant Selection

A key consideration with respect to occupational studies of spontaneous abortion or time to pregnancy is the potential for selection bias if participants are recruited from current employees (Axelsson, 1984) (Slama et al., 2014; Baird et al., 1986). Another potential bias may result from which pregnancy (first, pregnancy during defined time period, most recent) is selected as the index pregnancy in studies of spontaneous abortion. Studies that focus on the most recent pregnancy may be less sensitive due to time-lapse bias. The time between a pregnancy ending in spontaneous abortion and a subsequent pregnancy ending in a live birth is often shorter than two pregnancies, both ending in live births. This can result in a bias toward identifying live births as the most recent pregnancy (Wilcox, 2010).

Outcome ascertainment

The validity of retrospectively collected self-completed questionnaire data on time-to-pregnancy (TTP) closely reproduced the distributions of TTP in the group using a different data source (e.g., data collected during annual follow-up of a family planning cohort), even over recall durations greater than 14 years (Joffe et al., 1995). In addition, subfertility, defined as a TTP greater than 12 months using the questionnaire data, was identified with high sensitivity (79.9%) and specificity (94.9%) (Joffe et al., 1993). However, individuals recalled the number of months before conception with greater error, and these errors increased as the duration of time-to-pregnancy increased. Longer TTP was both over- and under-estimated (Joffe et al., 1995; Cooney et al., 2009). Therefore, while individual estimates of TTP may be less precise, the comparison of group means with respect to levels of formaldehyde exposure is likely to be informative. Validity studies indicate that recall of previous spontaneous abortions is relatively complete, particularly for losses that occurred after the 8th week of gestation (> 80% of recorded spontaneous abortions were recalled) (Wilcox and Horney, 1984). Completeness varies by occupation; completeness of recall among nurses was better than that among industrial workers (Lindbohm and Hemminki, 1988; Axelsson and Rylander, 1982). Although elapsed time since the event occurred may also influence the completeness of recall, this also varied by occupation in a similar way (not important among nurses) and was not important within the first 10 years after the event (Wilcox and Horney, 1984; Lindbohm and Hemminki, 1988). It is difficult to evaluate the validity of self-reports of spontaneous abortion occurring during the 1st trimester using medical records because these early events often

are not recognized or do not require medical intervention; medical records may not necessarily be an accurate reference (Slama et al., 2014; Lindbohm and Hemminki, 1988).

The criteria that were used for the domain ratings informing the confidence classifications for epidemiology studies of reproductive and developmental effects are included in Table 2-34.

Table 2-34. Criteria for domain ratings in epidemiology studies of reproductive and developmental effects

Evaluation domain	Primary criteria for domain ratings		
	Good	**Adequate**	**Deficient**
Population (SB)	**General population** *For time-to-pregnancy*: Birth cohort participants enrolled prior to or within first weeks of pregnancy. High participation rate. *For birth outcomes*: Birth cohort participants enrolled within first weeks of pregnancy. High participation rate. **Occupational settings** *For time-to-pregnancy*: Recruitment from registries, occupational payroll, or union records. High participation rate. *For spontaneous abortion or birth outcomes*: Cases and controls selected from same source. Controls selected from working population or during periods of employment. Case definition was first pregnancy or all pregnancies occurring during study period.	**General population** *For time-to-pregnancy*: Birth cohort participants enrolled after 1st trimester of pregnancy; hospital-based cohort. **Occupational settings** Case definition was most recent pregnancy (decreased sensitivity) **All settings**: Uncertainty regarding participant recruitment process or participation rate.	**General population**: Participant selection based on exposure status. **Occupational settings**: Recruitment process or self-selection likely to lead to inflated effect estimate.
Exposure (IB)	**General population**: Exposure measure based on at least 3-d sample; measures in more than one season if time window covers 12 mos or addressed season in the analysis. **Occupational settings**: Ability to differentiate between exposed and unexposed, or between low and high exposure. Exposure assessment specific to formaldehyde exposures and using some concentration measurements; includes assessment of intensity and frequency (for example, job exposure matrix).	**General population:** More limited exposure assessment (e.g., < 1 d) with details regarding measurement protocol provided. **Occupational settings**: Ability to differentiate between exposed and unexposed, or between low and high exposure but greater possibility of misclassification (for example, exposure definition not informed by measurements or job exposure matrix not validated for population).	**General population**: More limited exposure assessment (e.g., < 1 d) and no details regarding measurement protocol provided. **Occupational settings**: Exposure definition includes group with large variation in probability or intensity of exposure with likely attenuation of results; Exposure definition based only on industry/occupation codes or other exposure ascertainment with potential to include high numbers of nonexposed or inadequate sensitivity (e.g., use of open-ended question

Evaluation domain	Primary criteria for domain ratings		
	Good	**Adequate**	**Deficient**
	Etiologically relevant time window (all settings): **Time to pregnancy**: Period prior to or during pregnancy attempt. **Spontaneous abortion**: Preconception and during 1st trimester. **Period of spermatogenesis** (paternal exposure) **Other birth outcomes**: Exposure during pregnancy.	Referent group may be exposed to formaldehyde or to other exposures affecting respiratory conditions (potentially leading to attenuated risk estimates) **All settings**: Uncertainty regarding correspondence between measured levels and levels in the etiologically relevant time window.	regarding occupational exposures.) **All settings**: Large proportion (>50%) less than the LOD for analyses of continuous exposures or other ways in which exposure range does not allow analysis of risks above 0.010 mg/m^3; small exposure contrast between exposure groups limits ability to detect differences.
Outcome (IB):	**Time-to-pregnancy**: Based on interview/questionnaire among birth cohort during study period. **Spontaneous abortion**: Self-report with or without verification using hospital records. **Birth outcomes**: Gestational age, birth weight, birth length, head circumference obtained from birth records. Other methods with high sensitivity and specificity validated in target population. Birth defects reported in registry.	**Time-to-pregnancy**: Recall based on interview/ questionnaire. **Spontaneous abortion**: Hospital discharge records. Exclusion criteria potentially resulted in missing events (for example, pregnancies identified from birth register). **Birth outcomes**: Gestational age, birth weight, birth length, head circumference obtained from birth records. Other methods with high sensitivity and specificity, but not validated in target population.	**All endpoints:** No information about source of or methods for outcome ascertainment.
Confounding (Cf)	Confounding considered and addressed in design or analysis. Primary potential confounders were maternal age, smoking, and exposures associated with TTP or spontaneous abortion that were correlated with formaldehyde.	Confounding considered and addressed in design or analysis but some questions regarding degree of correlation between formaldehyde and other exposures associated with TTP or spontaneous abortion may remain. Adjustment for pregnancy history is considered to be a limitation.	High likelihood of confounding that makes it unable to differentiate effect of formaldehyde from effect of other exposure(s).
Analysis and Other (Oth)	Analysis allows for examination of variation in effect in relation to variation in exposure level using	Sample size limited in stratified analyses.	Limited data analysis (or analysis that is not appropriate for the data) or small overall

Evaluation domain	Primary criteria for domain ratings		
	Good	Adequate	Deficient
	analytic procedures that are suitable for the type of data.		sample size increased potential for unreliable results.

Animal Studies

Only in vivo inhalation exposure studies are used for hazard identification and dose-response assessment. These studies were conducted in inhalation chambers under controlled experimental conditions. Studies that exposed animals to formaldehyde via other routes or in vitro were not included because they are expected to result in significant distribution of formaldehyde past the portal of entry, which does not occur to an appreciable extent with inhalation exposures.

A key consideration for the interpretation of developmental and reproductive outcomes associated with inhalation exposures to formaldehyde in experimental studies was the potential for co-exposure to methanol, a known developmental and reproductive toxicant (U.S. EPA, 2013), when the test article was an aqueous solution of formaldehyde. Such studies were automatically assigned a *low* confidence classification (or *not informative* if additional study limitations were identified) and contributed little to the synthesis of evidence regarding formaldehyde effects on development or the reproductive system.

In addition to the general criteria discussed in Section 2.3.1, considerations specific to the evaluation of potential developmental or reproductive system effects are described in Table 2-35.

Table 2-35. Criteria for domain ratings in animal studies of developmental and reproductive effects

Evaluation domain	Overview of preferred study features	Primary criteria for domain ratings (Documentation shorthand used in Appendix B.3.7)		
		Good ('++')	Adequate ('+')	Deficient ('gray')
Exposure Quality	Well-characterized and appropriate inhalation exposure conditions (See methods in Section 2.3.1, documentation in Appendix B.3.1)	• "Good" Exposure Quality [Note: for non-POE endpoints such as this, methanol co-exposure is a major concern]	• "Adequate" Exposure Quality	• "Deficient" Exposure Quality [Note: interpretation of the tested exposure levels is discussed in the hazard synthesis]
Test Subjects	Sample size provides reasonable power to assess endpoint(s) in question; species, strain, sex, and age are appropriate for the endpoint; overt systemic toxicity not noted or expected; group allocations can	• Details on test subjects reported and appropriate • No toxicity observed or expected • Randomization preferred (but not required)	• Small N (e.g., N= >3 to <10) • Individual less essential test subject details (e.g., sex) unclear • Examination of only one sex • Potential concern for species, strain,	• Inadequate N ≤ 3 • Multiple less essential study details (e.g., sex, strain) unclear • Individual essential study detail (e.g., species) unclear • Allocations viewed as inappropriate

Evaluation domain	Overview of preferred study features	Primary criteria for domain ratings (Documentation shorthand used in Appendix B.3.7)		
		Good ('++')	**Adequate ('+')**	**Deficient ('gray')**
	be inferred as appropriate	• N ≥ 10 (preferably at least 20 dams/group, consistent with standard guideline developmental and reproductive toxicity studies)	or lifestage-related differences in reproductive schedules and outcome sensitivity • Study did not clearly evaluate toxicity (e.g., maternal) or it is a potential concern	• Evidence for a major concern with test subject insensitivity • Overt systemic toxicity expected to be a driver of effects
Study Design	A study focus was developmental or reproductive system effects; the exposure regimen is informative for the tested endpoint(s); manipulations other than formaldehyde exposure are adequately controlled	• Study design, including exposure duration and timing of exposure and endpoint evaluation, are considered informative, discerning, and appropriate.	• Components of the study design were unclear or insufficient. • Limited sensitivity of exposure timing or duration • Design of study is limited, not examining a wide range of potential effects	• Study design could not be evaluated or had critical flaws (e.g., timing or duration or exposure likely to compromise the integrity of the findings)
Endpoint Evaluation	The protocols used to assess the endpoint(s) are sensitive, complete, discriminating (specific), and biologically sound (reliable); experimenter bias minimized	• Adequate use and reporting of discerning endpoint protocols, including blinding • No potential confounding identified	• Limitation in conduct of evaluations (e.g., limited sampling; lack of blinding) • Other uncontrolled variables unrelated to exposure quality may affect results	• Uncontrolled variables are expected to confound the results • Multiple additive limitations
Data considerations and statistics	Statistical methods are reported, group comparisons and data/variability presentation are appropriate and discerning; selective reporting bias avoided	• Adequate reporting and presentation of results • No evidence of selective reporting • Statistical methods described • For developmental studies, litter was the primary unit of analysis	• Failure to report statistical analyses • Concern regarding selective reporting • Concern with presentation of results (e.g., pooling of lesions)	• Failure to report a sufficient amount of data to interpret reported findings • Multiple limitations • Significant concern for litter bias

2.3.9. Carcinogenicity Study Evaluation Criteria

The literature searches (see Section 2.2.9) identified observational epidemiology and experimental animal studies relevant to cancer. The specific criteria for evaluation are described below, with the documentation of the application of these criteria to individual studies provided in Appendix B.3.9.

Cancer Studies in Humans

The focus of EPA's examination is on several specific types of upper respiratory tract (URT) and lymphohematopoietic (LHP) cancer. The evaluation of LHP cancers includes four different subtypes: myeloid leukemia (including monocytic leukemia), lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma. Among upper respiratory cancers, four different types are reviewed: sinonasal (SNC), nasopharyngeal cancer (NPC), oro/hypopharyngeal cancer (OHPC), and laryngeal cancer.

Evaluation of Observational Epidemiology Studies of Cancer

The epidemiology studies examined occupational exposure to formaldehyde either in specific work settings (e.g., cohort studies) or in case-control studies. The considerations with respect to design, exposure assessment, outcome assessment, confounding and analysis differ for these different types of studies and are discussed in more detail below.

Each study identified by the literature search as potentially relevant to inform the causal evaluation of whether formaldehyde exposure causes cancer was evaluated and classified for the study's ability to inform a hazard conclusion for a particular cancer outcome. Study evaluation encompasses interpretations regarding a variety of methodological features (e.g., study design, exposure measurement details, study execution, data analysis). Developing an outcome-specific study evaluation for each cancer outcome encompasses two concepts: minimization or control of bias (internal validity), and sensitivity/appropriateness (the ability of the study to detect a true effect). The purpose of this step is not to eliminate studies, but rather to evaluate studies with respect to potential methodological considerations that could affect the interpretation of or confidence in the results.

1) Consideration of participant selection and comparability

- Whether there is evidence of selection into or out of the study (or analysis sample) that was jointly related to exposure and to outcome.

  For cohort studies, EPA considered the extent of follow-up, and the likelihood that completeness of follow-up was related to exposure level. Most of the cohort studies examining mortality data reported high rates of follow-up with respect to ascertainment of vital status and ascertainment of cause of death (90–95% or higher); in some cases, the latter figure (i.e., percentage of decedents with death certificates) was not provided by the study authors. Two studies were able to obtain only 79% (Hayes et al., 1990) or

75% (Walrath and Fraumeni, 1984) of the identified death certificates but as both studies were of embalmers who were all considered to have been exposed to formaldehyde, the absence of data (missingness) was considered to have been random.

For case-control studies, controls are optimally selected to represent the population from which the cases were drawn (e.g., similar geographic area, socioeconomic status, and time period). A variety of methods were used in the identified studies, including random digit dialing and use of population registries. The interest and motivation to participate is generally higher for cases than for controls, particularly in population-based settings. A low participation rate of either or both groups does not in itself indicate the occurrence of selection bias; a biased risk estimate is produced if exposure and disease are jointly related to participation rates, but not if either is independent of participation rates. For example, a bias is not necessarily produced if cases are more likely to participate than controls; a bias can be produced, however, if cases with high exposure are more likely to participate than cases with low exposure. Most of the case-control studies were conducted using incident (or recently diagnosed) cases, with participation rates ranging from approximately 75% to 99%. Participation among population-based controls generally ranged from 75% to 85%, with higher rates seen in some studies using hospital-based designs. Differences in participation rates between case and controls potentially related to exposure were considered more prone to bias (Beane Freeman et al., 2013). Certain studies used cases' next of kin to ascertain the cases' occupational history from which the individual's exposure to formaldehyde was derived. The difference in methods for recruiting cases and controls creates a potential for selection bias and a potential for information bias when the accuracy of exposure histories differs between deceased cases and the controls (e.g., (Yang et al., 2005; Vaughan et al., 1986a, b; Vaughan, 1989)).

- An uncommon issue related to potential selection bias was the "healthy worker effect" in cohort studies where a working population is compared to that of the general public—a bias which can result in underestimates of any adverse effect of exposure. While this phenomenon is generally considered to be a stronger influence in evaluation of cardiovascular health endpoints, there is evidence that there can be a strong healthy worker effect in studies of cancer endpoints (Sont et al., 2001). In cohort studies, the potential for selection bias due to the healthy worker effect was assessed by examination of the all-cause cancer effect estimates; studies with estimates <90% of expected were judged to be potentially biased towards lower overall cancer occurrence and lower levels of cases detection resulting in underestimates of any true effect. Severe underestimates of <80% of expected cases were noted as well (e.g., (Wesseling et al., 1996; Stroup et al., 1986; Robinson et al., 1987; Matanoski, 1989; Levine et al., 1984b; Harrington and Oakes, 1984; Hall et al., 1991)).

- For some cancers, the reliance of cohort studies on death certificates to detect cancers with relatively high survival may have underestimated the actual incidence of those cancers, especially when the follow-up time may have been insufficient to capture all cancers that may have been related to exposure. The potential for bias may depend upon the specific survival rates for each cancer. Five-year survival rates vary among the selected cancers (Table 2-36), from 86% for Hodgkin lymphoma (HL) to less than 50% for multiple myeloma (MM), myeloid leukemia (ML), and oro/hypopharyngeal cancer. EPA considered the likelihood of underreporting of incident cases to be higher for mortality-based studies of HL and LL which may result in undercounting of incident cases and underestimates of effect

estimates compared to general populations (e.g., (Solet et al., 1989; Mayr et al., 2010; Hayes et al., 1990; Hansen et al., 1994; Hansen and Olsen, 1995)).

Table 2-36. Lymphohematopoietic and upper respiratory cancers: age-Adjusted SEER incidence and U.S. death rates and 5-year relative survival by primary cancer site[a]

Cancer site	Incidence rate (per 100,000) 2008–2012	Expected cases[b] 2014	Mortality rate (per 100,000)[c] 2008–2012	Expected deaths[d] 2014	5-Year survival (%) 2005–2011
Lymphohematopoietic Cancers					
Hodgkin lymphoma (HL)	2.7	8,336	0.4	1,235	85.9
Multiple myeloma (MM)	6.3	19,451	3.3	10,189	46.6
Lymphatic Leukemia (LL)	6.6	20,377	1.9	5,866	77.6
Acute lymphatic leukemia (ALL)	1.7	5,249	0.4	1,235	67.5
Chronic lymphatic leukemia (CLL)	4.5	13,894	1.4	4,322	81.7
Other	0.4	1,235	0.1	309	80.6
Myeloid & monocytic leukemia (ML)	6.1	18,833	3.4	10,497	37.5
Acute myeloid leukemia (AML)	4.0	12,350	2.8	8,645	25.9
Chronic myeloid leukemia (CML)	1.7	5,249	0.3	926	63.2
Acute monocytic	0.2	617	0.0	0	23.5
Other	0.2	617	0.2	617	33.2
Upper Respiratory Tract Cancers					
Nose, nasal, & middle ear[e]	0.7	2,161	0.1	309	55.3
Nasopharynx	0.6	1,852	0.2	617	59.6
Oropharynx	0.4	1,235	0.2	617	41.7
Hypopharynx	0.6	1,852	0.1	309	32.2
Larynx	3.2	9,880	1.1	3,396	60.6

[a]Incidence rates and 5-year survival from Surveillance, Epidemiology, and End Results (SEER), 18 areas. Results. [http://seer.cancer.gov/csr/1975_2012/results_merged/topic_survival.pdf], last accessed August 14, 2015.
[b]EPA calculated the expected number of cases based on incidence rates applied to U.S. census population estimate for 2014 of 308,745,538 (http://www.census.gov/search-results.html?q=2014+population&page=1&stateGeo=none&searchtype=web).
[c]U.S. Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention
[d]SEER 18 areas. Based on follow-up of patients into 2012.
[e]SEER does not publish specific data on sinonasal cancer which would be included in the published category labeled "Nose, nasal & middle ear."

2) The reliance of case-control studies on prevalent cases rather than incident cases.

In order to accrue a sufficiently large population of rare cancer cases, some studies may include cases which have been detected over a long period of time and thus include many prevalent cases at the time of analysis. Restriction to only living cases may lead to over-representation of cancer survivors or, if next of kin are used to provide proxy information on cases, the quality of that data may then differ between cases and controls which can be a concern if differences may be related to exposure. Hence, EPA considers that there is some risk of selection bias in studies examining prevalent cases (Yang et al., 2005; Vaughan et al., 1986a, b; Vaughan, 1989; Pesch et al., 2008; Mayr et al., 2010; Armstrong et al., 2000).

3) Evaluation of exposure assessment

At a minimum, exposure to formaldehyde may be inferred based on the specific occupations (e.g., carpenter, embalmer, pathologist) or industry (e.g., production or use of formaldehyde resins, wood-products, paper, textiles, foundries). Independent testing of various workplaces may provide approximate exposure measurements and ranges for inferred exposures. Details in each study may reveal the extent of exposure within occupational groups or at the individual-level based on job histories. Some studies may have documented formaldehyde exposures using exposure monitors or quantified the absolute or relative exposure for different tasks, which may be matched to individual occupational patterns using" job exposure matrices" or JEMs. The quality of the exposure measure is evaluated with respect to the accuracy of the measures and their related potential for exposure measurement error which can lead to "information bias." The overwhelming majority of information bias in epidemiologic studies of formaldehyde stems from the use of occupational records to gauge exposures with some degree of exposure misclassification or exposure measurement error considered to be commonplace.

A primary consideration in the evaluation of these studies is the ability of the exposure assessment to reliably distinguish among levels of exposure within the study population, or between the study population and the referent population. A large variety of occupations are included within the studies; some represent work settings with a high likelihood of exposure to high levels of formaldehyde, and some represent work settings with variable exposures and in which the proportion of people exposed is quite small. In the latter case, the potential effect of formaldehyde would be "diluted" within the larger study population, limiting the sensitivity or informative nature of the study. EPA categorized the exposure assessment methods of the identified studies into four groups (A through D), reflecting greater or lesser degree of reliability and sensitivity of the measures (see Table B-55).

For cohort studies and nested case-control studies within cohort studies, the category of Exposure Group A included studies in industrial settings with extensive industrial hygiene data used to determine levels of exposure (and variability within a worksite); and a job exposure matrix that accounts for variability by time and job/task. This category also included studies with highly exposed professions (embalmers) with comparison to the general population, or with measures capturing variability within the cohort. For case-control studies, the category of Exposure Group A included studies with detailed lifetime job history, more extensive than industry and occupation codes, including information about specific tasks and setting, combined with job exposure matrix that accounts for variability by time, setting, and job/task. Also includes some kind of validation study or congruence of ratings based on different exposure ascertainment measures to be equivalent to Group A cohort studies with extensive industrial hygiene data.

For cohort studies and nested case-control studies within cohort studies, the category of Exposure Group B included studies with industrial settings with more limited industrial hygiene data. This category also included studies with exposed professions (e.g., pathologists) with comparison to general population, but that do not have measures capturing variability within the

cohort. For case-control studies, the category of Exposure Group B included studies with detailed lifetime job history, more extensive than industry and occupation codes, including information about specific tasks and setting, combined with job exposure matrix that accounts for variability by time, setting, and job/task.

For cohort studies and nested case-control studies within cohort studies, the category of Exposure Group C included studies with industrial settings that are only able to use duration as a way to distinguish variability in exposure and studies with self-report of exposure. For case-control studies, the category of Exposure Group C included studies with lifetime job history coding based only on industry and occupation; more detailed information about specific tasks and setting not included in assessment of exposure potential (or, information on what was collected was not provided). This category also included studies with self-report of exposure; and, studies with lifetime job history, including tasks/exposure information, but analysis conducted only for job categories rather than for an exposure category.

For cohort studies and nested case-control studies within cohort studies, the category of Exposure Group D included studies industrial settings that do not include data to distinguish variability in exposure (e.g., wood workers, with no information on which workers were exposed to formaldehyde; textile workers with no formaldehyde exposure measures), or that include few people classified as exposed. For case-control studies, the category of Exposure Group C included studies with Job history limited to information on a single job (e.g., based on tax record, death certificate, medical record, census data). This category also included studies with a high proportion of next-of-kin interviews (>40%).

Outcome-specific association based on Group A exposures were consider without appreciable information bias due to exposure measurement error while those based on Groups B–D were considered to be somewhat biased towards the null. The categorization of the exposure assessment methods for the assessed studies are documented in Appendix B.3.9.

Additional exposure measurement error may arise in circumstances when the time period of exposure assessment is not well aligned with the time period when formaldehyde exposure could induce carcinogenesis that develops to a detectable stage (incident cancer) or result in death from a specific cancer. Epidemiology studies regularly explore the analytic impact of different lengths of 'latency periods' which may exclude from the analyses the formaldehyde exposure most proximal to each individual's cancer incidence or cancer mortality. For analyses of the exposure-related risks of solid tumors, it is commonplace to evaluate latency periods of 10, 15, or 20 years by presenting results stratified by time since first exposure or to exclude (or in the parlance of epidemiology, to "lag") exposures in the 10, 15, or 20 years immediately prior to death from the analyses so as to more accurately (potentially) describe what may be the more biologically relevant window of exposure in time that could have caused carcinogenesis (sometimes called the etiologically relevant time period). Analyses which do not evaluate latency may be inducing

exposure measurement error by including irrelevant exposure and were considered to be somewhat biased towards the null.

An understanding of the effects of exposure measurement error on the results from epidemiologic analyses is important as it enables the reviewer to place these possible exposure measurement errors in context. The effect of exposure measurement error on estimates of the risk of cancer mortality potentially attributable to formaldehyde exposure depends upon the degree to which that error itself may be related to the likelihood of the outcome of interest. Exposure measurement error that is similar among both workers who died of a specific cancer, and those who did not die of that cancer, is termed nondifferential exposure measurement error. Exposure measurement error that is associated with the outcome (error that is differential with respect to disease status) can cause bias in an effect estimate towards or away from the null, while nondifferential exposure error typically results in bias towards the null (Rothman and Greenland, 1998).

4) Outcome measure

The diagnosis of cancers in epidemiologic studies has historically been ascertained from death certificates according to the version of the International Classification of Diseases (ICD) in effect at the time of study subjects' deaths [i.e., ICD-8 and ICD-9: (WHO, 1967, 1977)]. The most specific classification of diagnoses that is commonly reported across the epidemiologic literature has been based on the first three digits of the ICD code (i.e., Myeloid Leukemia ICD-8/9: 205) without further differentiation (i.e., Acute Myeloid Leukemia ICD-8/9: 205.0)—although some studies have reported results at finer levels. In the evaluation of the epidemiologic evidence for upper respiratory cancers, four different types are reviewed: sinonasal cancer, nasopharyngeal cancer, oro/hypopharyngeal cancer, and laryngeal cancer. In the evaluation of the epidemiologic evidence for LHP cancers, four different subtypes are reviewed: myeloid leukemia (including monocytic leukemia), lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma. In restricting the causal evaluation of LHP cancers to these four specific subtypes, another category of LHP cancer originating from white blood cells, which includes all lymphoma not classified as Hodgkin, was not evaluated.

In the review of study quality for cancer studies, the outcome measure was generally considered to be accurate as the source of this information was typically from death certificates, cancer registries, or hospitals. Some studies did provide additional information on histological typing, but the majority did not. Histological type can be informative in understanding the epidemiologic evidence, but the lack of such information was not judged as a major study limitation. While it is true that death certificates and other administrative records can occasionally contain errors, the impact of misclassification of outcome on epidemiologic results is to reduce precision in effect estimates and not to induce bias.

5) Consideration of likely confounding

EPA evaluated the potential for confounding based on exposures to identified risk factors for specific, or related, cancers, whether those exposures were found to be risk factors in the specific study and whether there was a known or likely correlation between those exposures and formaldehyde. Information on the presence of potential confounders in a particular study was gleaned from the study itself or from information from outside the study (e.g., information on exposure levels from other sources).

Risk factors for LHP cancers include pharmaceuticals (chemotherapeutic drugs), biological agents (e.g., viruses), radiation, and chemical exposures (Cogliano et al., 2011). The primary agents of interest that were considered in the study quality review are the potential occupational and environmental co-exposures that may be associated with formaldehyde exposure as well as LHP cancers. Chemotherapeutic drug exposures were not expected to be correlated with formaldehyde exposures during the etiologically relevant time period for potentially formaldehyde-related carcinogenesis and were not considered as potential confounders. Similarly, viral exposures and radiation exposures also were not expected to be correlated with formaldehyde exposures except, possibly, among embalmers and pathologists who may be co-exposed by deceased persons who had viral infections or had implanted radiation devices used in chemotherapy. Each of the chemical and occupational exposures that were reported to be associated with risks of LHP cancers (i.e., benzene, 1,3-butadiene, 2,3,7,8-tetrachlorodibenzo-para-dioxin, ethylene oxide, magnetic fields, paint, petroleum refining, polychlorophenols, radioisotopes and fission decay products, styrene, tetrachloroethylene, tobacco smoking, trichloroethylene; (Cogliano et al., 2011) was examined in the study quality review and evaluated as a potential confounder of any association between formaldehyde and specific LHP cancers.

Risk factors for URT cancers include biological agents (e.g., viruses), radiation, and chemical exposures (Cogliano et al., 2011). As described above, viral exposures and radiation exposures also were not expected to be correlated with formaldehyde exposures except, possibly, among embalmers and pathologists who may be co-exposed by deceased persons who had viral infections or had implanted radiation devices used in chemotherapy. Each of the chemical and occupational exposures which were reported to be associated with risks of URT cancers (i.e., acid mists, asbestos, chromium VI, isopropyl alcohol production, leather dust, nickel compounds, radioisotopes and fission decay products, rubber production, textile manufacturing, tobacco smoking, and wood dust (Cogliano et al., 2011)) was examined in the study quality review and evaluated as a potential confounder of any association between formaldehyde and specific URT cancers.

The specific chemical and occupational exposures listed above, which were reported to be associated with LHP or URT cancers are bolded in the lists of co-exposures in each study in the Exposure Measure column of the study evaluation documentation tables in Appendix B.3.9. This identifies any important co-exposures which are then evaluated for their potential correlation with formaldehyde exposure to identify potential confounders.

6) Analysis and results (estimate and variability)

Analyses should be appropriate with respect to study design. When analytic methods are not matched to the study design, the expected impact on the results was evaluated. For cancer endpoints, results that examined the effects of including various latency periods using lagged exposure of strata of time since first exposure allow for the focus of results on different etiological windows of time that may be more biologically relevant. Studies that did not report results looking at different latencies may be vulnerable to additional exposure measurement error as they evaluate the effects of formaldehyde exposures during times that may not have any causal effects such as in the years immediately preceding death.

7) Study sensitivity

In addition to potential bias, study sensitivity was specifically evaluated; study results with low sensitivity could result in effect estimates that underestimated a "true" association if it existed. Cohort studies should have a sufficiently long follow-up period to allow for any exposure-related cancer cases to develop and be detected and, ideally, allow for analyses of potential cancer latency. Outcome-specific effect estimates from cohort studies with short follow-up could be considered uninformative depending on the size of the study population and the baseline frequency of the cancer. Studies with small cases counts may have little statistical power to detect divergences from the null but are not necessarily expected to be biased and no study is excluded solely on the basis of cases counts as this methodology would exclude any study which saw no effect of exposure. Therefore, cohort studies with extensive follow-up which reported outcome-specific results on a number of different cancers, including very rare cancers such as NPC and SNC, are evaluated even when few or even no cases were observed, if information on the expected number of cases in the study population was provided so that confidence intervals could be presented to show the statistical uncertainty in the associated effect estimated. For example, Coggon et al. (2014) followed the mortality of 14,008 workers and yet expected only 1.7 deaths from nasopharyngeal cancer in the exposed workers and observed just one resulting in an unstable estimated RR=0.38 (95% CI: 0.02–1.90). Meyers et al. (2013) followed the mortality of 11,043 workers and expected only 1.33 deaths from nasopharyngeal cancer and did not observe any deaths, resulting in a SMR=0 (95% CI: 0–2.77). These studies were included in the evidence syntheses, but the limitation relating to size and resulting sensitivity was noted.

Another example of low sensitivity would be a study that might have relied on exposure-assessment methodologies that were unbiased, but were nonspecific in nature, so as to yield effect estimates that were likely biased toward the null and thus underestimated any true effect. In general, cohort studies should have a sufficiently long follow-up period for any exposure-related cancer cases to develop and be detected and ideally, allow for analyses of potential cancer latency. Outcome-specific effect estimates from cohort studies with short follow-up could be uninformative depending on the size of the study population and the baseline frequency of the cancer.

The outcome-specific confidence classifications for each study and cancer endpoint combination, as well as the individual domain evaluations are documented in Appendix B.3.9; as with other outcomes, the studies identified as *not informative* are not discussed in the Toxicological Review.

Cancer Studies in Animals

Respiratory tract cancers

All subchronic or chronic studies (and an 8-week exposure study in potentially vulnerable mice) in experimental animals that included histopathological evaluations of respiratory tract tissues (i.e., nose/nasal cavity, larynx, trachea, lung) were evaluated (see Appendix B.3.9), noting that evaluations of the pharynx or mouth were uncommon in these studies, probably because experimental rodents are obligate nose-breathers). Histopathological evaluations used standard cross-section levels of the nasal passages that paralleled the evaluations of respiratory tract pathology described in Section 2.3.5.

In addition to the general considerations outlined in Section 2.1, criteria specific to evaluating respiratory tract cancer were evaluated (see Table 2-37). With one exception (see synthesis in Section 3.2.5), studies of experimental animals exposed for at least subchronic duration (shorter exposure durations were not considered informative to this endpoint, given the robust database), and which performed histopathological evaluations of respiratory tract tissues, were evaluated. As these evaluations consider many of the same studies previously evaluated for inclusion in the noncancer respiratory tract pathology section (see Section 2.3.5), many parallels exist between both sets of evaluations. While the important considerations across the two sections are generally similar, several notable differences exist. For example, duration of exposure was seen as more important for evaluations of dysplasia and neoplasms, as compared with evaluations of noncancer respiratory tract lesions. Conversely, whereas a substantial emphasis was placed on the characterization of the severity of the lesion for noncancer respiratory tract changes, severity was not considered integral to the identification of cancers and dysplasia. Finally, although most studies of respiratory pathology used paraformaldehyde or freshly prepared formalin as the test article, some studies tested commercial formalin. While co-exposure to methanol is a major confounding factor for systemic endpoints, it is considered to be less of a concern when identifying effects of inhaled formaldehyde on respiratory pathology. Because of the abundance of animal respiratory pathology studies, only those ranked as having "Good" or "Adequate" exposure quality, and several ranked as having "Deficient" exposure quality studies solely because they tested formalin (see evaluations in Appendix B.3.9), were included in the synthesis for respiratory tract cancers. Additional considerations that might influence the interpretation of the usefulness of the studies during the hazard synthesis are noted, including limitations such as the use of only one test concentration or concentration that are all too high or too low to provide a spectrum of the possible

effects, as well as study strengths such as very large sample sizes or use of good laboratory practices (GLP); however, this information did not affect the study evaluation decisions.

Table 2-37. Criteria for categorizing study confidence in animal studies of respiratory tract cancers

Evaluation domain	Overview of preferred study features	Primary criteria for domain ratings (Documentation shorthand used in Appendix B.3.9)		
		Good ('++')	Adequate ('+')	Deficient ('gray')
Exposure Quality	Well-characterized and appropriate inhalation exposure conditions (See methods in Section 2.3.1, applied consistently across experimental studies; see documentation in Appendix B.3.1). Studies without tested exposure <15 mg/m^3 are flagged as such.	• "Good" Exposure Quality [Note: for POE endpoints such as this, methanol co-exposure was not a major concern]	• "Adequate" Exposure Quality or "Deficient" Exposure Quality if the driver of the domain rating was use of formalin (i.e., this was not considered a critical deficiency for this POE effect)	• "Deficient" Exposure Quality not based on use of formalin as the test article [Note: interpretation of the exposure levels is discussed in the hazard synthesis and is not, on its own, a reason for deficient]
Test Subjects	Sample size provides reasonable power to assess endpoint(s) in question (e.g., >20/group desired); species, strain, sex, & age relevant to endpoint; no overt systemic toxicity noted or expected	• Chronic study: N ≥ 20 (note: for this outcome, testing only one sex not a limitation) • Details on test subjects reported • Randomization preferred (but not required) • Mortality unlikely to interfere with interpretations	• Generally, N < 20 • Individual less essential test subject details (e.g., sex) unclear • High mortality complicates interpretation	• Generally, N < 10 • Multiple less essential study details (e.g., sex, strain) unclear • Individual essential study detail (e.g., species) unclear • High mortality prevents interpretation or mortality NR
Study Design	The study design is appropriate and informative for evaluating respiratory tract cancer or dysplasia, including a sufficient exposure duration and/or appropriate timing of endpoint evaluations to allow for cancer to develop, and a lack of additional modifying	• Long-term exposure (e.g., ~2 years in rodents) to allow for cancer to develop • Exposure periodicity and frequency appropriate • No evidence of potential confounding	• Exposure duration < 1 year with long-term follow-up • Minor concerns with confounding, or exposure periodicity or frequency	• Exposure duration < 1 year without long-term follow up • Factors likely to introduce confounding identified • Exposure periodicity or frequency likely to be insensitive (e.g., brief, intermittent exposures)

Evaluation domain	Overview of preferred study features	Primary criteria for domain ratings (Documentation shorthand used in Appendix B.3.9)		
		Good ('++')	Adequate ('+')	Deficient ('gray')
	variables introduced over the course of the study. GLP-compliant studies are highlighted			
Endpoint Evaluation	The protocols used to assess respiratory tract cancer or dysplasia are sensitive and complete (e.g., multiple tissues and sections examined), discriminating (specific), & biologically sound (reliable); experimenter bias minimized (e.g., slides blinded to evaluator)	• Pathology evaluations blinded • Sufficient sampling for coverage of URT tissues (and preferably including distal respiratory tissues) • Evaluation methods reported (including number and region of tissue sections, number of slides, etc.)	• Blinding not reported (only a minor limitation for these endpoints, as the pathology is expected to be overt and not reliant on subtle decisions that would be impacted by evaluator biases) • Minor limitations in reporting of evaluation methods • Limited sampling (e.g., only nasal cavity; only a few slides; only a subset of URT tissue locations; only certain lesion types considered)	• Multiple limitations (see 'adequate' column at left) • Key URT tissues (e.g., nasal cavity) not examined • Insensitive protocols used (e.g., multiple tissues and sections were not examined) • Protocols otherwise critically flawed
Data considerations and statistics	Statistical methods are reported, group comparisons and data/variability presentation are appropriate & discerning; mortality data are described	• Adequate reporting and presentation of results • No evidence of selective reporting • Statistical methods described	• Failure to report statistical analyses • Concern regarding selective reporting • Concern with presentation of results (e.g., pooling of lesions or incidence data) • Lack of clarity of reported data (e.g., unclear anatomical location of lesions; qualitative or example-based reporting)	• Failure to report enough data to interpret reported findings • Multiple limitations (see 'adequate' column at left)

Lymphohematopoietic cancers

Studies examining LHP cancers were evaluated using nearly identical approaches and criteria as those for respiratory cancers (above). Given the assumed differential distribution of inhaled formaldehyde as compared to exposure by other routes, only inhalation studies were considered relevant to the review of LHP cancers in animals. Detailed study evaluation tables of the four relevant inhalation studies are available in Appendix B.3.9. One notable difference from the evaluation of respiratory tract cancers involved consideration of the test article as a key component of the review, as co-exposure to methanol in studies using formalin could have a substantial impact on the interpretation of potential LHP cancers (see exposure quality evaluation in Appendix B.3.1). A minor difference involved the preference for microscopic examination of several tissues applicable to assessing potential LHP cancers.

Table 2-38 describes the criteria for domain ratings used to inform confidence classifications for animal studies of LHP cancers.

Table 2-38. Criteria for categorizing study confidence in animal studies of lymphohematopoietic (LHP) cancers

Evaluation domain	Overview of preferred study features	Primary criteria for domain ratings (Documentation shorthand used in Appendix B.3.9)		
		Good ('++')	Adequate ('+')	Deficient ('gray')
Exposure Quality [Note: for systemic endpoints such as this, methanol co-exposure is a major concern]	Well-characterized and appropriate inhalation exposure conditions (See methods in Section 2.3.1, applied consistently across experimental studies; documentation in Appendix B.3.1). Studies without tested exposure <15 mg/m^3 are flagged as such.	• "Good" Exposure Quality • Co-exposures unlikely	• "Adequate" Exposure Quality • Co-exposure likely but controlled (e.g., methanol control group with formalin exposure)	• "Deficient" Exposure Quality • Uncontrolled co-exposure likely [Note: formaldehyde levels are discussed in the synthesis and high levels are not a reason for deficient]
Test Subjects	Sample size provides reasonable power to assess endpoint(s) in question (e.g., >20/group desired); species, strain, sex, & age relevant to endpoint; no overt systemic toxicity noted or expected	• Chronic study: N ≥ 20 (note: for this outcome, testing only one sex not a limitation) • Details on test subjects reported • Randomization preferred (but not required)	• Generally, N < 20 • Individual less essential test subject details (e.g., sex) unclear • High mortality complicates interpretation	• Generally, N < 10 • Multiple less essential study details (e.g., sex, strain) unclear • Individual essential study detail (e.g., species) unclear • High mortality prevents interpretation or mortality NR

Evaluation domain	Overview of preferred study features	Primary criteria for domain ratings (Documentation shorthand used in Appendix B.3.9)		
		Good ('++')	**Adequate ('+')**	**Deficient ('gray')**
		• Mortality unlikely to interfere with interpretations		
Study Design	The study design is appropriate and informative for evaluating respiratory tract cancer or dysplasia, including a sufficient exposure duration and/or appropriate timing of endpoint evaluations to allow for cancer to develop, and a lack of additional modifying variables introduced over the course of the study. GLP-compliant studies are highlighted	• Long-term exposure (e.g., ~2 years in rodents) to allow for cancer to develop • Exposure periodicity and frequency appropriate • No evidence of potential confounding	• Exposure duration < 1-year with long-term follow-up • Minor concerns with confounding, or exposure periodicity or frequency	• Exposure duration < 1 year without long-term follow up • Factors likely to introduce confounding identified • Exposure periodicity or frequency likely to be insensitive (e.g., brief, intermittent exposures)
Endpoint Evaluation	The protocols used to assess respiratory tract cancer or dysplasia are sensitive and complete (e.g., multiple tissues and sections examined), discriminating (specific), & biologically sound (reliable); experimenter bias minimized (e.g., slides blinded to evaluator)	• Pathology evaluations blinded • Sufficient sampling for coverage of LHP tissues, including bone marrow • Evaluation methods reported (including number and region of tissue sections, number of slides, etc.)	• Blinding not reported • Minor limitations in reporting of evaluation methods • Limited sampling (e.g., one or few tissues; only certain lesion types considered; only certain tissues or exposure levels microscopically examined)	• Multiple limitations (see 'adequate' column at left) • Key LHP tissues (e.g., bone marrow) not examined • Only gross lesions quantified (i.e., no microscopic examinations)
Data considerations and statistics	Group comparisons, & data/variability presentation are appropriate & discerning; mortality data and statistical methods are clearly described	• Adequate reporting and presentation of results • No evidence of selective reporting • Statistical methods described	• Failure to report statistical analyses • Concern regarding selective reporting • Concern with presentation of results (e.g., pooling of lesions or incidence data)	• Failure to report enough data to interpret findings (e.g., incidence data, or lack of any tumors, not reported) • Multiple limitations (see

Evaluation domain	Overview of preferred study features	Primary criteria for domain ratings (Documentation shorthand used in Appendix B.3.9)		
		Good ('++')	Adequate ('+')	Deficient ('gray')
			• Lack of clarity of reported data (e.g., unclear anatomical location of lesions; qualitative or example-based reporting)	'adequate' column at left)

2.3.10. Study Evaluation Criteria for Mechanistic Information Related to Genotoxicity and Cancer

Approaches for Cancer Mode of Action

Consolidated, formal systematic approaches to evaluating the studies examining mechanistic data relevant to interpreting the potential for formaldehyde to cause either upper respiratory tract (URT) or lymphohematopoietic (LHP) cancers were not performed. Rather, these sections build from studies identified and evaluated through other health effect-specific literature searches and consider those studies in the context of the specific cancer etiology being reviewed alongside other relevant studies (e.g., those identified as described in Section 2.2.10). This includes supplemental literature relevant to interpreting the biological relevance of some mechanistic data from review articles and other national-level health assessments. Specifically, these sections rely heavily on searches and evaluations performed in the following sections: genotoxicity (see below), respiratory tract pathology (see Section 2.3.5), and mechanistic information related to noncancer respiratory effects, focusing on inflammation and immune effects (see Section 2.3.6). Studies identified outside of these specific searches (e.g., from reviews) were not individually evaluated. Rather, as described in Section 2.3.1, these studies were considered within the wider body of evidentiary support (or lack thereof) for specific, influential mechanistic events (e.g., those known to be associated with the cancer type of interest; those previously implicated in authoritative reviews as relevant to interpreting formaldehyde exposure-induced carcinogenicity), with judgments based on overarching interpretations across the different sets of inter-related studies using structured frameworks for the evaluations based on EPA's Cancer Guidelines (U.S. EPA, 2005a) (see Sections 3.2.5 and 3.3.3).

Genotoxicity-Specific Evidence Evaluation

Epidemiological studies examining genotoxic endpoints were evaluated for potential bias and other issues using the same domains as were assessed for studies in other health effects categories (i.e., exposure measures and range; outcome classification; consideration of participant selection and comparability; consideration of likely confounding; analysis and completeness of results; and study size). Rather than confidence conclusions of *low*, *medium,* or *high*, an overall conclusion of "no

obvious bias" was used if no concerns were identified; this equates to classifications of *high* or *medium* confidence. For studies with a potential bias identified, the potential bias or issue was summarized in the comment row. For each assay (e.g., chromosomal aberrations, CBMN, Comet assay), factors related to assay methods that could affect the endpoint values were identified using published reviews from collaborations that compared assay methods across epidemiological studies (Valverde and Rojas, 2009; Møller et al., 2020; Fenech et al., 2011; Fenech, 2020; Bonassi et al., 2005; Bonassi et al., 2011). Such factors included sample collection and processing flows, whether sample processing and analysis was blinded to exposure status, cell culture details, details of scoring (number of scorers, criteria, staining, number of cells scored). An appropriate citation to a standardized assay protocol was considered acceptable. These reviews noted that assay results have been found to vary by age, gender, and smoking status; studies that did not report assessing confounding by these factors were identified. In the study evaluation table for each study, row cells have been given a gray fill for evaluation domains with identified concerns about methods. Study evaluation concerns are discussed in the syntheses of genotoxic endpoints if they may explain observed heterogeneity in study results. The study-specific evaluations are documented in Appendix B.3.10.

2.4. DATA EXTRACTION METHODS

Data extraction and content management were carried out using Microsoft Word and Excel except for studies captured in the 2021 SEM, which also used EPA's Health Assessment Workspace Collaborative (HAWC). Study details are documented primarily in evidence tables within the evidence synthesis sections (Section 3). Studies evaluated as being *not informative* are not used in the assessment and study details are not provided. The same is true in some cases for *low*-confidence studies when many *medium*- and *high*-confidence studies were available, unless the *low*-confidence studies included study designs lacking in the higher confidence studies (e.g., testing lower exposure levels, or susceptible populations or lifestages). Data extraction was performed by one member of the evaluation team and checked by at least one other member.

2.5. EVIDENCE SYNTHESIS METHODS

Section 3 includes evidence syntheses for the following health hazard categories: sensory irritation; reduced pulmonary function, respiratory tract pathology, immune-mediated conditions, focusing on allergies and asthma; cancer (respiratory tract cancers, lymphohematopoietic cancers); nervous system effects (motor neuron disease, tests of general motor-related behaviors, neural sensitization, learning or memory, neuropathology); developmental and female reproductive toxicity; and male reproductive toxicity. Health hazard categories were chosen based on prior reviews, as well as the specifics of the available literature. The units of analysis within an overall hazard category for which a hazard conclusion was developed were determined based on biologic considerations (i.e., specific to an organ system and considering the degree to which endpoints are

related) and the number of studies that evaluated a particular outcome. Thus, hazard conclusions were developed for consolidated sets of related health endpoints within an overall hazard category in some instances (e.g., male reproductive toxicity).

For each unit of analysis (hazard category, or hazard subgrouping), and depending on the data available, separate syntheses were developed for each of the three streams of evidence: namely, human health effect studies, animal health effect studies, and mechanistic studies. These evidence syntheses, which incorporate the evaluations of the strengths and limitations of the available studies as well as considerations related to the toxicokinetics of inhaled formaldehyde, provide a discussion of the information provided by each stream of evidence regarding the potential for exposure to formaldehyde via inhalation to result in specific health effects. All *high*, *medium*, and *low* confidence studies (see Section 2.3.1), regardless of the magnitude or direction of results (i.e., whether yielding positive or null results) were considered in assessing the evidence; however, the focus of the synthesis was on the *high* and *medium* confidence studies, when available. Descriptive information about study methods and detailed results are generally presented in tabular or graphical displays, with supportive text. The narrative summaries discuss the nature and breadth of the available literature, highlighting details that contribute to the analysis of the strength of evidence regarding causality in the next section. In addition, to the extent the data allow, based on knowledge about the health outcome or organ system affected, the syntheses discuss analyses relating to potential susceptible populations, including factors such as demographics, genetic variability, lifestage, health status, behaviors or practices, social determinants, and exposure to other pollutants. This information informs both hazard identification and dose-response analyses.

The syntheses of the separate streams of evidence—human health effect studies, animal health effect studies, and mechanistic studies—involved consideration of a related set of factors, the evaluation of which differed due to the nature of the study designs and applicability of the data. Specifically, the syntheses inform an adapted set of considerations based on those introduced by Austin Bradford Hill (Hill, 1965), including consistency, exposure-response relationship, strength of the association (magnitude of effect) and precision, biological plausibility, and coherence, as well as "natural experiments" in humans (U.S. EPA, 1994, 2005a), as described in Table 2-39.

Table 2-39. Information most relevant to describing primary factors informing causality during evidence syntheses

Factor	Description and synthesis methods
Consistency	• Examines the similarity of results (e.g., direction; magnitude) across studies. When inconsistencies exist, the synthesis considers whether results were "conflicting" (i.e., unexplained positive and negative results in similarly exposed human populations or in similar animal models) or "differing" (i.e., mixed results explained by differences between human populations, animal models, exposure conditions, or study methods) (U.S. EPA, 2005a) based on analyses of potentially important explanatory factors such as:

Factor	Description and synthesis methods
	• Confidence in studies' results, including study sensitivity (e.g., some study results that appear to be inconsistent may be explained by potential biases or other attributes that affect sensitivity, resulting in variations in the degree of confidence accorded to the study results) • Exposure, including route (if applicable), levels, duration, etc. • Populations or species, including consideration of potential susceptible groups or differences across lifestages at exposure or endpoint assessment. • Toxicokinetic information as an explanation for any observed differences in responses across route of exposure, other aspects of exposure, species, or lifestages The interpretation of the consistency of the evidence and the magnitude of the reported effects will emphasize biological significance as more relevant to the assessment than statistical significance. Statistical significance (as reported by p-values, etc.) provides no evidence about effect size or biological significance, and a lack of statistical significance will not be automatically interpreted as evidence of no effect.
Strength (effect magnitude) and precision	• Examines the effect magnitude or relative risk, based on what is known about the assessed endpoint(s), and considers the precision of the reported results based on analyses of variability (e.g., confidence intervals; standard error). In some cases, this may include consideration of the rarity or severity of the findings (in the context of the health effect being examined). Syntheses will analyze results both within and across studies and may consider the utility of combined analyses (e.g., meta-analysis). While larger effect magnitudes and precision (e.g., $p < 0.05$) help reduce concerns about chance, bias, or other factors as explanatory, syntheses should also consider the biological or population-level significance of small effect sizes.
Biological gradient/dose-response	• Examines whether the results (e.g., response magnitude, incidence, severity) change in a manner consistent with changes in exposure (e.g., level, duration), including consideration of changes in response after cessation of exposure. Syntheses will consider relationships both within and across studies, acknowledging that the dose-response (e.g., shape) can vary depending on other aspects of the experiment, including the outcome and the toxicokinetics of the chemical. Thus, when dose-response is lacking or unclear, the synthesis will also consider the potential influence of such factors on the response pattern.
Coherence	• Examines the extent to which findings are cohesive across different endpoints that are known/expected to be related to, or dependent on, one another (e.g., based on known biology of the organ system or disease, or mechanistic understanding such as toxicokinetic/dynamic understanding of the chemical or related chemicals). In some instances, additional analyses of mechanistic evidence from research on the chemical under review or related chemicals that evaluate linkages between endpoints or organ-specific effects may be needed to interpret the evidence. These analyses may require additional literature search strategies. Syntheses will consider potentially related findings, both within and across studies, particularly when relationships are observed within a cohort or within a narrowly defined category (e.g., occupation, strain or sex, lifestage of exposure). Syntheses will emphasize

Factor	Description and synthesis methods
	evidence indicative of a progression of effects, such as temporal- or dose-dependent increases in the severity of the type of endpoint observed.
Mechanistic evidence related to biological plausibility	• There are multiple uses for mechanistic information (see Section 2.5.1), and this consideration overlaps with "coherence." This examines the biological support (or lack thereof) for findings from the human and animal health effect studies and becomes more impactful on the hazard conclusions when notable uncertainties in the strength of those sets of studies exist. These analyses can also improve understanding of dose- or duration-related development of the health effect. In the absence of human or animal evidence of apical health endpoints, the synthesis of mechanistic information will drive evidence integration conclusions (when such information is available). Syntheses can evaluate evidence on precursors, biomarkers, or other molecular or cellular changes related to the health effect(s) of interest to describe the likelihood that the observed effects result from exposure. This will be an analysis of existing evidence, and not simply whether a theoretical pathway can be postulated. This analysis may not be limited to evidence relevant to the PECO but may also include evaluations of biological pathways (e.g., for the health effect; established for other, possibly related, chemicals). The synthesis will consider the sensitivity of the mechanistic changes and the potential contribution of alternative or previously unidentified mechanisms of toxicity.
Natural experiments	• Specific to epidemiological studies and rarely available, these examine effects in populations that have experienced well-described, pronounced changes in exposure to the chemical of interest (e.g., blood lead levels before and after banning lead in gasoline). No well-conducted natural experiments were identified for this chemical.

Consistency, magnitude of effects, and dose-response gradients were emphasized in the synthesis of results of epidemiological and controlled human exposure studies. The primary considerations for synthesizing the results of animal studies were consistency (e.g., across species and across research groups, with consideration of study confidence), magnitude and severity of the effects, dose-response, and coherence of findings for related effects. Although the precision of reported results could add to the strength of evidence for a health effect, results that are both statistically significant and nonsignificant are summarized. The syntheses focus on evaluating the potential sources of heterogeneity within sets of related studies to discern whether inconsistent evidence can be reasonably explained by the respective study designs or other empirical factors (U.S. EPA, 2005a). Consistency between studies was examined by comparing study results by confidence level, specific methodological features that contributed to potential bias, exposure setting, and level of exposure. The information from mechanistic studies in humans or animals relevant to each apical outcome was synthesized, highlighting information that could inform either biological plausibility, coherence, susceptibility, relevance to humans or an improved understanding of dose-response; these considerations are grouped under "other inferences" in the evidence profile tables and elsewhere and can inform evidence synthesis judgments (Section 2.5, Table 2-43), evidence integration conclusions (Section 2.6) or decisions related to dose-response analysis (Section 2.7). Approaches and considerations for the synthesis of mechanistic information

are separately discussed in Section 2.5.1 below. Table 2-40 outlines the considerations for how the individual factors were evaluated to inform judgments about whether the formaldehyde-specific evidence increases or decreases the strength of the human or animal evidence for (or against) identifying a hazard.

Table 2-40. Primary considerations for assessing the strength of evidence for the health effects studies in human and, separately, animal studies[a]

Factor	Increased evidence strength (of the human or animal study evidence)	Decreased evidence strength (of the human or animal study evidence)
The structured categories and criteria in Tables VI and VII will guide the application of strength-of-evidence judgments for an outcome or health effect. Evidence synthesis scenarios that do not warrant an increase or decrease in evidence strength will be considered "neutral."		
Risk of bias; sensitivity (across studies)	• An evidence base of *high* or *medium* confidence studies increases strength.	• An evidence base of mostly *low* confidence studies decreases strength. An exception to this is when the primary issues resulting in *low* confidence are related to insensitivity. This may increase evidence strength in cases where an association is identified because the expected impact of study insensitivity is toward the null. • Decisions to increase strength for other considerations in this table should generally not be made if there are serious concerns for risk of bias.
Consistency	• Similarity of findings for a given outcome (e.g., of a similar magnitude, direction) across independent studies or experiments increases strength, particularly when consistency is observed across populations (e.g., location) or exposure scenarios in human studies, and across laboratories, populations (e.g., species), or exposure scenarios (e.g., duration, route, timing) in animal studies.	• Unexplained inconsistency (conflicting evidence) decreases strength. Generally, strength should not be decreased if discrepant findings can be reasonably explained by study confidence conclusions, variation in population or species, sex, or lifestage, exposure patterns (e.g., intermittent, or continuous), levels (low or high), duration or intensity. However, any decisions about decreased strength will be determined by the extent to which residual questions about the evidence may persist.
Strength (effect magnitude) and precision	• Evidence of a large magnitude effect (considered within or across studies), can increase strength. Increases in rare effects or effects of a concerning severity can also increase strength, even if they are small in magnitude. • Precise results from individual studies or across the set of studies increases strength, noting that biological significance is prioritized over statistical significance.	• The presence of small effects is not typically used to decrease confidence in a body of studies. However, if effect sizes that are small in magnitude are concluded not to be biologically significant, or if there are only a few studies with imprecise results, then strength is decreased. • In animal studies, an example of evidence that can decrease strength involves an effect for which there is a lesser level of concern under some conditions (e.g., rapid reversibility after removal of exposure). Note that many reversible effects are of high concern. Such a decision is informed by factors such as the toxicokinetics of the chemical and the conditions of exposure (see U.S. EPA (1998)), judgments regarding the potential for delayed or secondary effects, as well as the exposure context focus of the assessment (e.g., addressing intermittent or short-term exposures).
Biological gradient/dose-response	• Evidence of dose-response increases strength. Dose-response may be demonstrated across studies or within studies and it can be dose or duration dependent. It may also not be a monotonic dose-response (monotonicity should not necessarily be expected), and the analysis	• A lack of dose-response when expected based on biological understanding and having a wide range of doses/exposures evaluated in the evidence base can decrease strength. • In rare cases, and typically only in toxicology studies, the duration of exposure might reveal an inverse association with effect magnitude (e.g., due to tolerance or

Factor	Increased evidence strength (of the human or animal study evidence)	Decreased evidence strength (of the human or animal study evidence)
	will consider the extent to which this might be explained by the available evidence (e.g., different outcomes may be expected at low versus high doses due to activation of different mechanistic pathways or induction of systemic toxicity at very high doses). • Decreases in a response after cessation of exposure (e.g., symptoms of current asthma) also may increase strength by increasing certainty in a relationship between exposure and outcome (this is applicable to human observational studies, but not experimental studies).	acclimation). Similar to the discussion of reversibility above, a decision about whether this decreases strength depends on the exposure context focus of the assessment and other factors. • If the data are not adequate to evaluate a dose-response pattern, then strength is neither increased nor decreased.
Coherence	• Biologically related findings within an organ system, or across populations (e.g., sex) increase strength, particularly when a temporal- or dose-dependent progression of related effects is observed within or across studies, or when related findings of increasing severity are observed with increasing exposure.	• An observed lack of expected coherent changes (e.g., well-established biological relationships), particularly when observed for multiple related endpoints, will typically decrease evidence strength. The decision to decrease depends on the strength of the expected relationship(s), and considers factors (e.g., dose and duration of exposure) across studies of related changes.
Mechanistic evidence related to biological plausibility	• Mechanistic evidence of precursors or health effect biomarkers in well-conducted studies of exposed humans or animals, in appropriately exposed human or animal cells, or other relevant human or animal models (for the human or animal evidence, respectively) increases strength, particularly when this evidence is observed in the same cohort/population exhibiting the health outcome. • Evidence of changes in biological pathways or providing support for a proposed MOA in models also increases strength, particularly when support is provided for rate-limiting or key events, or changes are conserved across multiple components of the pathway or MOA.	• Mechanistic understanding is not a prerequisite for judging the evidence, and thus absence of knowledge should not be used a basis for decreasing strength NTP (2015); NRC (2014a).The human relevance of animal findings is assumed unless there is sufficient evidence to the contrary [see U.S. EPA (2005a); IARC (2006)]. • Mechanistic evidence in well-conducted studies that demonstrates that the health effect(s) are unlikely to occur, or only likely to occur under certain scenarios (e.g., above certain exposure levels), can decrease evidence strength. A decision to decrease depends on an evaluation of the strength of the mechanistic evidence supporting vs. opposing biological plausibility, as well as the strength of the health effect-specific findings (e.g., stronger health effect data require more certainty in mechanistic evidence opposing plausibility).

[a]These ideas build upon the discussion for assessing causality of disease in Hill (1965), although the use or interpretation of some of the terms differs.

[b]While humans are "exposed" and not "dosed," and nor are animals "dosed" via inhalation, "dose-response" is used for convention throughout the assessment, although it is acknowledged that 'exposure-response' may be more appropriate in many contexts.

[c]There is a clear overlap in the use of mechanistic evidence to interpret coherence (e.g., informing the relatedness or comparability of potentially coherent health findings) and biological plausibility. The available mechanistic information is also considered during the subsequent step of evidence integration across streams of evidence (see Section 2.6).

[d]Although it is not separately listed, Hill's consideration of 'analogy' (information for a similar but different association that supports causation) is indirectly encompassed by the evaluation of coherence during the review of environmental health studies; however, this use of analogous chemicals or exposure scenarios is less common.

Summary synthesis judgments regarding the strength of the evidence from the available human and animal studies were drawn based on evaluation of the aforementioned factors. These judgments incorporated mechanistic evidence (or MOA understanding) in exposed humans and animals, respectively, that informed the biological plausibility and coherence of the available human or animal health effect studies, both of which could add to or detract from the strength of evidence, as described in Table 2-40 above. Note, however, that a lack of mechanistic data explaining an association did not discount results from human or animal health effect studies. Evidence synthesis judgments regarding the strength of the human and, separately, the animal evidence (with consideration of mechanistic information in humans and animals, respectively, including in vitro or other relevant models) for each noncancer health effect (or groups of related effects) and specific cancer type (or groups of related cancer types) was summarized using the following terms: *robust, moderate, slight, indeterminate,* and *compelling evidence of no effect* based on structured decision frameworks.

These decision frameworks, with criteria described in Tables 2-41 and 2-42, were used to apply expert judgment to weigh the strengths and weaknesses of both positive and null studies. These frameworks add clarity, consistency, and transparency to the evidence evaluations and conclusions; are consistent with generally accepted principles in epidemiology and toxicology; and are meant to convey a distribution of confidence in each body of evidence pertaining to a hazard. In addition to the synthesis narrative and summary strength of evidence judgment, the factors (e.g., consistency) providing the primary support for each judgment, and their summary justifications, are bulleted at the end of each evidence synthesis narrative in Section 3.

Table 2-41. Framework for strength of evidence judgments (human evidence)

Strength of evidence judgment	Description
Robust *… evidence in human studies* *(strong signal of effect with little residual uncertainty)*	A set of *high* or *medium* confidence independent studies reporting an association between the exposure and the health outcome, with reasonable confidence that alternative explanations, including chance, bias, and confounding, can be ruled out across studies. The set of studies is primarily consistent, with reasonable explanations when results differ; an exposure-response gradient is demonstrated; and the set of studies includes varied populations. Additional supporting evidence, such as associations with biologically related endpoints in human studies (coherence) or large estimates of risk or severity of the response, may increase confidence but is not required. In exceptional circumstances, a finding in one study may be considered to be *robust*, even when other studies are not available (e.g., analogous to the finding of angiosarcoma, an exceedingly rare liver cancer, in the vinyl chloride industry). Mechanistic evidence from exposed humans or human cells, if available, may add support informing considerations such as exposure-response, temporality, coherence, and MOA, thus raising the level of certainty to *robust* for a set of studies that otherwise would be described as *moderate*.

Strength of evidence judgment	Description
Moderate … evidence in human studies *(signal of effect with some uncertainty)*	A smaller number of studies (at least one *high* or *medium confidence* study with supporting evidence), or with some heterogeneous results, that do not reach the degree of confidence required for *robust.* For multiple studies, there is primarily consistent evidence of an association, but there may be lingering uncertainty due to potential chance, bias or confounding. For a single study, there is a large magnitude or severity of the effect, or a dose-response gradient, or other supporting evidence, and there are not serious residual methodological uncertainties. Supporting evidence could include associations with related endpoints, including mechanistic evidence from exposed humans or human cells, if available, based on considerations such as exposure-response, temporality, coherence, and MOA, thus raising the level of certainty to *moderate* for a set of studies that otherwise would be described as *slight*.
Slight … evidence in human studies *(signal of effect with large amount of uncertainty)*	One or more studies reporting an association between exposure and the health outcome, where considerable uncertainty exists. In general, only *low* confidence studies may be available, or considerable heterogeneity across studies may exist. Supporting coherent evidence is sparse. Strong biological support from mechanistic evidence in exposed humans or human cells may also be independently interpreted as s*light*. This also includes scenarios where there are serious residual uncertainties across studies (these uncertainties typically relate to exposure characterization or outcome ascertainment, including temporality) in a set of largely consistent medium or high confidence studies. This category serves primarily to encourage additional study where evidence does exist that might provide some support for an association, but for which the evidence does not reach the degree of confidence required for *moderate*.
Indeterminate … evidence in human studies *(signal cannot be determined for or against an effect)*	No studies available in humans or situations when the evidence is inconsistent or primarily of *low* confidence
Compelling evidence of no effect … in human studies *(strong signal for lack of an effect with little uncertainty)*	Several *high* confidence studies showing null results (for example, an odds ratio of 1.0), ruling out alternative explanations including chance, bias, and confounding with reasonable confidence. Each of the studies should have used an optimal outcome and exposure assessment and adequate sample size (specifically for higher exposure groups and for susceptible populations). The set as a whole should include the full range of levels of exposures that human beings are known to encounter, an evaluation of an exposure-response gradient, and an examination of at-risk populations and lifestages.

Table 2-42. Framework for strength of evidence judgments (animal evidence)

Strength of evidence judgment	Description
Robust … animal evidence	The set of *high* or *medium* confidence experiments includes consistent findings of adverse or toxicologically significant effects across multiple laboratories, exposure routes, experimental designs (e.g., a subchronic study and a two-generation study), or species, and the experiments can reasonably rule out the potential for nonspecific effects (e.g., indirectly due to overt toxicity at high exposure levels) to have resulted in the findings. Any inconsistent evidence (evidence that cannot be reasonably explained by the respective study design or differences in animal model) is from a set of experiments of lower confidence. At least two of the following additional factors in the set of experiments increases certainty in the evidence for the health outcome(s): coherent effects across multiple related endpoints (may include mechanistic evidence); an unusual magnitude of effect, rarity, age at onset, or severity; a strong dose-response relationship; or consistent observations across animal lifestages, sexes, or strains. Alternatively, mechanistic data in animals or animal cells that address the above considerations or that provide experimental support for a MOA that supports causality with reasonable confidence may raise the level of certainty to *robust* for evidence that otherwise would be described as *moderate* or, exceptionally, *slight, or indeterminate*.
Moderate … animal evidence	A set of evidence that does not reach the degree of certainty required for *robust*, but which includes at least one *high* or *medium* confidence study and information strengthening the certainty in the evidence for the health outcome(s). Although the results are largely consistent, notable uncertainties remain. However, while inconsistent evidence or evidence indicating nonspecific effects (e.g., toxicity) may exist, it is not sufficient to reduce or discount the level of concern regarding the positive findings from the supportive experiments or it is from a set of experiments of lower confidence. The set of experiments supporting the effect provide additional information supporting causality, such as consistent effects across laboratories or species; coherent effects across multiple related endpoints (may include mechanistic evidence); an unusual magnitude of effect, rarity, age at onset, or severity; a strong dose-response relationship; or consistent observations across exposure scenarios (e.g., route, timing, duration), sexes, or animal strains. Mechanistic data in animals or animal cells that address the above considerations or that provide information supporting causality with reasonable confidence may raise the level of certainty to *moderate* for evidence that otherwise would be described as *slight*.
Slight … animal evidence	Scenarios in which there is a signal of a possible effect, but the evidence is conflicting or weak. Most commonly, this includes situations where only *low* confidence experiments are available and supporting coherent evidence is sparse. It also applies when one *medium* or *high* confidence experiment is available without additional information increasing the certainty in the evidence (e.g., corroboration within the same study or from other studies). Lastly, this includes scenarios in which there is evidence that would typically be characterized as *moderate*, but inconsistent evidence (evidence that cannot be reasonably explained by the respective study design or differences in animal model) from a set of experiments of higher confidence (may include mechanistic evidence) exists. Strong biological support from mechanistic studies in exposed animals or animal cells may also be independently interpreted as *slight*. Notably, to encourage additional research, it is important to describe situations where evidence exists that might provide some support for an association but is insufficient for a conclusion of *moderate*.
Indeterminate …animal evidence	No animal studies were available, or a set of *low* confidence animal studies exist that are not reasonably consistent or are not informative to the hazard question under evaluation.

Strength of evidence judgment	Description
Compelling evidence of no effect … in animal studies	A set of *high* confidence experiments examining a reasonable spectrum of endpoints relevant to a type of toxicity that demonstrate a lack of biologically significant effects across multiple species, both sexes, and a broad range of exposure levels. The data are compelling in that the experiments have examined the range of scenarios across which health effects in animals could be observed, and an alternative explanation (e.g., inadequately controlled features of the studies' experimental designs; inadequate sample sizes) for the observed lack of effects is not available. The experiments were designed to specifically test for effects of interest, including suitable exposure timing and duration, postexposure latency, and endpoint evaluation procedures, and to address potentially susceptible populations and lifestages.

2.5.1. Synthesis of Mechanistic Evidence

The mechanistic evidence syntheses inform multiple key decisions in the assessment, including the evidence synthesis judgments for human and animal studies (above), the evidence integration judgments for different health effect categories (Section 2.6), and decisions for dose-response analysis (Section 2.7). Examples of ways that mechanistic evidence is used to draw other inferences to inform the judgments drawn during evidence synthesis and integration (note: "other inferences" are described within the evidence profile tables in Section 3), and derivation of toxicity values, are described in Table 2-43. Given the exposure-related issues specific to formaldehyde and the abundance of data available, the mechanistic evaluations in this assessment focus almost exclusively on in vivo studies of inhalation exposures, with rare exception (e.g., evaluation of *in vitro* genotoxicity studies). As noted elsewhere (U.S. EPA, 2022), reflecting the increased scope and heterogeneity of the potentially relevant mechanistic information, the considerations and approaches used to synthesize and draw inferences about the mechanistic information differ from those used in synthesizing the human and animal health effect data; the specific approaches used in this assessment are summarized below.

Table 2-43. Examples of the interpretation and application of mechanistic evidence used to draw other inferences during evidence synthesis and integration, and dose-response analysis

Mechanistic inferences considered	Applications within the assessment
Biological plausibility: As applied herein, this applies to information that either strengthens or weakens an interpretation of the likelihood of an association between exposure and the health effect. Often, differing levels of biological plausibility (or certainty) can be drawn (i.e., it is often not a simple "yes" or "no" answer). It is important to note that the	***Evidence Synthesis Judgments (Section 2.5)*** • Observations of important mechanistic changes in exposed humans or animals that are plausibly associated with the health outcome in question can strengthen the confidence in the health effect findings for either the human or animal evidence base, particularly when the changes are observed in the same exposed population presenting the health effect. • Strong evidence supporting the absence of expected mechanistic changes in an exposed population might diminish

Mechanistic inferences considered	Applications within the assessment
lack of mechanistic data explaining an association is not used to discount observations from human or animal studies. The interpretation of biological plausibility considers the existing knowledge for how the health effect develops and can involve analyses of information at different levels of biological organization (e.g., molecular, tissue).	the plausibility of an association. This considers the sensitivity of the changes and the potential contribution of alternative or unidentified toxicity mechanisms. • Conflicting evidence (i.e., heterogeneous results for comparable mechanistic events using sufficiently similar methods) across different animal species or human populations might be explained by evidence that mechanisms differ or are not/less operant in the different populations (e.g., evidence demonstrating that certain animal species cannot metabolize a chemical to its reactive metabolite). Such analyses can also inform judgments regarding human relevance (see below).
Human relevance of findings in animals: In the absence of sufficiently justifiable mode of action (MOA) information, effects in animal models are assumed to be relevant to humans (U.S. EPA, 2005a). In this assessment, for potential health hazards where the evidence from animal models is likely to influence the overall hazard conclusion, the available mechanistic evidence was considered in light of human relevance.	***Evidence Integration Judgments (Section 2.6)*** • Evidence establishing that the mechanisms underlying the animal response do not operate in humans, or that animal models do not suitably inform a specific human health outcome can support the view that the animal response is irrelevant to humans. In these cases, the animal response provides neither an argument for nor an argument against an overall hazard judgment. • Observations of mechanistic changes in exposed humans that are similar or coherent with mechanistic or toxicological changes in experimental animals (and which are interpreted to be associated with the health outcome under evaluation) strengthen the human relevance of the animal findings.
Potential susceptibilities: When a mechanistic understanding of how a health outcome develops, or MOA, is known or hypothesized, knowledge about the presence and sensitivity (e.g., across lifestages), or modifying factors (e.g., genetics) of important events in that MOA can help identify susceptible groups.	***Evidence Integration (Section 2.6)*** • Identification of susceptible lifestages or groups can add clarity to hazard descriptions regarding whether those most likely to exhibit effects have been adequately tested, or if large data gaps exist. ***Dose-Response Analysis (Section 2.7)*** • Knowledge of potential or expected susceptibilities can inform selection of studies for quantitative analysis (e.g., prioritizing studies including such populations). • Consideration of identified susceptible groups can inform uncertainty factor selection and confidence in toxicity values.
Biological understanding, including the identification of precursor events: When mechanistic data can reasonably describe how effects develop, this information may inform the situations or scenarios expected to result in these effects. Further, well-studied MOAs can sometimes identify mechanistic precursor events that can be	***Dose-Response Analysis (Section 2.7)*** • Understanding how effects develop might support the use of, for example, particular models (e.g., models assuming effects do not occur below certain levels; biologically based models; models integrating data across several closely related outcomes) or measures of exposure (e.g., different external or internal metrics).

Mechanistic inferences considered	Applications within the assessment
qualitatively or quantitatively linked to the apical health effect in question with reasonable confidence.	• Uncertainty in the dose-dependence of responses in animals or humans can be influenced by the occurrence of precursor events, which can add to or subtract from the plausibility of the findings for use in dose-response analyses. Relatedly, in rare instances, well-established precursor events might be used as surrogates in dose-responses analyses when the health effect-specific data are less certain.

As described in Sections 2.2.10 and 2.3.10, consolidated systematic approaches to identifying and evaluating (and synthesizing) the mechanistic information relevant to interpreting the potential for formaldehyde to cause either upper respiratory tract (URT) or lymphohematopoietic (LHP) cancers were not performed. Rather, these syntheses intentionally addressed a broad collection of evidence built upon the other systematic reviews and pre-existing knowledge regarding the potential cancer mechanisms and precursor events related to inhaled formaldehyde. Consistent with the EPA cancer guidelines (U.S. EPA, 2005a) and approaches described in the IRIS Handbook (U.S. EPA, 2022), for both cancer type groupings, the findings were summarized and integrated into a proposed cancer MOA network that served as a framework for the evidence evaluation and MOA analysis. Like other sections, the evidence was synthesized following the Bradford Hill considerations, with an emphasis placed on observations following inhalation exposure in humans and experimental animals. The syntheses were developed in the context of carcinogenesis proceeding via one or more hypothesized, integrated cancer MOA(s), with alternative hypotheses examined.

The syntheses of the mechanistic information specifically informing noncancer health effects at systemic sites (i.e., developmental, and reproductive effects and nervous system effects) was much narrower, focusing on the few available *medium* and *high* confidence studies of inhalation exposure with relevant mechanistic information. To the extent the data allow, these syntheses focused on identifying mechanistic events[13] in appropriate tissues that could be plausibly linked to the apical changes observed in the human or animal studies; speculative hypotheses without supporting data were avoided. The evidence bases were not extensive enough to conduct formal MOA analyses, but the strengths and uncertainties of the evidence supporting each potential mechanistic change were summarized.

Syntheses of mechanistic data that might inform potential noncancer respiratory health effects involved an integrated and systematic review process (see additional discussion below, detailed documentation in Appendix B.2.6 and B.3.6, and integrated analyses in Appendix C.7), which emphasized for each potential health effect the sequence(s) of mechanistic events

[13] *Mechanistic event* is used in this assessment as a generic term for types of endpoints, which may or may not be required for—or even influence—a mode of action; thus, mechanistic events are not necessarily *key events*, which are necessary precursor steps (or markers of such) in a mode of action (U.S. EPA, 2005a).

interpreted to have the most reliable evidence, highlighting effects on specific tissue components and/or functions. Based on the known or presumed linkages, these events are organized from a "plausible initial effect of exposure" (e.g., a potential direct interaction between inhaled formaldehyde and biological materials) to each apical toxicity endpoint in a linear fashion, regardless of tissue region, and the summary MOA inferences are synthesized for each health effect in Section 3. Other mechanistic changes with less reliable information are summarized in Appendix C.7 only.

For these structured syntheses, due to the importance of considering the toxicokinetics of inhaled formaldehyde, the human and animal experiments interpreted with *high or medium confidence* and *low confidence* were organized according to the tissue compartment and general type of change being examined. Individual experiments or groups of closely related experiments across studies were divided into mechanistic events, representing empirically observable biological changes that may inform how formaldehyde exposure might be associated with a respiratory health effect(s). The level of evidentiary support for each mechanistic event was characterized as robust, moderate, slight, or indeterminate based on the criteria presented in Table 2-44. Similar to the factors emphasized during the human and animal health effect syntheses, these criteria emphasize the confidence and consistency of the data across studies. Other relevant considerations (e.g., effect magnitude, dose-response, coherence) are discussed when conclusions across studies could be drawn, but these judgments were often difficult due to the heterogeneous nature of the available mechanistic studies. Potential associations between mechanistic events were judged based on the tissue(s)/region(s) assessed and known biological roles within those tissues for the identified mechanistic events. The basis for each association was not individually documented; these are more generally discussed in the individual synthesis sections, or the study evaluation tables in Appendix B.3.6.

Table 2-44. Criteria and presentation of strength of the evidence for each mechanistic event and for potential associations between events relating to potential noncancer respiratory health effects

	Evidence judgment[a]	Mechanistic events		Associations between mechanistic events	
		Criteria for conclusions	Presentation[b]	Criteria for conclusions	Presentation[b]
Strongest	Robust	Direct evidence supporting an effect in multiple, consistent *high or medium* confidence studies[c]	◎ Emphasized in Syntheses	Formaldehyde-specific data demonstrate a linkage (i.e., inhibition of mechanistic event "A" prevents or reduces the occurrence of event "B"; events "A" and "B" are linked by concentration, location, or temporality)	→

	Evidence judgment[a]	Mechanistic events		Associations between mechanistic events	
		Criteria for conclusions	Presentation[b]	Criteria for conclusions	Presentation[b]
	Moderate	Direct or indirect (e.g., genetic changes) evidence supporting an effect in at least one *high or medium* confidence study, with supporting evidence (e.g., consistent changes suggesting an effect in *low* confidence studies)[b]	◯ Emphasized in Syntheses	• An association between events "A" and "B" is known based on established (basic) biology • An association has been demonstrated for similar chemicals or effects	→
	Slight	• Evidence supporting an effect in one hypothesis-generating *high or medium* confidence study • Evidence suggesting an effect in multiple, reasonably consistent *low* confidence studies	◌ Minimal Discussion in Syntheses	An association is justifiable, or even expected, based on underlying biology, but it has not been well established (note: events for which a biological association appears unlikely are not linked)	⇢
Weakest	Indetermin-ate	• Evidence suggesting an effect in one *low* confidence study • A set of *low* confidence studies with inconsistent results	Not included in figures; may be noted in synthesis text	N/A	N/A
		• Evidence cannot be interpreted (no data; no pattern in results within or across studies) • Data suggest no change	Not included in figures or synthesis text	N/A	N/A

[a]For consistency, the words used to describe the judgments for apical health effect endpoints in human or animal studies were applied (see subsequent section, Evidence Integration and Confidence Conclusions for Noncancer and Cancer Health Outcomes), although the criteria herein are less rigorous (i.e., when evaluating sets of studies), unlike the conclusions for apical health effects.

[b]Supporting evidence and documentation for these decisions is provided in Appendix B.3.6 and C.7, with only the evidence on mechanistic changes (irrespective of the results) most informative to the health effect-specific discussions synthesized in Section 3.

[c]The presence of a comparable or stronger set of studies with directly conflicting evidence results in the identification of the next weaker evidence descriptor (e.g., robust evidence with conflicting data would be moderate); note that the purpose of this evaluation was not to identify mechanistic events for which there was robust evidence of no change; however, the plausibility of the pathways (considering evidence for a lack of changes in expected events) is discussed in later sections.

For the integrated MOA analyses on each potential health effect, the most informative data (i.e., preference is given to robust evidence) were synthesized across tissue compartments, with the discussion spanning those mechanistic events interpreted as the most likely to be due to (or most closely related to) direct interactions with inhaled formaldehyde molecules (i.e., "plausible initial

effects of exposure") to important apical toxicity endpoints (i.e., "key features of a potential hazard", broadly representing the specific health effect findings observed in humans or animals). The health effect-specific syntheses sections are distilled from a broader network-based analysis of the interconnected mechanistic changes within and across tissue compartments, and across potential noncancer respiratory system health effects (see Appendix C.7 for the integrated analyses across the individually synthesized respiratory health effects) using an organizational structure similar to components of the adverse outcome pathway (AOP) approach (Villeneuve et al., 2014; Ankley et al., 2010). These distilled evidence syntheses attempt to simplify the data and emphasize the mechanistic events supported by the evidence interpreted with the highest confidence for each potential health effect, but they are not intended to convey most of the available information. They also only consider mechanistic events identified in formaldehyde-specific studies. These syntheses focus on generalized summary findings regarding the identified mechanistic events rather than observations in individual studies, and they include an overall summary interpretation regarding the biological plausibility of that sequence being a mechanism by which formaldehyde exposure might cause each noncancer respiratory health effects. Where data clearly suggest a dependence on exposure duration or exposure level to elicit an effect, these associations are discussed.

2.6. EVIDENCE INTEGRATION METHODS

For each unit of analysis or broader health effect category, an overall evidence integration conclusion(s) about the evidence for health effects in humans was drawn by integrating the animal and human evidence synthesis judgments (Section 2.5) and incorporating "other inferences" (see Table 2-43 in Section 2.5), namely the human relevance of the animal evidence (i.e., based on default assumptions or empirical evidence), coherence across the human and animal evidence, and susceptibility. This is summarized in an evidence integration narrative for each health effect in Section 3. As with the evidence synthesis judgments, the overall evidence integration conclusion(s) were reached using decision frameworks adapted from considerations originally described by Austin Bradford Hill (Hill, 1965). During evidence integration, the body of evidence (across evidence streams) was integrated based on a structured framework to draw an overall summary evidence integration judgment regarding the evidence for causation (Table 2-45).

This evidence integration framework is consistent with the IRIS Handbook (U.S. EPA, 2022) and interprets the instructions and examples provided in the cancer guidelines (U.S. EPA, 2005a) to allow clarity and consistency in the evaluation of each potential human hazard. The framework is consistent with the cancer guidelines in that evidence in humans generally has greater weight than evidence in animals. Likewise, in the absence of sufficiently justifiable MOA information, effects in animal models are assumed to be relevant to humans. For potential health hazards where the evidence from animal models influenced the overall evidence integration judgment, the available mechanistic evidence was evaluated to inform the human relevance of those findings in animals.

For each potential health effect evaluated, a narrative evidence integration summary and judgment was developed. The overall evidence integration judgments of **evidence demonstrates**, **evidence indicates [likely]**, **evidence suggests**, **evidence inadequate** (to judge hazard), and **strong evidence supports no effect** are defined in Table 2-45 and presented as bolded text throughout the assessment, accompanied by a description of the conditions of expression (e.g., exposure levels, exposure patterns) in the studies that served as the basis for the judgment. This is separate from the "sufficient exposure conditions" statements for noncancer health effects that highlight for the reader that the exposure conditions (i.e., levels, duration, timing) for each health outcome identified as a potential human health hazard during evidence integration are further explored and elaborated upon through dose-response analyses (Section 2.7).

Table 2-45. Overall evidence integration judgments for characterizing potential human health hazards (noncancer health effects and cancer outcomes) in the evidence integration narrative

Overall evidence integration judgment in narrative	Explanation and example scenarios
Evidence demonstrates	This signifies a very high level of certainty that formaldehyde exposure causes the health effect in humans. • This category was[a] used if there was *robust* human evidence supporting an effect. • This category could also be used with *moderate* human evidence and *robust* animal evidence if there was strong mechanistic evidence that MOAs and key precursors identified in animals were anticipated to occur and progress in humans.
Evidence indicates (likely)[b]	This reflects a reasonable certainty that the relationship between formaldehyde exposure and the health outcome is causal, although there may be some outstanding questions that remain. • This category was used if there is *robust* animal evidence supporting an effect and *slight*-to-*indeterminate* human evidence, or with *moderate* human evidence when strong mechanistic evidence was lacking. • This category could also be used with *moderate* human evidence supporting an effect and *slight or indeterminate* animal evidence, or with *moderate* animal evidence supporting an effect and *slight* or *indeterminate* human evidence. In these scenarios, any uncertainties in the *moderate* evidence were not sufficient to reduce or discount the level of concern, or mechanistic evidence in the *slight* or *indeterminate* evidence base (e.g., precursors) existed to increase confidence in the *moderate* evidence.
Evidence suggests (but is not sufficient to infer)[c]	This conveys some concern that formaldehyde may cause a particular health effect in humans, but there were very few studies that contributed to the evaluation, the evidence was very weak or conflicting, or the methodological conduct of the studies was poor. Given the substantial degree of uncertainty, additional research would provide valuable information for future evaluations.

Overall evidence integration judgment in narrative	Explanation and example scenarios
	• This category was used if there was *slight* human evidence and *slight-to-indeterminate* animal evidence. • This category was also used with *slight* animal evidence and *slight-to-indeterminate* human evidence. • This category could also be used with *moderate* human evidence and *slight or indeterminate* animal evidence, or with *moderate* animal evidence and *slight* or *indeterminate* human evidence. In these scenarios, there were outstanding issues regarding the *moderate* evidence that reduced the level of concern or confidence in the reliability of the findings, or mechanistic evidence in the *slight* or *indeterminate* evidence base (e.g., null results in well-conducted evaluations of precursors) existed to decrease confidence in the *moderate* evidence. • Exceptionally, when there is general scientific understanding of mechanistic events that result in a hazard, this category could also be used if there was strong mechanistic evidence that was sufficient to identify a cause for concern—in the absence of adequate conventional studies in humans or in animals (i.e., *indeterminate* evidence in both).
Evidence inadequate[d]	This conveys either a lack of information or an inability to interpret the available evidence. • This category was used if there was *indeterminate* human and animal evidence. • This category could also be used with *slight*-to-*robust* animal evidence and *indeterminate* human evidence if strong mechanistic information indicated that the animal evidence was unlikely to be relevant to humans. A conclusion of **inadequate** is not a determination that the agent does not cause adverse health outcomes or is safe. It generally indicates that further research is needed.
Strong evidence supports no effect	This represents a situation in which extensive evidence across a range of populations and exposure levels has identified no effects/associations. This scenario requires a high degree of confidence in the conduct of individual studies, including consideration of study sensitivity, and comprehensive assessments of the endpoints and lifestages of exposure relevant to the heath effect of interest. • This category was used with *compelling evidence of no effect* in human studies and *compelling evidence of no effect* or *slight* evidence in animal studies. • This category was also used with *indeterminate* human evidence and *compelling evidence of no effect* in animal models concluded to be relevant to humans. • This category could also be used with *compelling evidence of no effect* in human studies and *moderate-to-robust* animal evidence if strong mechanistic information indicates that the animal evidence is unlikely to be relevant to humans.

Note: This table does not supersede or alter direction provided in EPA guidelines. It is meant only to provide added transparency for conclusions drawn regarding the level of evidence from human, animal, and mechanistic studies.
[a]Terminology of "was" refers to the default option; terminology of "could also be" refers to alternative options.

[b]For some applications, such as benefit-cost analysis, to better differentiate the categories of **evidence demonstrates** and **evidence indicates (likely)**, the latter category should be interpreted as evidence that supports an exposure-effect linkage that is likely to be causal.

[c]Health effects characterized as having **evidence demonstrates** and **evidence indicates** (likely) (and, in some cases, **evidence suggests**) are evaluated for use in dose-response assessment. When the database includes at least one well-conducted study and a judgment of **evidence suggests** is drawn, quantitative analyses may still be useful for some purposes (e.g., providing a sense of the magnitude and uncertainty of estimates for health effects of potential concern, ranking potential hazards, or setting research priorities), but not for others [see related discussions in U.S. EPA (2005b)]. It is critical to transparently convey the extreme uncertainty in any such estimates.

[d]Specific narratives for each of the health effects with an evidence integration judgment of **evidence inadequate** may be deemed unnecessary.

For the purposes of this assessment, the same evidence integration approach was used to draw evidence integration judgments for both noncancer health effects and specific cancer types, noting that the approach is based on the methods and considerations described in the EPA cancer guidelines (U.S. EPA, 2005a). Also consistent with these guidelines, for carcinogenicity, a final step of categorizing the weight of evidence as to whether formaldehyde inhalation exposure is carcinogenic to humans was summarized using "descriptors," consistent with EPA cancer guidelines (U.S. EPA, 2005a) (Table 2-46). Thus, the descriptors build upon the overall evidence integration judgments for individual cancer types; however, this does not alter or supersede direction provided in EPA guidelines. These descriptors are bolded and italicized throughout the assessment.

Table 2-46. Criteria for applying cancer descriptors to overall confidence conclusions for cancer types

Cancer descriptor	Criteria
Carcinogenic to humans	This descriptor was used if the **evidence demonstrates** that, for at least one cancer type, formaldehyde inhalation exposure caused the increase in cancer incidence or mortality. This descriptor could also be used in rare instances if the **evidence indicates** that formaldehyde inhalation exposure likely causes different cancer types across evidence bases (e.g., when one type of cancer is based on human evidence and tumors at another site is supported by animal evidence), consistent with EPA guidelines (U.S. EPA, 2005a) that site concordance is not required. Such a decision would depend on mechanistic understanding (i.e., in this example, the decision would consider differences in tumor types or ADME across species).
Likely to be carcinogenic to humans	This descriptor was used if the **evidence indicates** that, for at least one cancer type, formaldehyde inhalation exposure likely caused the increase in cancer incidence or mortality. Similar to the rationale provided above, this descriptor could also be used in rare instances when the **evidence suggests** formaldehyde inhalation exposure may cause multiple tumor types, depending on mechanistic inference.
Suggestive evidence of carcinogenic potential	This descriptor was used if, for the evidence relating to carcinogenicity, the **evidence** was only **suggestive** that formaldehyde inhalation exposure may cause any of the observed increases in cancer incidence or mortality for any cancer type. This would reflect a substantial degree of uncertainty in any potential causal inference.

Cancer descriptor	Criteria
Inadequate evidence to assess carcinogenic potential	This descriptor was used if the **evidence** was **inadequate** to draw a conclusion regarding cancers of any type with any confidence. This might reflect a lack of information or highly conflicting information.
Not Likely to be carcinogenic to humans	This descriptor conveys a high degree of certainty that there is negligible concern for carcinogenic effects. A substantial amount of evidence would be required to support this descriptor (see (U.S. EPA, 2005a).

2.7. DOSE-RESPONSE ASSESSMENT METHODS

This formaldehyde assessment includes development of organ/system-specific RfCs (osRfC) for noncancer health effects identified as human hazards and an overall RfC for noncancer effects, as well as an IUR for carcinogenic effects, all presented in units of μg/m^3.[14] The dose-response analyses (Section 5) build from the hazard identification decisions, exploring and better defining the "sufficient exposure conditions" mentioned in Section 3. This highlights that, for those assessment-specific health effects identified as potential hazards, the exposure conditions associated with those health effects are defined (as are the uncertainties in the ability to define those conditions) during dose-response analysis (U.S. EPA, 2022).

Based on the data available for this assessment, the subset of studies used to develop RfCs and inhalation unit risk estimates were from those noncancer health outcomes and specific cancer types with an overall judgment of **evidence demonstrates** or **evidence indicates [likely]** regarding the potential for formaldehyde inhalation to cause those effects. For noncancer toxicity values, the dose-response analyses attempt to characterize the exposure conditions (i.e., levels, duration, timing) that are interpreted as "likely to be without an appreciable risk of deleterious effects during a lifetime" in any individual (i.e., RfCs are health-protective values). For cancer toxicity values, the dose-response analysis provides an upper-bound estimate of the increased lifetime risk of cancer from continuous exposure to an agent at a concentration of 1 μg/m^3 formaldehyde in air.

From among the large body of evidence used for the hazard identification, selection of the studies for dose-response assessment relied first on the study confidence evaluations (i.e., for this extensive evidence base, only *high* or *medium* confidence studies were evaluated for potential use in dose-response analyses), with particular emphasis and reconsideration (in the context of utility of the study for dose-response analysis) of expert ratings regarding potential co-exposure and confounding. The characteristics of the study population, details regarding exposure levels, the accuracy of formaldehyde exposure, and the reliability of the outcome measures are also separately reconsidered. In addition, study selection considered factors not necessarily considered during individual study evaluations, including interpretations regarding the severity of the observed effects, potential susceptibility, the study-specific formaldehyde exposure conditions (levels,

[14] Throughout this assessment, a conversion of 1 ppm = 1.23 mg/m^3 formaldehyde is used.

duration, periodicity), and the utility of the results for quantitative analyses. The considerations for study selection are outlined in Table 2-47. As with the study evaluations (see Section 2.3), the application of these considerations cannot be reduced to a formula and a scoring approach was not used. Rather, for the evaluation of each factor, study-specific limitations interpreted to potentially impact the utility of the study results for dose-response analysis were documented, based on expert judgment. Specifically, considering the context of the other available studies on the effect of interest, limitations interpreted to introduce a "**critical concern**" with the use of the study data in dose-response analysis resulted in that dataset not being advanced for POD derivation. Less significant limitations interpreted to introduce "*some concern*" may or may not prevent the dataset from advancing for POD derivation; if advanced, these limitations informed later dose-response decisions (e.g., confidence in the cRfC; see below). The evaluation of these considerations applied to individual *medium* and *high* confidence studies for potential use in dose-response analysis is documented in Sections 5.1.1 and 5.2.

Table 2-47. Considerations for study selection for quantification of dose response and derivation of toxicity values

Factor		Considerations
Study Confidence and Confounding	Study Confidence	For this assessment, studies of *low* confidence are not considered for quantification. The available *high* and *medium* confidence studies are further differentiated on the basis of the study attributes below, as well as the specific limitations identified and their potential impact on dose- response analyses.
	Co-exposure and Confounding	Studies with a design (e.g., matching procedures, blocking) or analysis (e.g., covariates or other procedures for statistical adjustment) that adequately address the relevant sources of potential meaningful confounding for a given outcome are preferred. For experimental studies, those with better inhalation exposure quality ratings are preferred and studies interpreted to include potential confounding by methanol are not modeled.
Population or Subjects		Human studies are typically preferred over animal studies to eliminate interspecies extrapolation uncertainties. Animal studies are considered the studies of primary interest when adequate human studies are not available. For some hazards, studies of particular animal species known to respond similarly to humans would be preferred over studies of other species. Dose-response information for the most susceptible subgroups is also preferred, if appropriate given the other considerations herein and permissible based on the available information.
Exposure	Exposure Measures and Levels	Exposure metrics most relevant to quantifying the effects of lifetime formaldehyde exposure for the health outcome of interest are preferred. Exposures near the range of typical environmental human exposures are preferred. Studies with a broad exposure range and multiple exposure levels are preferred to the extent that they can provide information about the shape of the exposure-response relationship (see (U.S. EPA, 2012), Section 2.1.1) and facilitate extrapolation to more relevant (generally lower) exposures.

Factor		Considerations
	Exposure Duration and Frequency	When developing the (lifetime) RfC, chronic or subchronic studies are preferred over studies of acute exposure durations. Exceptions exist, such as when a susceptible population or lifestage is more sensitive in a particular time window (e.g., developmental exposure). Likewise, studies reflecting formaldehyde exposures most relevant to constant, lifetime exposure (e.g., of a given periodicity or frequency) are prioritized.
Outcome Measure(s)		Studies that can reliably distinguish the presence or absence of the outcome are preferred. Outcome ascertainment methods using generally accepted or standardized approaches are preferred. Among several relevant health outcomes, preference is generally given to those outcomes that better represent the identified hazard (e.g., more apical, or translatable [to human disease] outcomes are generally preferred), and outcomes interpreted to have greater biological significance or severity. Studies with sufficient latency for measuring the outcome of interest are also preferred.
Results Utility	Study Size and Design	Preference is given to studies using designs expected to have power (e.g., considering sample size or number of cases) to detect responses of suitable magnitude. This does not mean that studies with substantial responses, but low power would be ignored, but that they should be interpreted in light of a confidence interval or variance for the response. Studies that address changes in the number at risk (e.g., through decreased survival) are preferred. Experimental studies with evidence of selective reporting and cohort studies with apparent loss to follow up are generally not preferred.
	Results Reporting	Reasonably complete reporting of the results of interest is preferred. Studies with risk estimates for multiple exposure levels or regression coefficients per unit of formaldehyde concentration are generally preferred over LOAELs or NOAELs because they provide information about the shape of the concentration-response curve and allow for benchmark dose modeling. Studies with individual-level data are preferred in general. For example, individual-level data allow for the characterization of experimental variability more realistically and to characterize overall incidence of individuals affected by related outcomes.

[a] A NOAEL/LOAEL approach may also be used in cases when data are not amenable to BMD modeling (e.g., those resulting from incomplete data availability or from a lack of models that can describe the data adequately).

The ubiquitous endogenous presence of formaldehyde in the body can complicate quantitative risk assessment for several reasons. The role of endogenously generated formaldehyde in human diseases is largely unknown. This includes endogenous formaldehyde generated during normal cellular metabolic processes, as well as formaldehyde produced endogenously within cells (e.g., in the liver) as a breakdown product of external exposures to other chemicals, including ingestion of caffeine (Summers et al., 2012; Hohnloser et al., 1980) and methanol-rich foods or beverages, such as fruit-based liquors (Riess et al., 2010). The mode of action by which toxicity at distal sites, such as bone marrow or reproductive tissues, may occur in response to inhalation of formaldehyde over long periods, also is not known. Once formaldehyde is inhaled and interacts with extracellular aqueous matrices such as mucus in nasal passages and is hydrated, the biochemical reactivity of inhaled formaldehyde and endogenous formaldehyde are presumably very similar, given that there are no differences in chemical structure. However, no specific data are available to inform whether there may be differences in interactions with specific extracellular or

intracellular macromolecular targets in vivo. While the rate of cellular detoxification of exogenous formaldehyde remains unknown, the production and subsequent detoxification of endogenous formaldehyde appears to be kept under strict control and has been well described (Burgos-Barragan et al., 2017b).

The focus of the assessment is to estimate the risk over background that results from only the exogenous exposure, and the assessment assumes that background incidence of cancer or other health hazards that may potentially be attributed to endogenous formaldehyde is already accounted for in the background incidence. Endogenous formaldehyde might be responsible for some portion of background risks for some health outcomes, particularly when normal detoxification pathways are deficient (Pontel et al., 2015); but that possibility is not the purpose of this review. This assessment does consider and discuss the potential impact of normal levels of endogenous formaldehyde on the penetration and distribution of inhaled formaldehyde, based on dosimetric models ((Schroeter et al., 2014; Campbell Jr et al., 2020); see Sections 3.1, 5.1.2, and 5.2.1). In addition, efforts to incorporate the unknown contribution of endogenous formaldehyde to background cancer incidence in an attempt to bound low-dose human cancer risks from formaldehyde exposure have been published using a measure of internal dose for inhaled formaldehyde. These papers are discussed in Section 5.2.5 and Appendix D.2.4.

For each health effect for which a toxicity value was derived, one or more animal or human studies were determined to be suitable for use in quantitative dose-response assessment and points of departure (PODs) were determined (see Section 5). In some cases, estimates considered information from mechanistic studies. Specifically, for some outcomes (i.e., nasal cancers; noncancer respiratory tract pathology), analyses included efforts to apply dosimetry models estimating the uptake of inhaled formaldehyde, including an evaluation of modeling efforts to account for the potential contribution of endogenous formaldehyde on uptake. Study-specific PODs were adjusted as appropriate (e.g., for constant, lifetime exposure) and used to calculate candidate toxicity values. For noncancer analyses, cRfCs for were calculated for each potential health effect and one or more cRfCs were selected to represent the osRfC for that effect. For cancer analyses, cancer type-specific unit risks were estimated and, for one mechanism that contributes to cancer risk and appears to involve a threshold, cRfCs were derived. IURs addressing cancers shown to operate through a mutagenic MOA include application of age-dependent adjustment factors (ADAFs), consistent with EPA cancer guideline recommendations to address early life cancer risk (U.S. EPA, 2005b). The strengths and limitations of each estimate are described, and the associated uncertainties are discussed and weighed in selecting the final toxicity values.

A confidence level of **high**, **medium**, or **low** (or a combination of two of these) was assigned to each noncancer toxicity value.[15] This confidence level was determined based on evaluations of

[15] For hyphenated confidence classifications, the order of the terms is used to provide greater transparency in the confidence judgment for the purposes of this assessment, which also aids selection of osRfCs from amongst the

several more narrowly defined confidence determinations for each cRfC that address the interpreted accuracy, reliability, and stability of the value (see Table 2-48), each of which is separately documented and justified in Section 5.1. Specifically, the overall confidence classification was primarily based on confidence in the accuracy of the associated POD calculation(s) and the reliability of the studies used to calculate the PODs, the latter of which considers the strength of the evidence for concluding that formaldehyde inhalation results in the study-specific health effects of interest. To a lesser extent, it also considered the interpreted confidence regarding the completeness of the evidence base for each broader health effect category.

Table 2-48. Considerations for confidence in noncancer toxicity values

Factor	Confidence considerations
Confidence in the POD	This reflects a judgment regarding how well the study-specific data are able to estimate the POD (i.e., a NOAEL, LOAEL, or BMCL). For example, a lower level of confidence would be applied to high-concentration studies that required extrapolation far below the lowest tested concentration to estimate a POD. A confidence classification of **Low** confidence indicates that the POD derived is expected to be appreciably less accurate than **Medium** or, more so, **High** confidence classifications.
Confidence in the Study	This confidence classification builds from the individual study evaluation judgments and the interpreted reliability of those studies for use in dose-response analysis laid out in Table 2-47. It considers the appropriateness of the population and study design for use in deriving the value of interest, including an emphasis on considerations related to its generalizability, interpretability (e.g., as an effect representative of the relevant evidence integration judgment), and its ability to address potential susceptibility. A confidence classification of **Low** confidence means the reliability of the study data for use in deriving the specific value of interest is interpreted as appreciably lower than **Medium** or, more so, **High** confidence classifications.
Confidence in the Evidence Base	Although a $UF_D = 1$ was applied to all candidate and selected toxicity values for this assessment given the extensive formaldehyde database and the expectation that additional study wouldn't substantially lower the selected overall RfC, it is recognized that the evidence databases for the various health effects are not equal. This confidence classification builds from the broader evidence integration judgments and primarily emphasizes the health effect-specific areas where additional research could reduce existing uncertainties. A confidence classification of **Low** confidence means the degree of certainty regarding the stability of the value to additional study is appreciably lower than **Medium** or, more so, **High** confidence classifications.

These confidence judgments were used with other considerations (i.e., the composite UF for each value and the sensitivity of compared values of similar confidence) to inform toxicity value selection. Specifically, confidence in the cRfCs informed selection of the osRfCs, and confidence in the osRfCs informed selection of the RfC. Considering confidence in the relevant osRfC(s) and also the completeness of the formaldehyde literature database overall, an overall level of confidence in

available cRfCs and selection of the RfC from amongst the available osRfCs. Specifically, when hyphenated, the first term reflects the confidence category and the second term indicates whether the judgment is closer to a higher or lower confidence category, based on the term used (e.g., **Medium-high** would reflect a **medium** confidence judgment that is almost a judgment of **high** confidence). Confidence judgments are a matter of expert judgment based on the evidence available and it can be difficult to compare confidence classifications across assessments, particularly when developed to inform different decision purposes.

the RfC was drawn. For noncancer dose-response analyses, multiple graphical depictions were developed to display PODs, uncertainty factors, and candidate toxicity values across outcomes and studies, as well as the context of these estimates (e.g., in relation to the study-specific results; in relation to known human exposures to formaldehyde).

For the derivation of the cancer inhalation unit risk (IUR) estimate, an overall level of confidence was assigned as described in the EPA cancer guidelines (U.S. EPA, 2005a).

3. EVIDENCE SYNTHESIS AND INTEGRATION

Potential health hazards from the inhalation of formaldehyde were evaluated across multiple health domains, including sensory irritation; pulmonary function; immune system effects, focusing on allergies and asthma; respiratory tract pathology; nervous system effects; reproductive and developmental toxicity; and cancer. Research results for several cancer sites were evaluated, specifically cancers of the upper respiratory tract ([URT]; i.e., nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx and hypopharynx, laryngeal cancer) and of the lymphohematopoietic system (i.e., Hodgkin lymphoma, multiple myeloma, myeloid leukemia, lymphatic leukemia). The evidence regarding the potential for formaldehyde exposure to cause other cancer types (i.e., lung, non-Hodgkin lymphoma, brain, bladder, colon, pancreas, prostate, skin) were not systematically evaluated because only a few studies reported analyses for these cancer sites (see Appendix B.3.9 for detail). Multiple health endpoints were evaluated within each of these hazard domains using primary research studies in human populations and experimental animals and in supporting mechanistic studies. The mechanistic studies informing all potential respiratory effects were considered and analyzed together due to the potential interdependencies of the mechanisms involved (see Appendix C.7, with supporting documentation in Appendix B.2.6 and B.3.6). The majority of studies evaluating the potential toxicity of formaldehyde inhalation exposure have focused on effects at the portal of entry (POE), primarily the URT, with less research available to inform potential systemic, or nonrespiratory, effects. Although some uncertainties remain, the organization and analyses in the assessment assume that inhaled formaldehyde is not distributed to an appreciable extent beyond the upper respiratory tract to distal tissues (see Section 3.1); thus, it is assumed that inhaled formaldehyde is not directly interacting with tissues distal to the portal of entry (POE) to elicit systemic effects. Thus, the synthesis of the evidence for each identified health endpoint is provided in Section 3.2 for potential respiratory system-related effects (including cancer and noncancer endpoints) and in Section 3.3 for potential nonrespiratory health effects.

3.1. TOXICOKINETICS OF INHALED FORMALDEHYDE

Formaldehyde is a respiratory irritant for which the human body has developed several detoxification and removal processes, especially at the site(s) of first contact (i.e., nasal passages for inhalation). Thus, this discussion of the toxicokinetics of inhaled formaldehyde at the POE is organized according to the most likely sites of first contact between inhaled formaldehyde and biological materials, in the context of the known anatomy and potential elimination processes of the respiratory tract tissues. A more comprehensive summary of what is known about the absorption, distribution, metabolism, and excretion of inhaled formaldehyde is provided in Appendix C.1. This

section also includes a discussion of published analyses of the potential impact of endogenous levels of formaldehyde produced during normal cellular metabolism on the toxicokinetics of inhaled formaldehyde.

3.1.1. Distribution of Inhaled Formaldehyde

Much of what is known about the uptake and distribution of formaldehyde is based on experimental animal studies, primarily in monkeys and rats. Several of the key considerations for evaluating the toxicokinetics of inhaled formaldehyde at the POE in the rat nose are represented schematically in Figure 3-1. Species differences in the structure of the airways and breathing patterns, as well as the composition of the surface epithelium at various nasal locations, are important considerations when interpreting results in experimental animals and extrapolating observations to humans. While the nasal passages in humans are generally similar to those in other mammalian species, one key difference is that humans and nonhuman primates have nasal passages adapted for both oral and nasal (oronasal) breathing, as opposed to obligate nasal breathing in rodents. A second key difference regards the shape and complexity of the nasal turbinates, with relatively simple shapes in humans, and complex, folded patterns in rodents. In general, these differences provide better protection of the rodent lower respiratory tract against inhaled toxicants than is provided to the human lower respiratory tract (Harkema et al., 2006).

Uptake of formaldehyde (defined as retention within the respiratory tract tissue), based on rough estimates determined from the amount of formaldehyde removed from the air, indicates that the vast majority of formaldehyde is removed from inhaled air by the upper respiratory tract (URT) in monkeys (Monticello et al., 1989; Casanova et al., 1991), dogs (Egle, 1972) and rats (Kimbell et al., 2001b; Kerns et al., 1983; Heck et al., 1983; Chang et al., 1983). Further, dosimetric modeling studies in humans have shown close agreement with observations of exposed rodents, namely, that 90–95% of inhaled formaldehyde is deposited in the URT (Yang et al., 2020; Subramaniam et al., 1998; Overton et al., 2001; Kimbell et al., 2001b). Most recently, Yang et al. (2020) conducted inhalation studies in 120 (70 female and 50 male) healthy human volunteers and measured their absorption of formaldehyde and selected volatile organic compounds. The absorbed formaldehyde $C_{inh} - C_{exh}$ was seen to be linearly related to C_{inh}. The slope of this straight line, which expresses a mean deposition rate for the range of concentrations from 2 ppb to 18 ppb was determined to be 0.97, indicating that most of the inhaled formaldehyde is absorbed, on average, at these low concentrations. This is consistent with prior understanding regarding the extent of formaldehyde absorbed. A detailed description of dosimetry modeling efforts in humans, monkeys, and rats is provided in Appendix C.1. As demonstrated in monkeys and rats, and as modeled in humans, a concentration gradient of inhaled formaldehyde follows an anterior-to-posterior distribution, with high concentrations of formaldehyde distributed to squamous, transitional, and respiratory epithelium, and less uptake by olfactory epithelium. Except under exercise conditions or with exposure to high formaldehyde concentrations, very little formaldehyde reaches more distal sites such as the lung. The possibility that more extensive distribution to the LRT may occur when people

are regularly breathing through the mouth or when they have an upper respiratory tract infection has not been directly investigated (see Sections 3.2.2 and 3.2.3 for discussions of the available, indirect evidence). Likewise, no specific toxicokinetic studies focusing on the possibility of inhaled formaldehyde distributing to the developing fetus were identified; however, based on current understanding of its reactivity and distribution, it is unlikely that inhaled formaldehyde would reach the developing fetus.

Asgharian et al. (2012) developed a pharmacokinetic model for transport of formaldehyde and other gases in the human lung, across the air-tissue interface towards arterial blood, that explicitly incorporates information on partition coefficient, metabolism, and tissue reactivities (considered as saturable and first-order clearance pathways). This was a substantial improvement over the approach in Overton et al. (2001) that was used for providing formaldehyde dose to the lung in the Conolly et al. (2004) model for extrapolating cancer risk to the human; Overton et al. (2001) did not model the tissue kinetics [and hence the systemic dose] but assumed a constant mass transfer coefficient. There are several noteworthy results from this paper:

- Surface flux rates of formaldehyde appeared to be predictive of local tissue concentrations.
- 97% of the inhaled formaldehyde was absorbed.
- Formaldehyde did not penetrate beyond 60 μm of tissue depth in any breathing scenario, thus predicting that systemic penetration is not likely to take place.
- This model predicted a 25% higher tracheal mass flux of formaldehyde, and correspondingly lesser flux to the deep lung, than Overton et al. (2001). It is important to note that this quantitative result is not relevant to the dose-response modeling in this assessment (see Sections 5.1 and 5.2). While the extrapolation model by Conolly et al. (2004) uses formaldehyde dose to the human lung as input, this model is not used in this assessment and lung cancer is not identified as a hazard (see Section 3.2.5).

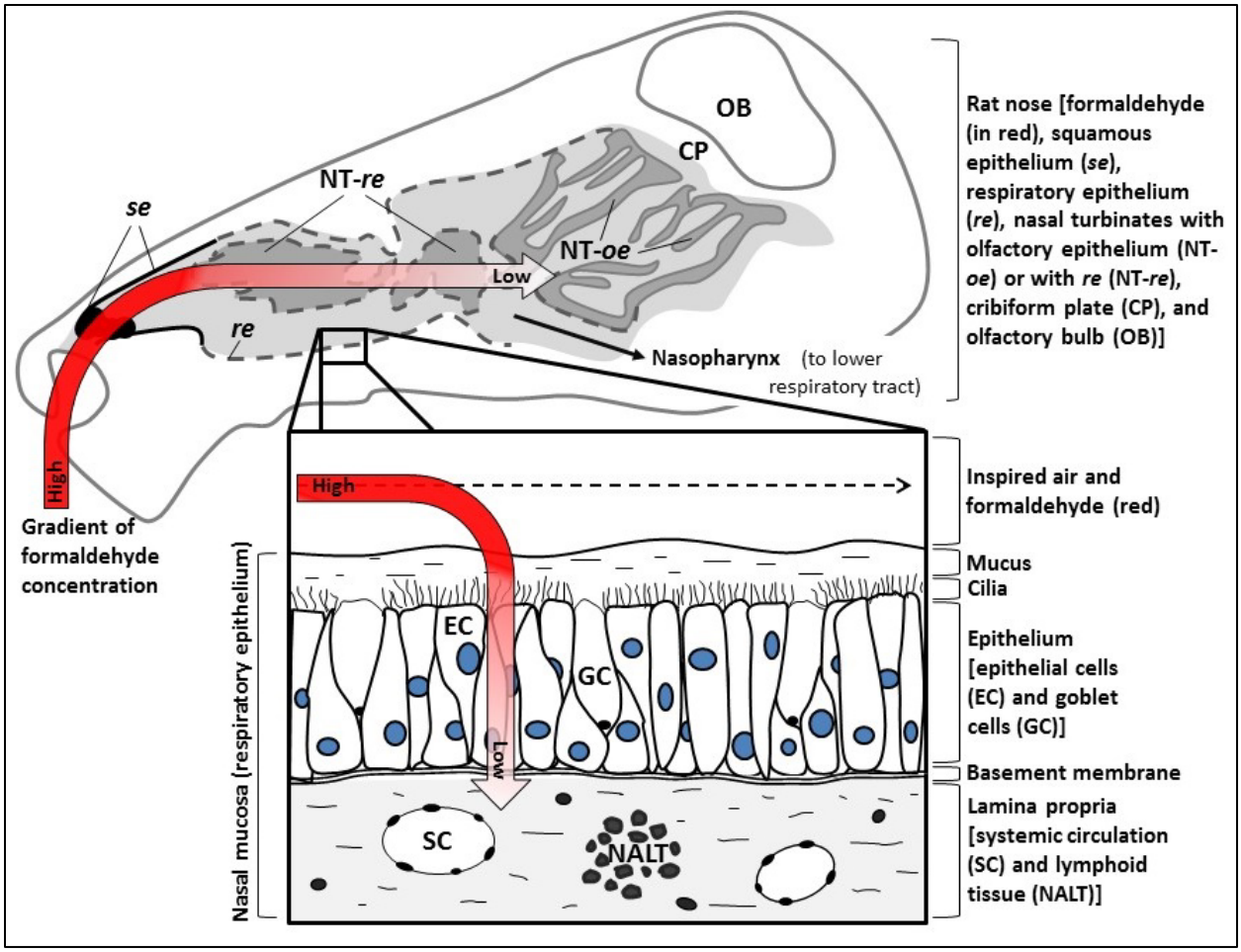


Figure 3-1. Schematic of the rat upper respiratory tract depicting the gradient of formaldehyde concentration formed following inhalation exposure, both from anterior to posterior locations, as well as across the tissue depth.

Modeling based on observations in rodents predicts a similar pattern of distribution in humans. Drawing is based in part on images by NRC (2011) and Harkema et al. (2006). Note: Other components (e.g., naris, transitional epithelium) have been omitted for clarity.

Corley et al. (2015) developed integrated air and tissue transport models for predicting airway region-specific tissue dose of tobacco smoke in the rat and human, upper and lower, respiratory tracts. Their approach coupled computational fluid dynamics (CFD) models for gas transport in the airways with airway region-specific PBPK models for tissue transport, and included realistic, transient breathing patterns. Although the paper was aimed at tobacco smoke, results were separately provided for the acrolein, formaldehyde and acetaldehyde constituents. Metabolic interactions and reactions were described by clearance through a saturable enzymatic pathway, a first order pathway representing intrinsic tissue reactivity, and a first order binding to DNA to form DPX. Details on regional distribution of metabolic enzymes and local blood perfusion rates were incorporated and the simulations were carried out until breath-by-breath, steady-state kinetics was

achieved in all tissues. These calculations of regional tissue concentrations as a function of tissue depth are a substantial improvement over other dosimetry models that could model only airway wall flux rates of formaldehyde. The primary results relevant to this assessment were as follows:

- Formaldehyde does not penetrate deep into epithelial or subepithelial tissue even in the olfactory region where the penetration was greatest, and therefore does not transport directly to the systemic blood circulation at moderate exposure concentrations.
- As with prior formaldehyde rat dosimetry models, their model predicted greatest initial uptake rates of the gas in the anterior respiratory nasal region. However, the uptake was greater in the anterior dorsal olfactory epithelium when area under the curve (AUC) concentrations were calculated by integrating the concentration profile over time of exposure as well as depth normal to the air-tissue interface under more realistic transient breathing profiles.
- The simulation covered only oral inhalation in the human because the purpose of the research was to investigate uptake from cigarette smoke. In the human, oral and laryngeal tissues received the greatest local tissue dose. Overall formaldehyde absorbed was 97% at 2 and 6 ppm and about 94% at 15 ppm exposure concentrations.
- Formaldehyde surface fluxes did not correlate well with local time dependent tissue concentration AUCs for all nasal tissues in the rat; the AUCs were significantly higher in the olfactory region than would be predicted by surface flux alone. This finding was counter to the conclusion in Asgharian et al as detailed above.

The modeling approach in Corley et al. (2015) could potentially make a tangible difference in extrapolated dose over that computed by solely surface flux-based models in the case of reactive gases that result in adverse effects in the rat olfactory region. Because the findings of formaldehyde induced cancer or noncancer effects in the URT of the rat are not observed in the olfactory region (see Section 3.2.5), this modeling approach by Corley et al. (2015) was not applied.

As inhaled formaldehyde enters the URT, it interacts with the mucociliary apparatus, the first line of defense against inhaled materials in the nose. In nasal mucus, most of the formaldehyde is rapidly converted to methanediol (~99.9%) and a minor fraction remains as free formaldehyde (~0.1%) (Bogdanffy et al., 1986). Inhaled formaldehyde induces mucostasis and ciliastasis in the rat that extends from anterior to posterior regions of the nasal cavity depending on the concentration and duration of exposure (Morgan et al., 1986a). Thus, inhalation of higher concentrations can potentially slow clearance mechanisms and increase the proportion of formaldehyde that is available to react with cellular components or that is distributed to epithelium and systemic circulation. Whether mucostasis or ciliastasis is induced with longer exposure duration to low levels of formaldehyde is not known. Methanediol is assumed to be better able to penetrate the tissues while free formaldehyde reacts with macromolecules. It is assumed that the equilibrium is rapid, hence that the methanediol: free formaldehyde equilibrium ratio is maintained (Fox, 1985). Formaldehyde levels are reduced through interactions with components of the mucus and through mucociliary clearance, through reactions with cellular materials at the plasma membrane of the

respiratory epithelium, via interactions with glutathione (GSH) and other macromolecules in the intracellular and extracellular space, through localized metabolism and conjugation reactions, and through reversible interactions with intracellular materials. These processes result in the formation of a gradient of formaldehyde across the tissue space, with the greatest formaldehyde concentration at the apical surface of the mucosa, and the lowest levels of formaldehyde at deeper components of the tissue, such as the nasal-associated lymphoid tissues (NALT) and blood vessels.

Several uncertainties exist regarding the transition of inhaled formaldehyde from the mucociliary layer to the underlying epithelium. Although direct experimental evidence is lacking, the biochemical properties of formaldehyde make it likely that inhaled formaldehyde (in the hydrated or anhydrated form) undergoes passive transport, via simple diffusion, across biological membranes. As a result, higher extracellular formaldehyde levels would be expected to result in increased diffusion into the cell owing to the concentration gradient formed. However, this concentration gradient may be affected by endogenous formaldehyde levels, since in humans, as in other animals, formaldehyde is an essential metabolic intermediate in all cells (Thompson et al., 2009).

Two groups of researchers, Schroeter et al. (2014) and Campbell Jr et al. (2020) developed toxicokinetic models of formaldehyde uptake that incorporate the production of endogenous formaldehyde in nasal tissue. Schroeter et al. (2014) revised the fluid dynamic modeling by (Kimbell et al., 2001a; Kimbell et al., 2001b) to explicitly include tissue pharmacokinetics. The Campbell Jr et al. (2020) model simulates observed data for formaldehyde-induced DNA mono-adducts (N^2-hydroxymethyl-dG) using exogenous and endogenous formaldehyde adduct data published after 2010. This model was based on a modification of Andersen et al. (2010) which simulated formaldehyde-induced DNA-protein cross-links (DPX). Both models, Schroeter et al. (2014) and Campbell Jr et al. (2020), interpreted their modeling results as indicating endogenous formaldehyde to reduce uptake of inhaled formaldehyde from the air phase to the tissue compartment.

In the first model, net desorption of the gas was predicted at exposure concentrations below 1 ppb in humans. While Schroeter et al. (2014) interpreted calculations they made on "net nasal uptake" of formaldehyde as showing a reduction in the uptake of formaldehyde at low concentrations, EPA believes that this mischaracterizes the modeling results. Appendix C.1.12 discusses problems with the net uptake calculations in Schroeter et al. (2014) and notes that examination of that paper's tabulated results on formaldehyde flux into nasal tissues indicates a process that is linear in the lower concentration range. In the second model developed only for the rat, the model was calibrated with the restriction that formaldehyde absorption in the nose occurs only at exposure concentrations above 0.3 ppm based upon the available experimental DNA adduct data, and the model predicted that the inhalation rate must exceed the tissue clearance rate for formaldehyde to be absorbed by the tissue. The results from both these pioneering projects add to our characterization of uncertainties related to formaldehyde dose-response at low exposures; at

sufficiently low levels of exogenous formaldehyde, the contribution of endogenous formaldehyde could become significant. Additionally, when including endogenous formaldehyde in an analysis it is important to incorporate considerations of the large variability in these levels. [The impact of this variability was apparent, for example, from the individual animal data on DNA adducts formed by formaldehyde in Swenberg et al. (2013), kindly made available to EPA by the authors. A number of animals in these data had very high endogenous levels of these adducts; in these animals, the total (endogenous plus exogenous) internal dose even at a low inhaled exposure concentration of 2 ppm, as measured by the level of DNA adducts, was comparable to the mean total internal dose measured in the group of animals exposed at 10 ppm. At this dose, considerable carcinogenicity was observed in animal bioassays in other studies.] There are also crucial uncertainties in the measurements of free endogenous formaldehyde levels as highlighted by Campbell Jr et al. (2020) and discussed further in Appendix C.1.

EPA evaluated the Schroeter et al. (2014) model and determined that the model predicts *any* external exposure to cause some increase in formaldehyde tissue concentration over background levels. EPA's evaluation, as detailed in Appendix C.1, pointed to critical uncertainties in model assumptions; therefore, this model was not directly used in EPA calculations. However, as a sensitivity analysis, it was seen that EPA benchmark concentrations based on formaldehyde as a dose metric in Sections 5.1.2 and 5.2.1 do not change appreciably when results from Schroeter et al. (2014) are used.

Extrapolation of results in Campbell Jr et al. (2020) to humans is not possible because the data and the model are specific to rats. These models and a discussion of studies of formaldehyde distribution in the URT are discussed further in context of the toxicokinetics of inhaled formaldehyde in Appendix C.1.

3.1.2. Metabolism, Binding, and Removal of Inhaled Formaldehyde

In the URT, formaldehyde is predominantly metabolized by glutathione-dependent class III alcohol dehydrogenase (ADH3) and by a minor pathway involving aldehyde dehydrogenase 2 (ALDH2) to formate. Formate can either enter the one-carbon pool leading to protein and nucleic acid synthesis or is further metabolized to CO2 and eliminated in expired air or excreted in urine unchanged. ADH3 and ALDH2 show region-specific differences in distribution in the respiratory and olfactory mucosa, and higher levels of ADH3 activity have been reported in the cytoplasm of the respiratory and olfactory epithelial cells of rats and in the nuclei of olfactory sensory cells, as compared to other regions of the nasal mucosa (Keller et al., 1990). The presence of areas of high enzyme activity highlights a significant barrier to the penetration of inhaled formaldehyde beyond the respiratory epithelium.

Formaldehyde can interact with macromolecules either by noncovalently binding to glutathione (GSH), tetrahydrofolate (THF), or albumin in nasal mucus or by covalently forming DNA protein crosslinks (DPXs), DNA-DNA crosslinks (DDCs), hydroxymethyl-DNA (hm-DNA) adducts

(see Appendix C.1), or protein adducts, such as N6-formyllysine (Edrissi et al., 2013b; Edrissi et al., 2013a). In rats and monkeys, a concentration-dependent increase in DPX formation is observed in nasal passages. Metabolic incorporation studies with 14C-formaldehyde have shown both covalent binding and metabolic incorporation in nasal tissues (Casanova-Schmitz et al., 1984b; Casanova and Heck, 1987). Inhaled formaldehyde induces a concentration-dependent increase in N2-hydroxymethyl deoxyguanosine (N2-hm-dG) adducts, another form of formaldehyde-induced covalent DNA modification, in the nasal passages of monkeys and rats. Recently, analytical methods have been developed that can distinguish between N2-hm-dG adducts from exogenous (inhaled) formaldehyde and N2-hm-dG adducts from endogenous formaldehyde (Moeller et al., 2011; Lu et al., 2010a; Lu et al., 2011; Lu et al., 2012). For example, an increase in exogenous formaldehyde adducts has been observed in rat nasal tissue at 0.7–15 ppm (0.86–18.45 mg/m^3) formaldehyde without any significant increases in endogenous adducts following a single 6-hour exposure (Lu et al., 2011) or at 10 ppm (12.3 mg/m^3) after exposure to formaldehyde for 1 or 5 days (6 hrs/day) (Lu et al., 2010a). However, in a more recent study with a lower detection limit for adducts and testing lower formaldehyde exposure levels, Leng et al. (2019) did not observe an increase in exogenous hmDNA adducts or DPXs, including in nasal and respiratory tissues as well as at systemic sites (e.g., bone marrow), at formaldehyde levels of 0, 1, 30, or 300 ppb (up to 0.37 mg/m^3) after exposure for 28 days. The lack of detectable exogenous adducts in the URT at 0.3 ppm (0.37 mg/m^3) helps to inform the evolving understanding of formaldehyde induced DPX at lower concentrations, which would benefit from additional study. DNA monoadducts (Yu et al., 2015a; Moeller et al., 2011; Lu et al., 2010a; Lu et al., 2011) and DPXs (Lai et al., 2016) derived from exogenous formaldehyde were detectable in nasal tissues, but not in distal tissues (including the bone marrow), of experimental animals exposed by inhalation, supporting that exogenous formaldehyde is not systemically distributed. Also, toxicokinetic studies showed that labeled carbon from inhaled formaldehyde measured in bone marrow of rats was the result of metabolic incorporation from the 1-Carbon (1C) pool, not covalent binding, further supporting the lack of transport of formaldehyde or metabolites of formaldehyde to the distal tissues (Casanova-Schmitz et al., 1984b). Finally, inhalation exposure to formaldehyde does not appear to alter blood formaldehyde levels (approximately 0.1 mM across different species), suggesting that inhaled formaldehyde is not significantly absorbed into blood (Kleinnijenhuis et al., 2013; Heck et al., 1985; Casanova et al., 1988).

The toxicokinetics of formaldehyde may be influenced by certain formaldehyde-related effects, such as mucociliary clearance (Morgan et al., 1983), reflex bradypnea (rodents only) and corresponding reductions in minute volume (Chang et al., 1981; Chang and Barrow, 1984), and dynamic changes in tissue structure (Kamata et al., 1997), all of which have the potential to modulate formaldehyde uptake and clearance. For example, during repeated inhalation exposure to formaldehyde, mice but not rats lower their minute volume thereby restricting the intake of the gas (Chang et al., 1981; Chang and Barrow, 1984), which may impact dosimetric adjustment if the dose-

response results from these studies are extrapolated to humans. Exposure to formaldehyde can also cause a perturbation of ADH3-dependent pathways involved in cell proliferation (Nilsson et al., 2004; Hedberg et al., 2000), protein modification and cell signaling (Que et al., 2005), S-nitrosoglutathione (GSNO) metabolism, and deregulation of nitric oxide-dependent pathways (Thompson et al., 2010). In rats exposed by inhalation to high concentrations of formaldehyde, a rapid GSH depletion can occur, which may result in more free formaldehyde available for covalent binding and a decrease in metabolic incorporation (Casanova and Heck, 1987).

Assumptions based on what is known about the distribution and metabolism of formaldehyde and its detoxification products allow inferences to be made about how inhaled formaldehyde is eliminated as CO_2 in expired air or in various forms in urine. Approximately one third of inhaled formaldehyde is estimated to be removed in the URT mucus (Schlosser, 1999). It is expected that the majority of this formaldehyde would be removed from the URT via esophageal clearance and excreted in urine in various forms. A large amount of inhaled formaldehyde penetrating the mucociliary layer of the URT is metabolized in the nasal cavity, giving rise to formate, which can be excreted in urine. Part of this formate may also be further oxidized and eliminated in the exhaled breath as CO_2. Some formaldehyde is incorporated into the 1C pool and repurposed for protein and nucleic acid synthesis.

3.2. EVIDENCE FOR EFFECTS ON THE RESPIRATORY SYSTEM

Research on several noncancer respiratory health effects was synthesized for the following health domains: sensory irritation (see Section 3.2.1), pulmonary function (see Section 3.2.2), immune system effects focusing on allergies and asthma (see Section 3.2.3), and respiratory tract pathology (see Section 3.2.4).

Synthesis of the evidence relevant to potential carcinogenicity at respiratory sites focused on cancers in the upper respiratory tract ([URT]; see Section 3.2.5), as less has been reported concerning cancer associations at other respiratory sites (see Appendix B.3.9 for details).

As previously described, inhaled formaldehyde is highly reactive at the portal of entry (POE), that is, nose and upper airways, which results in alterations to the local tissues that could give rise to respiratory system health effects. The potential noncancer effects involve many of the same biological processes; thus, a high degree of overlap across the mechanistic changes underlying these responses is expected. Similarly, because the potential respiratory health effects are interrelated, effects on one outcome may affect others. Accordingly, an overarching evaluation of the mechanistic information pertinent to any or all potential noncancer respiratory system health effects (some of which is relevant to carcinogenicity) was performed (see Appendix C.7, with supporting documentation in Appendix B.2.6 and B.3.6). The primary mechanistic conclusions drawn from this overarching evaluation are summarized in the MOA analyses in Sections 3.2.1-3.2.4. Section 3.2.3 includes a discussion expanded to include mechanistic changes in

nonrespiratory tissues that might relate to respiratory system health effects, although these findings are also relevant to the nonrespiratory (systemic) health effects reviewed in Section 3.3.

Finally, an essential component of the analysis of potential carcinogenicity at respiratory sites involves evaluating whether inhaled formaldehyde causes genotoxicity or mutagenicity. Because abundant information exists on this topic, the data are comprehensively described in Appendix C.3, with the primary conclusions summarized in Section 3.2.5. Some of the conclusions from the genotoxicity evidence analyzed in Appendix C.3 are also relevant to interpretations regarding potential cancers at nonrespiratory (distal) sites in Section 3.3.3.

3.2.1. Sensory Irritation

This section describes research on formaldehyde inhalation and sensory irritation in experimental and observational studies in humans. As described in Section 2.2.2, studies describing reports of sensory irritation prevalence based on questionnaire responses or objective measures, such as eye blink frequency or conjunctival redness, were the focus of this review. Although not systematically evaluated, formaldehyde inhalation-induced sensory irritation in animals is a well-established phenomenon (Nielsen et al., 1999; Kane and Alarie, 1977; Chang et al., 1981; Barrow et al., 1983), as summarized in Appendix C.2.

Formaldehyde has been found to be a sensory irritant of the eyes and respiratory tract in several epidemiological studies causing mild to severe symptoms, including itching, stinging, burning, and watering eyes; sneezing and rhinitis; sore throat; coughing; and bronchial constriction. Exposure levels in the residential studies ranged from 0.01 (the limit of detection [LOD] in the available studies) to approximately 1 mg/m^3, with a large proportion of residences having levels less than 0.1 mg/m^3. Symptoms of eye irritation were reported at lower concentrations than symptoms of the nose or throat. Many epidemiology studies evaluated symptoms of irritation among residents exposed to formaldehyde in their homes, workers involved in the production or use of formaldehyde products, and anatomy students participating in the dissection of formaldehyde-preserved cadavers. In addition, data from several controlled human exposure studies are available that evaluated acute responses among healthy or asthmatic volunteers during rest or exercise (see Table 3-1). The controlled exposure studies evaluated formaldehyde concentrations above 0.1 mg/m^3, showing that the irritant response to formaldehyde is an immediate phenomenon apparent at concentrations of 0.1 mg/m^3, the lowest concentration evaluated, and higher. The irritation resolves when exposure is removed (Sauder et al., 1986; Krakowiak et al., 1998; Andersen, 1979; Andersen and Molhave, 1983). Concentration was related to both prevalence and severity of symptoms. In addition, a large variability in sensitivity to the irritant properties of formaldehyde at specific concentrations was observed (Mueller et al., 2013; Berglund et al., 2012). Because of the wide variability in responses, it has been difficult for experimental studies to characterize the exposure-response relationship in the lower range of concentrations experienced by the general population. Sensory irritation is understood to occur as a result of direct interactions of formaldehyde with cellular macromolecules leading directly or

indirectly to stimulation of trigeminal nerve endings; branches of the trigeminal nerve responsible for chemosensation innervate the oral, ocular, and nasal cavities. However, the most notable and well-studied of these is activation within the nasal mucosa (i.e., in the respiratory epithelium) and stimulation in the oral cavity is unlikely to lead to eye irritation or similar symptoms.

Studies in humans provide *robust* evidence of sensory irritation based on the controlled human exposure studies and observational epidemiology studies, and this effect also is well described and accepted across a range of experimental animal species (*robust*). Further, there is an established MOA for this well-studied health effect, based primarily on mechanistic evidence in experimental animals, and this MOA is interpreted to be operant in humans. Overall, a judgment was drawn that the **evidence demonstrates** that inhalation of formaldehyde causes sensory irritation in humans, given sufficient exposure conditions. The primary support for this conclusion is based on residential studies with mean formaldehyde concentrations >0.05 mg/m^3 (range 0.01 to approximately 1.0 mg/m^3) and controlled human exposure studies testing responses to concentrations 0.1 mg/m^3 and above.

Human Studies

The following discussion is organized by exposure setting, starting first with evidence from controlled human exposure studies, followed by studies of residential exposure, and then laboratory and occupational studies. Evidence tables for each exposure setting (see Tables 3-1 and 3-2) are organized by level of confidence (*high*, *medium,* and *low*) in the study's results and then by publication year. Fifteen studies were considered *not informative* ((Yang et al., 2001; Wei et al., 2007; Wantke et al., 1996a; Thun et al., 1982; Schuck et al., 1966; Sauder et al., 1986; Saowakon et al., 2015; Salonen et al., 2009; Norsted et al., 1985; Lovreglio et al., 2009; Day et al., 1984; Dally et al., 1981; Cometto-Muñiz and Hernández, 1990; Bracken et al., 1985; Akbar-Khanzadeh et al., 1994)). The study evaluations are included in Appendix B.3.2.

Controlled human exposure studies (acute exposure)

Controlled human exposure studies testing exposures from less than 1 hour to 5 hours reported slight-to-moderate irritation of the eyes, nose, and throat detected by subjects at formaldehyde concentrations beginning at around 0.3–0.4 mg/m^3 (see Table 3-1), although the data do not clearly identify the concentration at which symptoms of irritation begin. Eye irritation was reported at lower concentrations than nasal or throat irritation, and symptoms increased in frequency and severity with exposure level.

Both prevalence and severity of symptoms were associated with increasing concentration between 0.12 and 2.5 mg/m^3 (see Table 3-1). Overall, the prevalence of eye irritation increased from <10 to >80% across several studies with formaldehyde concentrations of 0–4 mg/m^3 (see Figure 3-2). The prevalence of mild-to-moderate irritation varied among individuals at specific concentration levels. For example, at concentrations above 2 mg/m^3, prevalence ranged from 53 to 100% (Witek et al., 1987; Schachter et al., 1986; Schachter et al., 1987; Kulle et al., 1987; Andersen

and Molhave, 1983). Possible reasons for the variation may include differences in exposure duration or differences in the characteristics of the volunteers (e.g., interindividual variation due to smoking status, prior exposure history, or respiratory health). In addition, one research group reported a much lower symptom prevalence (27%) among healthy and asthmatic subjects exposed to 3.7 mg/m^3 formaldehyde for 60 minutes (Green et al., 1987); however, this response is not directly comparable to the other studies because the authors only presented irritation prevalence for more severe symptoms (moderate severity or greater). Two *high* confidence controlled human exposure studies that were also not directly comparable to the studies above used a different metric to measure symptoms, a subjective symptom score using a validated questionnaire (Mueller et al., 2013; Lang et al., 2008). The results of the two studies differed; Lang et al. (2008) reported an increase in symptom scores for eye irritation at 0.3 mg/m^3, although with control for responses to questions that assessed "negative affectivity," the association was not observed until 0.5 mg/m^3, and Mueller et al. (2013) reported no effect related to formaldehyde exposure at concentrations up to 0.86 mg/m^3. Participants in all of the studies were 18 to 39 years old.

Only a few studies evaluated whether symptom prevalence or severity changed over the course of the exposure period. One research group recruited university volunteers and compared their responses to controlled formaldehyde exposure against responses in hospital laboratory workers with routine exposure to formaldehyde; responses were similar between the two groups during the 40-minute period at 2 ppm (Schachter et al., 1986; Schachter et al., 1987). The study of the laboratory workers was concluded to have *medium* confidence because some study aspects may have reduced the study's sensitivity, including that the previous formaldehyde exposure was not characterized, and other characteristics, such as being a smoker, were not controlled. The university volunteers reported the highest symptom scores when subjects first entered the exposure chamber with declines over the 40-minute exposure period. Andersen and Molhave (1983) also found that eye irritation was experienced earlier in the exposure period among subjects exposed to higher concentrations (1 and 2 mg/m^3) and that symptom severity increased and then plateaued or decreased after 3 hours. However, the initiation of symptoms was delayed at lower concentrations (0.3 and 0.5 mg/m^3), and symptom severity continued to increase over the rest of the exposure period. Other studies involving exposures from a few minutes to 1 hour also reported irritation responses that slightly decreased or plateaued (Green et al., 1987; Bender et al., 1983). Note that Bender et al. (1983) used a protocol involving exposure to the eyes only, which may involve a different type of response compared to inhalation. Therefore, these few studies suggest that some acclimatization may occur over a few hours at higher concentrations; however, this phenomenon may not be apparent when concentrations are lower (<1 mg/m^3). Further, based on the few studies available, individuals with long-term occupational exposure to formaldehyde do not appear to respond differently than individuals with no previous known exposure.

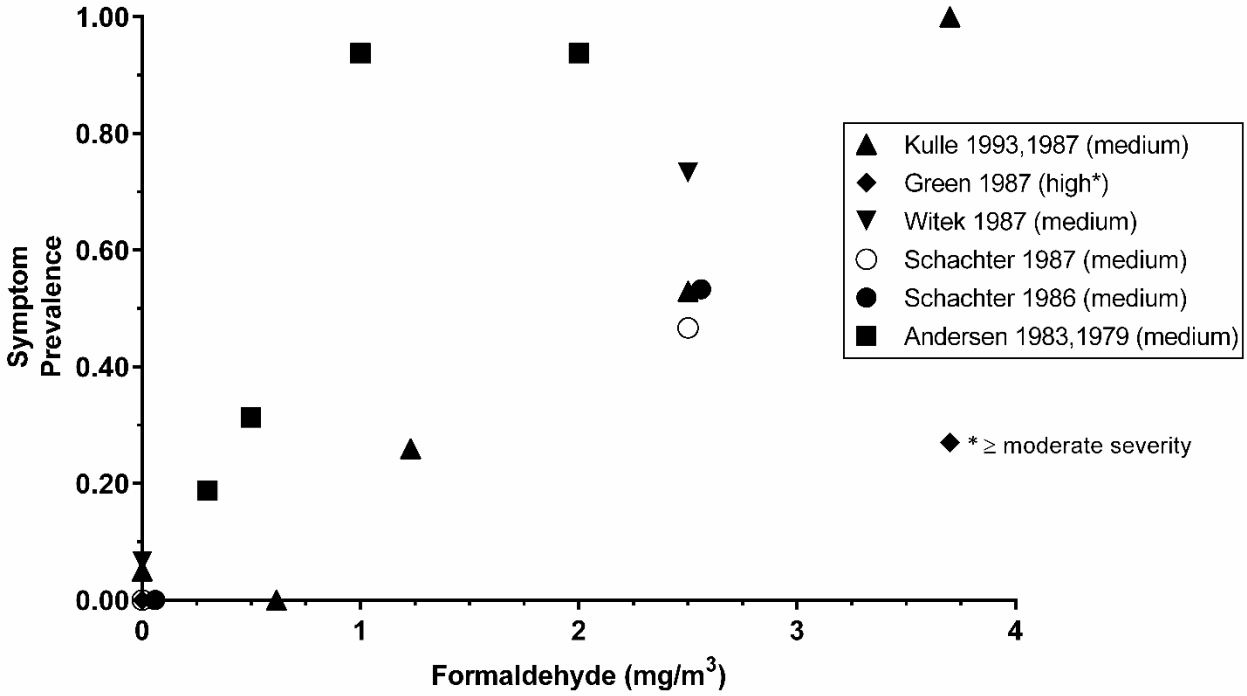


Figure 3-2. Prevalence of eye irritation in *medium* and *high* confidence controlled human exposure studies of acute formaldehyde exposure.

Medium and *high* confidence studies (all of which randomly assigned the order of exposure levels) are graphed in relation to formaldehyde concentration. The results from Schachter et al. (1987) are graphed in open symbols because subjects were also exposed to formaldehyde through their occupations or cigarette smoke. *The *high* confidence study included in this graphic provided prevalence only for irritation severity of moderate or greater (as compared to other studies reporting any severity, for example mild or greater). Not included in the graph are three *high* confidence studies reporting increases in symptom intensity or scores for eye irritation but not reporting prevalence data by formaldehyde exposure level (Mueller et al., 2013; Lang et al., 2008; Green et al., 1989) and one *medium* confidence study attempting to identify a threshold for irritation based on "sniffs" of formaldehyde (Berglund et al., 2012). Note that the figure does not convey differences in severity scores, which also increased with formaldehyde exposure level.

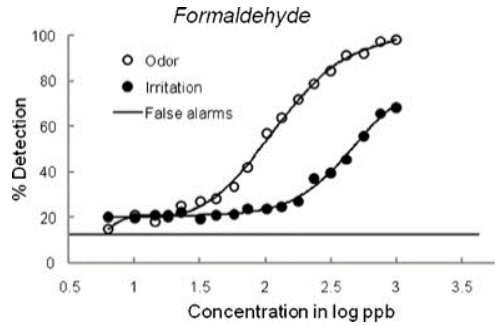
In addition to subjective reports, some investigators evaluated objective measures, including eye blink frequency, conjunctival redness, and nasal flow and resistance (Mueller et al., 2013; Lang et al., 2008; Andersen, 1979; Andersen and Molhave, 1983). Eye blink frequency was increased at exposure levels above those where subjective symptoms were reported. For example, two studies evaluated responses to a combination of concentration peaks superimposed on a constant formaldehyde exposure (Mueller et al., 2013; Lang et al., 2008). Lang et al. (2008) found that increased eye blink frequency and conjunctival redness occurred at 0.62–1.2 mg/m^3 among subjects who also reported symptoms of eye irritation at 0.37 mg/m^3. Mueller et al. (2013) found no exposure-related effect on blinking frequency and conjunctival redness, although total symptom scores increased beginning at 0.37 mg/m^3 with peaks of 0.7 mg/m^3 in a group with nasal

hypersensitivity. Studies using objective measures of nasal irritation reported variable results including no change in nasal flow and resistance between 0.19 and 0.62 mg/m^3 (Lang et al., 2008), a decrease in nasal mucus flow at a concentration of 0.37 mg/m^3 and higher (Andersen and Molhave, 1983), and an increase in nasal flow rate among hypersensitive participants at 0.86 mg/m^3 (Mueller et al., 2013). Subjects exhibited a large degree of individual variability in sensitivity for both objective and subjective responses (Mueller et al., 2013; Lang et al., 2008; Berglund et al., 2012).

Table 3-1. Summary of controlled human exposure studies of formaldehyde and human sensory irritation

Study and design	Results
Mueller et al. (2013) **Design:** *N* = 41, age 32 ± 9.9 years, nonsmoking, healthy male volunteers; categorized into hyposensitive and hypersensitive based on CO_2 sensitivity measurements in nasal mucosa (cutpoint median 80.3 mm on visual analogue scale [VAS]). Exposure order randomly assigned; repeated measures cross-over design; blinding not described. Five 4-hour exposure conditions, 1 per day, over 5 days. Four 15-minute cycle exercise segments during exposure period. **Outcome:** Irritation assessed by conjunctival redness (digital photographs), blinking frequency (blinks counted in 60-second segments from 5-minute video, two counters blind to concentration), tear film break-up time (time to first close of eyelid while staring at mark on wall), nasal flow and resistance (rhinomanometry), and validated symptom questionnaire (SPES German version) measured before exposure and shortly before the end of exposure. Severity rated using VAS with 100-mm scale. **Exposure:** 4 hours in groups of 2. Clean air, 0.3 + 4 peaks of 0.6 ppm, 0.4 + 4 peaks of 0.8 ppm, 0.5 ppm and 0.7 ppm (0.0, 0.37 + 0.74, 0.49 + 0.98, 0.62, and 0.86 mg/m^3).[a] Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported. **Study evaluation**: *High* confidence	Results presented in graphs of difference between pre- and end of test values. Large interindividual variability in scores between subjects for all measures. Blinking frequency and conjunctival redness—no exposure-related effect, tear film break-up time—increased in 0.4/0.8 ppm and 0.5 ppm ($p < 0.05$), nasal flow rate increased in hypersensitive 0.7 ppm ($p < 0.01$); total symptom score increased in hypersensitive at 0.3/0.6 ppm ($p < 0.001$) and 0.4/0.8 ppm ($p < 0.01$), perception of impure air increased in hypersensitive at all exposure levels (including clean air, 0.01 ppm). Control for "negative affectivity" did not alter associations. Combined eye symptom score reported to be increased with higher scores among hypersensitives at all exposures except 0.7 ppm (0.86 mg/m^3). Changes in scores were not statistically significant and no exposure-response was observed (results in online supplemental resource 10 in Mueller et al. (Mueller et al., 2013)). Severity measured using VAS ranged between −0.2 and 2.1 mm). **SPES Symptom Score (SD)—Eye Irritation** mg/m^3 Average/peak / Hypo-sensitive[a] / Hyper-sensitive[a] 0 / −0.17 (2.02) / 1.96 (7.59) 0.37/0.74 / 0.23 (2.65) / 2.13 (4.71) 0.49/0.98 / 0.62 (5.71) / 1.43 (5.31) 0.62 / −0.09 (2.14) / 1.24 (2.84) 0.86 / 0.94 (4.56) / 0.52 (4.14) [a]Sensitivity categorized as above or below median for nasal sensitivity to CO_2 irritation.

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Lang et al. (2008)
Design: *N* = 21, age 19–39 yrs, nonsmoking, healthy volunteers. Exposure order randomly assigned; double blinded. Ten 4-hour exposure conditions, 1 per day, over 10 days. Three 15-minute cycle exercise segments during exposure period.
Outcome: Irritation assessed by conjunctival redness (digital slit lamp photographs, two scorers), blinking frequency (90-second count from 6-minute video), nasal flow and resistance (rhinomanometry), and symptom questionnaire (SPES German translation) measured before, three times during, and after exposure, and after last exposure day. Rated on 5 levels (0–5).
Exposure: 4 hours in groups of 4. Clean air, 0.15, 0.3, and 0.5 ppm (0.0, 0.19, 0.37, and 0.62 mg/m^3); additional 0.3 and 0.5 ppm with peaks up to 1.0 ppm (1.23 mg/m^3).[a]
Additional 0.0, 0.3, and 0.5 ppm with ethyl acetate (EA) introduced as a “mask” for formaldehyde odor.
Formaldehyde generation via thermal depolymerization of paraformaldehyde, quasi-static chamber, analytical concentrations reported.
Study evaluation: *High* confidence</td><td>Blinking frequency, conjunctival redness significantly increased at 0.5 ppm with peaks of 1.0 ppm.
Symptoms: Maximum scores at 195 minutes; eye and olfactory symptom scores were elevated at 0.3 ppm ($p < 0.05$). With control for “negative affectivity,” eye irritation symptoms significantly associated with 0.5 ppm with EA or 0.5 ppm with peaks. Severity: Average severity scores were less than 2 (“somewhat”).
Nasal irritation: no significant increase in objective measures; symptoms significantly increased at 0.5 ppm and 0.3 ppm with coexposure to EA (also an irritant; $p < 0.05$).</td></tr>
<tr><td>Green et al. (1989)
Design: N = 24, 10 male, mean age 24 ± 0.7 yr. nonsmoking, no history of allergies or hay fever. Random assignment to order of exposure; double blinded. Four 15-min exercise segments in the 2-hr exposure period.
Outcome: Symptoms questionnaire (presence and severity, scored none = 0 to severe = 5) before, and four times during exposure. Testing pre- and during exposure period (approximate 15-min intervals).
Exposure: 2 hr, four exposures over 4 wks, clean air, 3 ppm (3.69 mg/m3)a, 0.5 mg/m3 activated carbon aerosol (ACA), HCHO + ACA.
Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported.
Study evaluation: High confidence</td><td>Symptom scores presented graphically for 80-min time point. Formaldehyde treatment elevated symptom scores ($p < 0.05$) at all time points for eye, nasal and throat irritation, odor, chest discomfort. No effect modification by ACA exposure. Average eye irritation scores <1.5 at 80 minutes; similar response at all measurements (20, 50, 80, and 110 minutes).
No separate effect on cough by formaldehyde, but combined formaldehyde and ACA exposure resulted in elevated score for cough at 20 minutes ($p < 0.02$) and 80 minutes ($p < 0.05$).</td></tr>
<tr><td>Green et al. (1987)
Design: *n* = 22, mean age 26.9 ± 3.6 years, nonsmoking, no history of allergies or hay fever. Random assignment to order of exposure; single blinded. Two 15-min exercise segments in the 60-min exposure period.
Outcome: Symptoms questionnaire (presence and severity, scored none = 0 to severe = 5) before, and four times during exposure. Testing pre- and during exposure period (approximate 15-min intervals).
Exposure: 60 minute, clean air and 3 ppm (3.69 mg/m^3).[a]
Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported.
Study evaluation: *High* confidence</td><td>Mean symptom scores associated with 3-ppm exposure at all time points, difference from clean air statistically significant for odor, nose or throat irritation, and eye irritation. Individual severity scores ranged from none to severe.
Prevalence of scores ≥ moderate severity at 3 ppm ($p < 0.01$)
<table><tr><th></th><th>Healthy (%)</th><th>Asthmatic (%)</th></tr><tr><td>Odor</td><td>23</td><td>31</td></tr><tr><td>Nose/throat</td><td>32</td><td>31</td></tr><tr><td>Eye</td><td>27</td><td>19</td></tr></table></td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Berglund et al. (2012)
Design: N = 31 healthy volunteers, 52% male, age 24.5 years, nonsmokers. Exposure concentrations randomly presented; blinding not described.
Outcome: Participants evaluated detection of odor and nasal irritation for each “sniff” with forced-choice responses (yes-yes, yes-no, no-yes and no-no). Goal was to identify the concentration at which a participant detected nasal irritation in all (100%) of the 12 presentations.
Exposure: Series of 18 concentrations; 6.36−1,000 ppb (0.0078−1.23 mg/m^3).[a]
12 presentations at each concentration plus 72 blanks; 1 sniff in exposure hood (<3 seconds) followed by clean air, 3 sniffs per minute; 36 exposures per each of eight 12-minute sessions over 4 hours.
Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported.
Study evaluation: Medium confidence
Blinding not described; Focus on detection threshold rather than symptom prevalence.</td><td>None of the 31 participants detected nasal irritation in 100% of 12 presentations at any formaldehyde concentration. 13% false alarms (reports of detection of odor or irritation for blanks). Large variation in individual distributions of percentage detections for nasal irritation vs. log concentration. Authors could not calculate threshold distributions for irritation. See pooled data below (see Figure 5 in paper).
 
</td></tr>
<tr><td>Kulle et al. (1987); Kulle (1993)
Design: Group 1 (N = 10), Group 2 (N = 9), nonsmoking healthy, age 26.3 ± 4.7 years, 53% male. Exposure order randomly assigned; Blinding not reported. 3-hour exposures each week, at same time on five occasions. 8-minute exercise segment every half hour during 2-ppm exposure.
Outcome: Symptom questionnaires before and after each exposure, and 24-hours postexposure. Severity was scored none, mild, moderate, severe (0−5).
Exposure: 3 hour, Group 1: 0.0, 0.5, 1.0, or 2.0 ppm (0.0, 0.62, 1.23, 2.46 mg/m^3)[a] at rest, and an additional 2.0 ppm with exercise; Group 2: 0.0, 1.0, or 3.0 ppm (0.0, 1.23, or 3.69 mg/m^3) at rest, and an additional 2.0 ppm with exercise.
Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported.
Study evaluation: Medium confidence
Deficiencies in reporting detail regarding blinding and quantitative results</td><td>Mean difference in scores before and after exposure period: Linear dose-response (N = 19) for odor and eye irritation, 0, 1, and 2 ppm ($p < 0.0001$); and nose/throat (Group 2, $p = 0.054$). Log-linear dose-response for odor and eye irritation, 0, 0.5, 1.0 and 2.0 ppm (Group 1, $p < 0.05$). Test for nonlinearity not significant. Data presented graphically, prevalence reported in Kulle et al. (1993), Table 3 in the paper.
<table>
<tr><th>Concentration (mg/m^3)</th><th>N (#)</th><th>Prevalence (mild/moderate)</th><th>SE[a]</th></tr>
<tr><td>0</td><td>19</td><td>0.05</td><td>0.050</td></tr>
<tr><td>0.62</td><td>10</td><td>0</td><td>-</td></tr>
<tr><td>1.23</td><td>19</td><td>0.26</td><td>0.101</td></tr>
<tr><td>2.46</td><td>19</td><td>0.53</td><td>0.115</td></tr>
<tr><td>3.69</td><td>9</td><td>1.0</td><td>-</td></tr>
</table>
[a]Estimated as: SE = sqrt(p*(1-p)/N)</td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Schachter et al. (1987)
Design: N = 15 healthy hospital laboratory workers routinely exposed to formaldehyde as part of their job, age 32 ± 11.3 years, 33.3% male, N = 2 smokers. Random assignment to order of exposure, double blinded. Two dose levels, four exposure conditions, 2 days at rest and 2 days with exercise. One 10-minute exercise segment at 5 minutes in the 40-minute exposure period.
Outcome: Symptoms diary, scores 0–4, at t = 0, t = 30 minutes, and 4–8 hours and 24 hours postexposure.
Exposure: 40 minutes; clean air and 2.0 ppm (2.46 mg/m^3).[a] Formaldehyde generation via thermal depolymerization of paraformaldehyde over boiling 2-propanol, dynamic chamber, analytical concentrations reported.
Study evaluation: Medium confidence
Co-exposure to 2-propanol, potential confounding by smoking</td><td>Symptoms during exercise not different from rest.
Prevalence and scores during rest
<table>
<tr><th></th><th colspan="4">Concentration (ppm)</th></tr>
<tr><th></th><th colspan="2">0</th><th colspan="2">2</th></tr>
<tr><th></th><th># (%)</th><th>S[a]</th><th># (%)</th><th>S[a]</th></tr>
<tr><td>Odor</td><td>7 (46.7)</td><td>10</td><td>12 (80.0)</td><td>22</td></tr>
<tr><td>Eye</td><td>0</td><td>0</td><td>7 (46.7)</td><td>9</td></tr>
<tr><td>Nose</td><td>1 (0.07)</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>Throat</td><td>1 (0.07)</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td colspan="5">[a]Total Score Across all Subjects</td></tr>
</table>
Eye Irritation Severity by Exposure, # (%)
<table>
<tr><th></th><th>0 ppm</th><th>2 ppm</th></tr>
<tr><td>Mild</td><td>0</td><td>5 (33.3)</td></tr>
<tr><td>Moderate</td><td>0</td><td>2 (13.3)</td></tr>
<tr><td>Severe</td><td>0</td><td>0</td></tr>
</table></td></tr>
<tr><td>Witek et al. (1986); Witek et al. (1987)
Design: n = 15 with asthma, ages 18–35 years, nonsmoking. Random assignment to order of exposure; double blinded. Two protocols (at rest and during exercise).
Outcome: Symptoms questionnaire, severity scores (0–4). Testing at beginning and at 30 min during and 4- to 8-hr and 24-hr postexposure.
Exposure: 40 minutes, 0 and 2 ppm (2.46 mg/m^3).[a] Formaldehyde generation via thermal depolymerization of paraformaldehyde over boiling 2-propanol, dynamic chamber, analytical concentrations reported.
Study evaluation: Medium confidence
Co-exposure to 2-propanol</td><td>Symptoms during exercise not different from rest.
Prevalence (%) and severity scores during rest
<table>
<tr><th></th><th colspan="2">0 ppm</th><th colspan="2">2 ppm</th></tr>
<tr><th></th><th># (%)</th><th>S[a]</th><th># (%)</th><th>S[a]</th></tr>
<tr><td>Odor</td><td>5 (33.3)</td><td>7</td><td>15 (100)</td><td>30</td></tr>
<tr><td>Eye</td><td>1 (6.7)</td><td>2</td><td>11 (73.3)</td><td>16</td></tr>
<tr><td>Nose</td><td>3 (20)</td><td>4</td><td>7 (46.7)</td><td>10</td></tr>
<tr><td>Throat</td><td>4 (26.7)</td><td>4</td><td>5 (33.3)</td><td>6</td></tr>
<tr><td colspan="5">[a]Total severity score across all subjects</td></tr>
</table>
Symptoms reported to have disappeared postexposure.</td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Witek et al. (1986); Schachter et al. (1986)
Design: N = 15 healthy, age 18−35 year, nonsmokers. Random assignment to order of exposure, double blinded. Two protocols (at rest and during exercise), separated by 4 days.
Outcome: Symptoms questionnaire at beginning and at 30 min during exposure and at 8 and 24 hr after exposure, severity scores (0−4).
Exposure: 40 min; clean air and 2 ppm (2.46 mg/m^3).[a] Formaldehyde generation via thermal depolymerization of paraformaldehyde over boiling 2-propanol, dynamic chamber, analytical concentrations reported.
Study evaluation: Medium confidence
Co-exposure to 2-propanol</td><td>Symptoms during exercise not different from rest; highest symptom scores at beginning of exposure with decrease by 30 minutes.
Prevalence (%) and severity scores during rest
<table>
<tr><th></th><th colspan="2">0 ppm</th><th colspan="2">2 ppm</th></tr>
<tr><th></th><th># (%)</th><th>S[a]</th><th># (%)</th><th>S[a]</th></tr>
<tr><td>Odor</td><td>7 (46.7)</td><td>7</td><td>12 (80.0)</td><td>18</td></tr>
<tr><td>Eye</td><td>0</td><td>0</td><td>8 (53.3)</td><td>12</td></tr>
<tr><td>Nose</td><td>4 (26.7)</td><td>4</td><td>6 (40.0)</td><td>7</td></tr>
<tr><td>Throat</td><td>2 (13.3)</td><td>2</td><td>4 (26.7)</td><td>4</td></tr>
</table>
[a]Total severity score across all subjects
<table>
<tr><th colspan="3">Eye Irritation Severity by Exposure, n (%)</th></tr>
<tr><th></th><th>0 ppm</th><th>2 ppm</th></tr>
<tr><td>Mild</td><td>0</td><td>5 (33.3)</td></tr>
<tr><td>Moderate</td><td>0</td><td>2 (13.3)</td></tr>
<tr><td>Severe</td><td>0</td><td>1 (7)</td></tr>
</table></td></tr>
<tr><td>Andersen (1979); Andersen and Molhave (1983)
Design: N = 16 healthy students, age 30−33, 68.8 % male, 31.2% smokers, groups of four over 4 days. Exposure order determined by Latin square design, blinding not described. Testing before (during 2-hour clean air) and two times during exposure.
Outcome: Subjects used a pointer to express the degree of airway irritation (scale 1 to 100) while being exposed.
Exposure: 5 hours; 0.3, 0.5, 1.0 and 2.0 mg/m^3 (0.24, 0.40, 0.81 and 1.61 ppm respectively).
Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported as within 20% of target.
Study evaluation: Medium confidence
Variation in exposure concentrations, reporting deficiencies regarding blinding, potential confounding by smoking</td><td>Irritation prevalence with clean air was not reported. At end of exposure to 0.3, 0.5, 1.0, and 2.0 mg/m^3 of formaldehyde; 3, 5, 15 and 15 subjects respectively of the 16 who participated reported conjunctival irritation, dryness in the nose and throat. Smokers were found to be less sensitive than nonsmokers.

Severity: Maximum individual scores ranged from 30 (slight discomfort) at 0.3 mg/m^3 to 50 (discomfort) at 3 mg/m^3. After the first 2 hours, discomfort increased during the exposure period at 0.3 and 0.5 mg/m^3. In two highest concentrations, discomfort reported during first hour, increased to hour 3, then plateaued or decreased.

Eye blinking increased at 2.0 mg/m^3 (1.70 ppm).
Subjects reported no symptoms the next morning.</td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Bender et al. (1983)
Design: Panels of seven volunteers from Battelle Memorial Institute (age, health status, smoking status, and gender not reported) exposed to clean air and formaldehyde. Individuals who responded to 1.3 and 2.2 ppm formaldehyde were tested.
Order of exposure assignment not reported, blinding not described. Eye-only exposures for 6 minutes.
Outcome: Response time (seconds); proportion of subjects with shorter response time to formaldehyde than to clean air. Subjective score (0–3) when first detected and after 6 minutes.
Exposure: 6 minutes, eye only, 0, 0.35, 0.56, 0.7, 0.9 and 1.0 ppm (0.0, 0.43, 0.69, 0.86, 1.11, and 1.23 mg/m^3).[a] Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations not reported.
Study evaluation: *Low* confidence
Reporting deficiencies regarding analytical concentrations, random allocation, and blinding. Sample size <10.</td><td>Median time to first irritant response decreased with increasing concentration (Cochran's χ^2 test for trend). Severity index increased with increasing concentration.

Proportion with shorter response to formaldehyde compared to clean air
<table><tr><th></th><th></th><th colspan="2">Respondents</th></tr><tr><th>PPM</th><th>Total</th><th>#</th><th>%</th></tr><tr><td>0</td><td>28</td><td>–</td><td>–</td></tr><tr><td>0.35</td><td>12</td><td>5</td><td>41.7</td></tr><tr><td>0.56</td><td>26</td><td>14</td><td>53.8</td></tr><tr><td>0.7</td><td>7</td><td>4</td><td>57.1</td></tr><tr><td>0.9</td><td>5</td><td>3</td><td>60.0</td></tr><tr><td>1.0</td><td>27</td><td>20</td><td>74.1*</td></tr></table>*$p < 0.05$, compared to control</td></tr>
</table>

Organized by study confidence, then descending publication year. Results for *low* confidence studies are shaded gray.
Abbreviations: ACA = activated carbon aerosol; ATS = American Thoracic Society; EA = ethyl acetate; HCHO = formaldehyde; NASA = National Aeronautics and Space Administration; S = Symptom score; SPES = symptom questionnaire; UFFI = urea foam insulation.
[a]Concentrations reported by authors as ppm or ppb converted to mg/m^3.

Studies in residential settings

Three studies investigated the prevalence of irritation symptoms in relation to residential formaldehyde exposure [(Zhai et al., 2013; Liu et al., 1991; Hanrahan et al., 1984); see also (Sexton et al., 1986) for exposure details of Liu et al. (1991)]. Two studies of occupational exposure in mobile trailers (Olsen and Dossing, 1982; Main and Hogan, 1983) are included with this group because the exposure settings (mobile homes with particle board paneling) are similar. Formaldehyde exposure was associated with an increasing prevalence of eye irritation as well as nose and throat irritation (see Table 3-2 and Figure 3-3). One study, Olsen et al. (1982), assessed the severity of symptoms as well as their presence within the previous month using a linear analogue scale. Among those reporting symptoms of eye irritation, a severity at approximately the midpoint of the scale was reported, which is consistent with the mild or moderate severity reported by the controlled human exposure studies. Two studies in residential populations analyzed exposure-response relationships and observed a statistically significant relationship between increasing formaldehyde concentration (from the LOD of 0.01 mg/m^3 to >0.98 mg/m^3) and symptoms of irritation using logistic regression models with adjustment for age, gender, smoking behavior and other potential confounders (Sexton et al., 1986; Liu et al., 1991; Hanrahan et al., 1984). Data were collected on symptoms occurring after participants had moved into their homes (Hanrahan et al., 1984) or those that occurred during the week prior to the end of the one-week formaldehyde sampling period (Liu et al., 1991). Although the sampling period used by Hanrahan et

al. (1984) was shorter (1 hour), the method was consistent with NIOSH method 3500 (NIOSH, 1994) and was considered to have high accuracy for the 1-hour samples. In addition, the presence of smokers or gas appliances in the home, sources that might contribute to variability in concentrations, was not associated with indoor formaldehyde concentrations. However, the lack of concordance of the one-hour sampling period for formaldehyde with the period of symptom ascertainment assessed by Hanrahan et al. (1984) adds some uncertainty regarding the reported dose-response relationship. Other emissions released from the same sources as formaldehyde that also can contribute to eye irritation, such as phenols from resins in floor or wall coverings or pinene and terpenes from wood products, were not analyzed. However, a strong exposure-response relationship with formaldehyde, as a cumulative measure (ppm-hr) or a 1-hour concentration, was reported by two *medium* confidence studies, which is unlikely to be explained to a great extent by unmeasured confounding. Although limited by low participation rates, participants were randomly selected for recruitment, and the investigators noted that the characteristics of the respondents and nonrespondents, such as age of housing stock, demographics, and formaldehyde concentrations, were comparable.

Figure 3-3 graphs prevalence of eye irritation (or burning eyes) by formaldehyde concentration reported by *high* or *medium* confidence controlled human exposure studies and residential studies. These results are complementary for the most part and indicate a consistent pattern in response to formaldehyde concentrations between 0 and 1 mg/m^3. As seen in Figures 3-2 and 3-3, the concentration-response curve for eye irritation in the Kulle et al. (1987) study was shifted to the right compared to other studies that evaluated multiple concentration levels.

Other URT symptoms were reported by these studies as well, including irritation of the nose and throat. A study of formaldehyde levels in redecorated homes in China and respiratory symptoms among residents exposed from 1 month to 3 years, reported a higher prevalence of nasal irritation and throat irritation among adults and children at concentrations above 0.08 mg/m^3 (Zhai et al., 2013). There was also an increased odds ratio for any symptoms of irritation that was independent of other factors including age, gender, smoking in the family, occupation, education, presence of domestic animals, family history of allergy, and ventilation frequency.

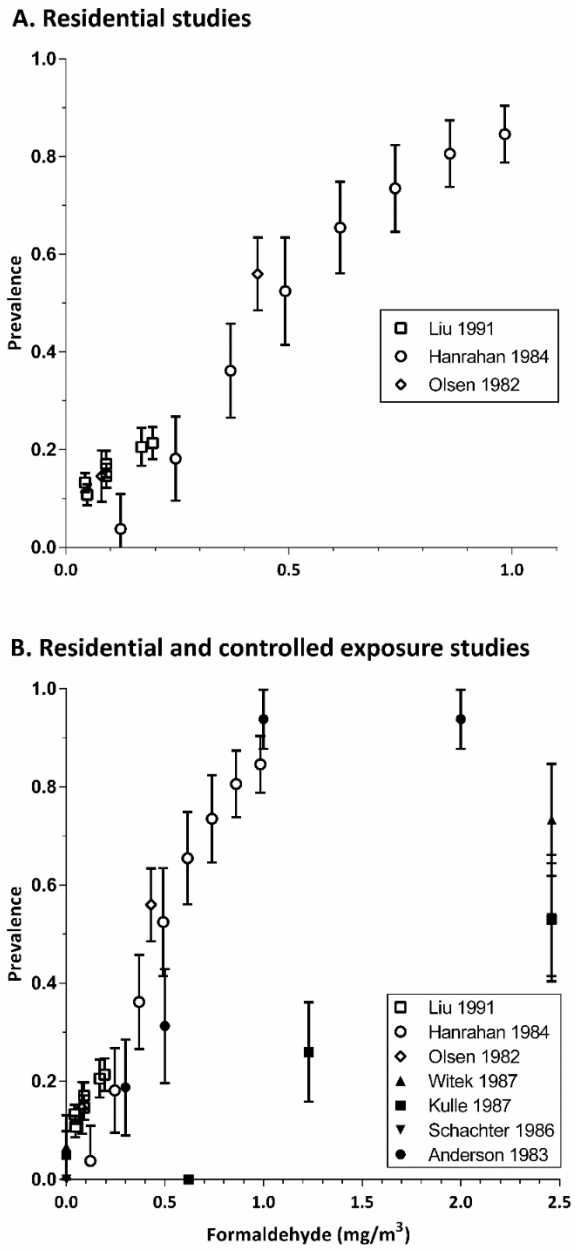


Figure 3-3. Prevalence of eye irritation in *medium* confidence studies of groups exposed to formaldehyde in residential settings and *medium* confidence controlled human exposure studies.

Panel (A): Hollow symbols reflect *medium* confidence observational studies with formaldehyde exposure in residential settings. The data for Liu et al. (1991) reflect reconstructed exposure information based on (Sexton et al., 1986) as reported in Table 3-2 and Appendix D.1.1. Panel (B): Hollow symbols reflect *medium* confidence observational studies and closed symbols reflect the *medium* confidence controlled (intentional) exposure studies for comparison purposes. Two controlled exposure studies from Figure 3-2 are not included as those results are less comparable due to reporting of prevalence of moderate or greater severity only (Green et al., 1987) or formaldehyde exposure through the subjects' occupations or cigarette smoke (Schachter et al., 1987). SEs were calculated as described in the associated evidence tables or using the formula: SE = sqrt(p*(1-p)/N).

Table 3-2. Summary of epidemiological studies of residential exposures to formaldehyde and human sensory irritation

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Zhai et al. (2013)
Jan 2008–Dec 2009 (China) (prevalence)
Population: 186 homes in Shenyang surveyed, homes were decorated in past 4 years and occupied within the past 3 years; randomly selected one adult from each house, plus 82 children (assisted by parents); characteristics of participants were not described.
Outcome: Reported symptoms and disorders via questionnaire Ferris (1978)
Exposure: Cited code for indoor environmental pollution control of civil building engineering (GB50325-2001); sampling duration not reported. Samplers in breathing zone in bedroom, living room, and kitchen; N = 558 in 186 homes; exposure groups “polluted” homes: >0.08 mg/m^3, mean 0.09–0.13 mg/m^3, range 0.01–0.55 mg/m^3, in three rooms; nonpolluted ≤0.08 mg/m^3, mean 0.04–0.047 mg/m^3.
Analysis: Compared symptom prevalence for children and adults by exposure category (reported p-values); multivariate logistic regression of respiratory system symptoms (all) in children and adults, adjusting for age, gender, smoking in family, occupation, education, ventilation frequency, domestic pets, house facing, family history of allergy, height, weight.
Evaluation:[a]
For analysis of combined symptoms:
Medium confidence
Combined analysis does not distinguish URT irritation symptoms from asthma-related symptoms; Sampling period duration not reported; timing of questionnaire administration in relation to air monitoring uncertain. Although potential confounders were not considered in symptom-specific analysis, the magnitude of the differences is unlikely to be explained by confounders.</td><td>Respiratory system symptoms and disorders by exposure group (N = 186 adults, 82 children)
<table><tr><th>Symptom</th><th>>0.08 mg/m^3 (%)</th><th>≤0.08 mg/m^3 (%)</th></tr><tr><td>Cough, adults</td><td>16.0*</td><td>4.5</td></tr><tr><td>Cough, children</td><td>25</td><td>8.1</td></tr><tr><td>Phlegm, adults</td><td>6.7</td><td>3.0</td></tr><tr><td>Phlegm, children</td><td>15</td><td>6.7</td></tr><tr><td>Wheeze, adults</td><td>5.0</td><td>3.0</td></tr><tr><td>Wheeze, children</td><td>10</td><td>6.6</td></tr><tr><td>Nasal irritation, adults</td><td>52.1**</td><td>16.4</td></tr><tr><td>Odor disorder, adults</td><td>21**</td><td>3.0</td></tr><tr><td>Throat irritation, adults</td><td>31.9*</td><td>13.4</td></tr></table>*p < 0.05, **p < 0.01
Association of formaldehyde exposure with respiratory system symptoms in adults and children (N = 186 adults, 82 children)
<table><tr><th></th><th>Odds Ratio</th><th>95% CI</th></tr><tr><td>Adults[a]</td><td>2.6</td><td>1.8, 3.8</td></tr><tr><td>Children[b]</td><td>4.3</td><td>2.1, 8.8</td></tr></table>[a]Other statistically significant covariates were ventilation frequency (OR = 1.6) and domestic pets (OR = 1.5)
[b]Other statistically significant covariates were ventilation frequency (OR = 1.8) and family history of allergy (OR = 1.9)</td></tr>
<tr><td>Sexton et al. (1986); Liu et al. (1991) (California)
Prevalence survey, 1984–1985.
Population: 2,203 randomly selected mobile home occupants recruited 44% response (836 of 1,895 contacted). 1,394 residents in 663 mobile homes in summer and 1,096 residents in 523 mobile homes in winter. 20–64 years of age.
Outcome: Symptoms (occurrence during 1 week prior to end of sampling period) from mailed questionnaire, questionnaire not described.
Exposure: Formaldehyde sampling using passive monitors mailed to participants, 7-day samples, two rooms.
Average concentration: 0.091 (SD 0.069, range <0.01 (LOD)–0.464) ppm in summer and 0.091 (SD 0.052, range 0.017–0.314) in winter. (0.11 (SD 0.095), range <0.012–0.57 mg/m^3)
Cumulative formaldehyde: formaldehyde concentration × hours spent in the residence (ppm-hr).</td><td>Significant associations with burning/tearing eyes, stinging/burning skin in summer, and burning/tearing eyes, chest pain, sore throat in winter (effect estimates from logistic regression model were not presented).
Prevalence Burning/Tearing Eyes (Liu, 1991)
<table><tr><th>ppm-hr</th><th>Summer (%)</th><th>Winter (%)</th></tr><tr><td><7.0</td><td>13.3</td><td>10.8</td></tr><tr><td>7.0–12</td><td>17.1</td><td>14.7</td></tr><tr><td>>12.0</td><td>21.4</td><td>20.6</td></tr></table>Burning/tearing eyes higher among females in regression models (note: females exhibit a higher</td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Analysis: Logistic regression adjusting for age, gender, smoking status, time spent at home, and chronic respiratory/allergy status.
Evaluation:[a]
Medium confidence
Questionnaire not described but outcomes reported without knowledge of formaldehyde levels. Low participation rate but uncertain whether possible selection bias, if any, was nondifferential or differential.</td><td>background prevalence of dry eye disease; (Farrand et al., 2017))
Prevalence (p) Burning/Tearing Eyes (EPA reconstruction; see Appendix D.1.1)
<table><tr><th>ppm</th><th>Summer (p, %)</th><th>Winter (p, %)</th><th>N (homes)</th><th>95% CI (%)[a]</th></tr><tr><td>0.0431</td><td>13.3</td><td>-</td><td>315</td><td>1.91</td></tr><tr><td>0.0475</td><td>-</td><td>10.8</td><td>205</td><td>2.17</td></tr><tr><td>0.0906</td><td>17.1</td><td>-</td><td>192</td><td>2.72</td></tr><tr><td>0.0912</td><td>-</td><td>14.7</td><td>208</td><td>2.46</td></tr><tr><td>0.1698</td><td>-</td><td>20.6</td><td>110</td><td>3.86</td></tr><tr><td>0.1943</td><td>21.4</td><td>-</td><td>156</td><td>3.28</td></tr></table>[a]Estimated as: SE = sqrt(p*(1-p)/N)</td></tr>
<tr><td>Hanrahan et al. (1984) (Wisconsin)
Prevalence survey, 1979
Population: 61 teenage and adult occupants from 65 of 208 randomly selected mobile homes. Mean age 48 years, 61% female. Participants blinded to exposure status.
Outcome: Current symptoms with occurrence since moving into home from self-administered questionnaire, questionnaire not described.
Exposure: Formaldehyde measurements: 1-hour samples, average of measurements in two rooms.
Median: 0.16 ppm (0.2 mg/m^3). Range: <0.1 ppm to 0.80 ppm (<0.12 to 0.98 mg/m^3). Outdoor mean (SD) = 0.04 (0.03) ppm. Windows closed, smoking banned, gas appliances turned off for 30 minutes prior to measurements.
Analysis: Logistic regression adjusting for age, gender, and smoking.
Evaluation:[a]
Medium confidence
Low participation rate, but exposure and demographic characteristics were comparable among respondents and nonrespondents to the health questionnaire. Differential participation in the study based on symptom severity is unknown but cannot be ruled out. Uncertainty regarding correspondence of one hour exposure measurement with period for symptom ascertainment (years); Questionnaire not described but outcomes reported without knowledge of formaldehyde levels.</td><td>A statistically significant concentration-response relationship was reported individually for burning eyes and eye irritation; no regression coefficients provided.
Burning Eyes
<table><tr><th>Formaldehyde (ppm)</th><th>Prevalence (%)[a]</th><th>Upper 95% CI (%)[a]</th><th>SE (%)[b]</th></tr><tr><td>0.1</td><td>3.8</td><td>18</td><td>7.2</td></tr><tr><td>0.2</td><td>18.2</td><td>35</td><td>8.6</td></tr><tr><td>0.3</td><td>36.2</td><td>55</td><td>9.6</td></tr><tr><td>0.4</td><td>52.5</td><td>74</td><td>11</td></tr><tr><td>0.5</td><td>65.5</td><td>84</td><td>9.4</td></tr><tr><td>0.6</td><td>73.5</td><td>91</td><td>8.9</td></tr><tr><td>0.7</td><td>80.6</td><td>94</td><td>6.8</td></tr><tr><td>0.8</td><td>84.6</td><td>96</td><td>5.8</td></tr></table>[a]Predicted response estimated by EPA from graphical presentation of logistic regression results normalized to mean age (see Appendix D.1.1).
[b]Estimated as: SE (%) = (upper 95% CI- central estimate)/1.96

Formaldehyde concentration not associated with presence of smoker in home or gas appliances. Regression model showed higher prevalence of eye irritation in younger persons.</td></tr>
<tr><td>Olsen and Dossing (1982) (Denmark)
Prevalence survey, 1979.
Exposed Population: 66 of 70 employees of seven mobile day care centers (average building age ~6 months old) paneled indoors with urea formaldehyde glued particle board; mean age 29 years, 10/90 percentiles 19/40 years. Referent: 26 of 34 employees randomly selected from three control (nonmobile home) centers with no materials containing formaldehyde. Mean age 32 years, 10/90 percentiles 25/38 years. All worked in day care centers for >3 months.
Outcome: Prevalence (yes/no), Severity of symptoms experienced within 1 month measured in centimeters on scale from 0 to 10, “linear” analogue self-assessment method.”</td><td>The average frequency of mucous membrane irritation of eyes, nose, and throat was 3× higher among staff of mobile units vs. stationary institutions ($p < 0.01$). Symptoms disappeared after end of work.
Percentage (p) with affirmative answer
<table><tr><th>Irritation</th><th>Exposed (%)[a]</th><th>SE (%)[b]</th><th>Referent (%)[a]</th><th>SE (%)[b]</th></tr><tr><td>Eye</td><td>56</td><td>5.93</td><td>14.6</td><td>5.24</td></tr><tr><td>Nose/throat</td><td>74</td><td>6.06</td><td>25</td><td>7.43</td></tr></table></td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Exposure: Formaldehyde measurements taken after questionnaire study: 2-hour samples in 2–4 locations in the homes. Mean mobile units = 0.43 mg/m^3 (range 0.24–0.55 mg/m^3).
Mean referent = 0.08 mg/m^3 (range 0.05–0.11 mg/m^3).
Analysis: Prevalence and average impact scores compared.
Evaluation:[a]
Medium confidence
Some uncertainties regarding temporal concordance of exposure (< one day) and symptom assessments (within last month), but not expected to be substantial. Sample size in referent group small.</td><td>[a]Estimated by EPA from bar chart in Figure 1 in the paper.
[b]Estimated as: SE = sqrt(p*(1-p)/N)</td></tr>
<tr><td>Ritchie and Lehnen (1987) (Minnesota)
Prevalence survey, 1979
Population: Over 2000 occupants residing in 900 mobile and conventional homes referred by physician to health department for formaldehyde monitoring.
Outcome: Symptom prevalence reported by interview administered at time of air monitoring.
Exposure: Area samples; average of 30-min samples in 2 rooms. Bedroom mean: Mobile homes 0.43 mg/m^3, Conventional 0.15 mg/m^3, range 0.012 (LOD) to 6.79 mg/m^3.
Analysis: Logistic regression using formaldehyde concentration categorized in 3 levels (< 0.12 mg/m^3, 0.12 - 0.36 mg/m^3, > 0.36 mg/m^3), by age, smoking status, and sex.
Evaluation: [a]
Low confidence (↑)
Potential selection based on exposure and outcome status.</td><td>Eye Irritation Prevalence (% (SE); N))
Mobile Homes (by smoking status)
<table><tr><th>mg/m^3</th><th>Active</th><th>Passive</th><th>Non-smoker</th></tr><tr><td>< 0.12</td><td>2 (1.6)
N = 36</td><td>1 (0.9)
N = 46</td><td>1 (0.8)
N = 53</td></tr><tr><td>< 0.12 - 0.36</td><td>32 (4.8)
N = 65</td><td>20 (3.8)
N = 69</td><td>18 (2.9)
N = 126</td></tr><tr><td>>0.36</td><td>93 (1.5)
N = 143</td><td>88 (2.3)
N = 133</td><td>86 (2.2)
N = 180</td></tr></table>Conventional Homes (any smoking status)
<table><tr><td>< 0.12</td><td>1 (0.5); N = 695</td></tr><tr><td>< 0.12 - 0.36</td><td>12 (1.7); N = 380</td></tr><tr><td>>0.36</td><td>89 (3.5); N = 81</td></tr></table>Nose and Throat Irritation Prevalence (% (SE); N)
Mobile Homes (by smoking status)
<table><tr><th>mg/m^3</th><th>Active</th><th>Passive</th><th>Non-smoker</th></tr><tr><td>< 0.12</td><td>8 (3.1)
N = 36</td><td>10 (4.2)
N = 17</td><td>5 (2.1)
N = 34</td></tr><tr><td>< 0.12 - 0.36</td><td>25 (4.2)
N = 65</td><td>30 (6.5)
N = 24</td><td>17 (3.1)
N = 93</td></tr><tr><td>> 0.36</td><td>85 (2.6)
N = 143</td><td>88 (3.1)
N = 65</td><td>78 (3.2)
N = 132</td></tr></table>Conventional Homes (by smoking status and age)
<table><tr><td></td><td>Age 7 – 54 years</td><td></td><td></td></tr><tr><td>< 0.12</td><td>4 (1.3)
N = 83</td><td>2 (1.0)
N = 84</td><td>2 (0.6)
N = 274</td></tr><tr><td>< 0.12 - 0.36</td><td>23 (4.4)
N = 59</td><td>15 (4.0)
N = 50</td><td>12 (2.2)
N = 160</td></tr><tr><td>> 0.36</td><td>86 (4.6)
N = 17</td><td>79 (6.5)
N = 16</td><td>74 (6.7)
N = 21</td></tr><tr><td></td><td>Age 55+ years</td><td></td><td></td></tr><tr><td>< 0.12</td><td>7 (2.8)
N = 17</td><td>5 (2.0)
N = 15</td><td>4 (1.3)
N = 64</td></tr><tr><td>< 0.12 - 0.36</td><td>36 (8.8)
N = 9</td><td>25 (8.4)
N = 1</td><td>20 (5.7)
N = 19</td></tr><tr><td>> 0.36</td><td>92 (3.5)
N = 3</td><td>87 (5.6)
N = 2</td><td>84 (6.0)
N = 7</td></tr></table></td></tr>
<tr><td>Main and Hogan (1983)
Prevalence survey</td><td>Symptom Prevalence While at Work:</td></tr>
</table>

Study and design	Results
Population: 21 exposed individuals working in two mobile trailers for 34 months (mean [SD] age 38 [9] years, 76% male) 18 referent staff members who did not work in the trailers (mean [SD] age 30 [6] years, 50% male) **Outcome:** Modified ATS questionnaire **Exposure:** Three 1-hour area samples taken on four occasions (August, September, December, April) always on a Monday. At least one sample was taken from each office in both trailers. Concentration range 0.12–1.6 ppm (0.15–1.97 mg/m^3)[a] **Analysis:** Group comparisons, χ^2 statistic **Evaluation:**[a] *Low* confidence Potential dissimilarity between comparison groups; more exposure to ETS among referent; small sample size increased potential for unreliable results. Uncertainty regarding participant recruitment process or participation rate. Responses among exposed likely not blinded to exposure status.	Symptom / Exposed (*n* = 21) / Referent (*n* = 18) / χ^2 (*p*-value) Eye irritation: 0.71 / 0.0 / 20.9 (<0.001) Nasal symptoms: 0.33 / 0.0 / 7.3 (0.01) Throat irritation: 0.48 / 0.0 / 11.5 (0.001)

Organized by study confidence, then descending publication year. Results for *low* confidence studies are shaded gray.
LOD = limit of detection; RD50 = concentration resulting in a 50% reduction in the respiratory rate; RIL = recommended indoor limit; VOC = volatile organic compound.
[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.2).
Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Laboratory and occupational exposure

The studies of anatomy students and formaldehyde-exposed workers provide further evidence that formaldehyde exposure is associated with symptoms of eye, nose, and throat irritation. These studies are summarized in tables in the appendix for sensory irritation (Appendix C.4). Exposure levels experienced during anatomy laboratory courses and in occupational settings were high and variable. Formaldehyde levels during anatomy courses generally averaged 0.9 mg/m^3 and above during the lab, with short-term peaks above 5 mg/m^3 (Wantke et al., 2000; Uba et al., 1989; Takahashi et al., 2007; Kriebel et al., 1993; Kriebel et al., 2001). These exposures were episodic, one to two sessions per week, for 1–4 hours. Study designs that analyzed reported symptoms and formaldehyde levels measured in close temporal proximity were considered less subject to information bias. The intensity of symptoms (Kriebel et al., 2001) and prevalence or frequency of occurrence (Wantke et al., 2000; Takigawa et al., 2005) of symptoms was related to exposure during the lab. Over time, the magnitude of the increase in symptoms during a laboratory session was reported to decline over the succeeding weeks of the course (Kriebel et al., 1993; Kriebel et al., 2001). Kriebel et al. (2001) modeled average formaldehyde concentration during each lab session in relation to irritation symptoms (separate models for eye, nose, and throat irritation) and reported that intensity of eye irritation symptoms increased by 1.22% per unit increase in ppm, and the magnitude of the increase in intensity declined with each successive week during the course.

Formaldehyde concentrations in the workplace varied by industry. Examples of industrial formaldehyde levels include mean levels of 0.26 mg/m^3 in a formaldehyde-producing plant in Sweden (Holmström and Wilhelmsson, 1988), 0.96 mg/m^3 in a melamine formaldehyde resin-producing plant (Neghab et al., 2011) in Iran, and 1.04 mg/m^3 in a particleboard plant (Horvath et al., 1988). Excursions above 2 mg/m^3 were measured in some industries. Most of the studies compared responses in exposed groups to those in a referent group, and symptoms of URT and eye irritation were associated with exposure status in these studies. One study also reported a strong exposure-related trend for burning nose, stuffy nose, burning eyes, itchy nose, sore throat, and itchy eyes in multiple regression models, although quantitative results were not reported (Horvath et al., 1988).

Summary of Human Evidence Synthesis Judgments

The following factors, in particular the strong consistency and observed dose-dependence, were influential to the synthesis judgment that the human studies on sensory irritation provide *robust* evidence of formaldehyde exposure-induced effects.

- *Consistency and Study Confidence*: Increases in sensory irritation of the eye, nose and throat from formaldehyde exposure were consistent across 10 *high* and *medium* confidence studies involving acute controlled exposure and four *medium* confidence studies of symptom prevalence in residential settings. This evidence is supported by consistent findings from several studies with longitudinal designs following formaldehyde exposure in laboratory or occupational settings.
- *Dose-Response*: Demonstrated exposure-response trends for symptom prevalence and symptom severity were observed in multiple studies.
- *Coherence*: Different manifestations of irritation, including various symptoms and objective measures, were observed.

In addition to the judgment above, a general inference can be drawn based on the human studies. Specifically, although the evidence base does not completely address the uncertainties associated with such an observation, the currently available studies indicate that the irritant effects of formaldehyde do not appear to appreciably worsen with longer formaldehyde exposures.

Animal Studies

Summary of Animal Evidence Synthesis Judgments

Although not formally synthesized, the wealth of data for this effect in animals is inferred to provide *robust* evidence for formaldehyde inhalation exposure-induced effects on sensory irritation. As previously described, the sensory irritant effects of formaldehyde in animals represent a well-established phenomenon (see Summary in Appendix C.2). In addition, the mode of action information (discussed below) describing how formaldehyde inhalation can cause sensory

irritation is primarily based on experimental studies in animals, supporting the biological plausibility of the animal evidence and reinforcing this judgment.

Evidence on Mode of Action

Sensory irritation is understood to occur as a result of direct interactions of formaldehyde with cellular macromolecules i leading directly or indirectly to stimulation of trigeminal nerve endings; branches of the trigeminal nerve responsible for chemosensation innervate the oral, ocular, and nasal cavities. However, the most notable and well-studied of these is activation within the nasal mucosa (i.e., in the respiratory epithelium) and stimulation in the oral cavity is unlikely to lead to eye irritation or similar symptoms. While other mechanistic changes (e.g., oxidative stress; airway inflammation; damage or dysfunction of the respiratory epithelium) and biological differences (e.g., tissue morphology; underlying allergy, infection, or other respiratory conditions) are expected to be strong modifiers of this sequence of events, the pathway leading to stimulation of trigeminal nerve endings is likely to be the dominant mechanism by which formaldehyde exposure causes sensory irritation. The primary evidence for this conclusion includes mechanistic changes in the URT, which are supported by robust or moderate formaldehyde-specific data (see summary interpretations in Figure 3-4 and Table 3-3; Appendix C.7 includes additional details and evidence supporting other relevant mechanistic changes, some of which are discussed briefly below), and the relationships described are largely well understood biological phenomena, or they have been demonstrated following formaldehyde exposure. Access of airborne formaldehyde to other chemosensory afferents (e.g., in the eye) is expected to contribute to this response. This mechanistic understanding provides strong support for the biological plausibility of this effect. Although the primary support for an MOA reliant on stimulation of receptors on nasal trigeminal nerve endings is from studies in experimental animal models, the mechanistic events presumed to be driving sensory irritation after formaldehyde exposure are expected to be conserved in humans.

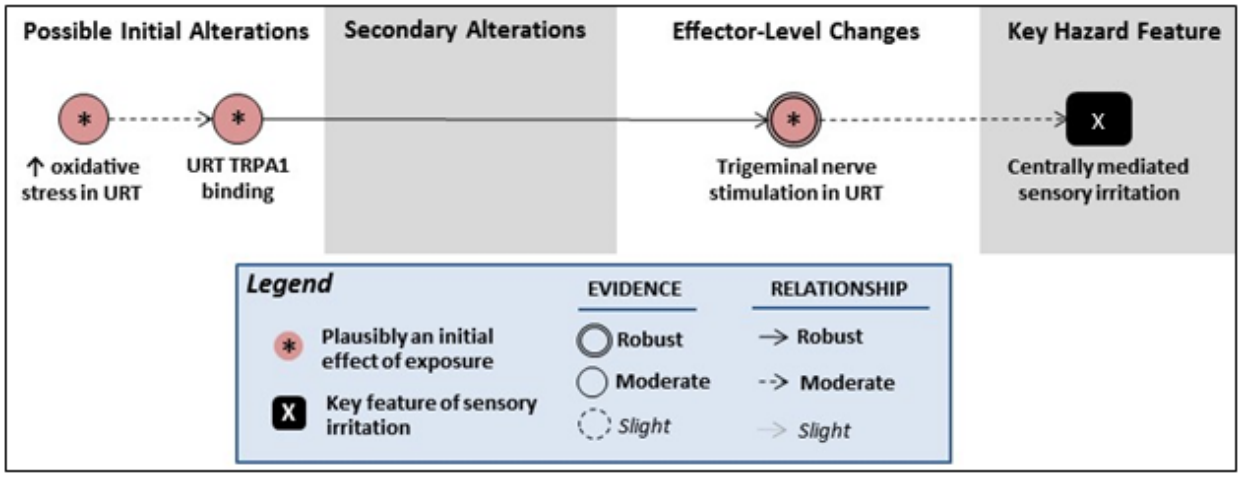


Figure 3-4. Possible mechanistic associations between formaldehyde exposure and sensory irritation.

An evaluation of the formaldehyde exposure-specific mechanistic evidence informing the potential for formaldehyde exposure to cause respiratory health effects (see Appendix C.7 for clarifying details) identified this sequence of mechanistic events as likely to be the dominant mechanism by which formaldehyde inhalation could cause sensory irritation.

As illustrated in Figure 3-4, formaldehyde exposure appears to result in activation of chemosensory afferents, likely trigeminal nerve C fibers, including in the URT, presumably in the anterior third of the nasal cavity, based on the pattern of chemosensory activation and consistent with the distribution of inhaled formaldehyde (see Appendix C.7). This activation (which can also occur in the eyes) initiates central signals that result in the burning sensation characteristic of sensory irritation. The rapid detection of these sensations in exposed individuals, as well as insights from other irritants, suggest a receptor-mediated event that is dependent on formaldehyde penetration to the nerve endings, which may not have an exposure duration threshold. Thus, mechanisms that prevent access of formaldehyde to these sites[16], or that reduce the number or response of receptors at these sites, would be expected to reduce such irritant responses. In vitro and ex vivo studies suggest that activation of the trigeminal nerve by formaldehyde is mediated, at least in large part, through cation channels, primarily the Transient Receptor Potential A1 channel (TRPA1). Alongside the centrally mediated physiological response, the initial activation of the trigeminal nerve is also known to cause a localized release of neuropeptides, such as substance P, from nerve terminals (not shown in Figure 3-4), which can affect local inflammatory and immune

[16] For example, although only indirectly applicable to formaldehyde exposure-induced sensory irritation, dry eye disease is far more prevalent in older individuals (age 50+) than younger individuals (under 18) (Farrand et al., 2017). This is based, at least in part, on differences in tissue physiology that help regulate access of airborne irritants to sensitive components of the eye (e.g., reduced tear production and changes in lipid composition with aging). While this may also apply to the direct irritant effects of airborne formaldehyde on the eye, it is unclear the extent to which parallel, protective, age-dependent mechanisms exist within the nasal epithelium.

responses. Observations of these local neuropeptide changes have been reported at slightly higher formaldehyde levels than those shown to activate the trigeminal nerve, generally at >1 mg/m^3, although the data suggest that they too may be dependent on TRPA1 activation. All of these direct and indirect interactions could act independently or together in a concentration- and duration-dependent manner.

While the response to some irritant chemicals exhibits desensitization or fading of the irritant response over time (e.g., through receptor downregulation) (Nielsen, 1991), it is not clear this is the case with formaldehyde. As previously discussed, results from acute, controlled human exposure studies indicate that some acclimatization may occur over exposures of a few hours at higher concentrations; however, this reduction in symptoms is less apparent (or may be absent) when concentrations are lower (<1 mg/m^3), and changes to this response pattern in humans over time, particularly with exposure longer than 1 day, remain poorly tested. Studies of reflex bradypnea in rodents (see Appendix C.2), a phenomenon dependent on the activation of the trigeminal nerve, show that repeated exposure for up to a month elicits a similar level of activation of this pathway. However, uncertainties with the rodent data include a nonconstant exposure (i.e., there is at least partial recovery from the reflex effects in rodents with continued exposure in acute studies of minutes to hours, while the available short-term studies employed work hour-like exposure periodicity) and testing only at reflex bradypnea-inducing levels (e.g., >1 mg/m^3). It is unclear whether the results based on acute or episodic exposures apply to long-term responses to constant oronasal exposure in humans (who do not exhibit reflex bradypnea) at lower formaldehyde levels.

Sensitivity (i.e., the threshold for activation of this pathway) is expected to vary between individuals due to differences in TRPA1 channel sensitivity or access of formaldehyde to TRPA1 channels, as might occur due to differences in tissue structure, mucus production, or TRPA1 channel density in the airways or eyes. Thus, enhanced irritation could plausibly occur directly as a result of sensitization of the receptors to formaldehyde with prolonged exposure or due to the accumulation of other factors that could reduce the threshold for TRPA1 activation by formaldehyde, or indirectly by increased access of formaldehyde to trigeminal nerve endings, for example following damage to juxtaposed epithelial cells or reduced mucociliary function. Airway inflammation has been shown to reduce the threshold for activation of afferent fibers, through an unknown mechanism (Carr and Undem, 2001), and lipid peroxidation byproducts can independently stimulate sensory nerve activation. These latter possibilities are of particular relevance, as exposure to formaldehyde (possibly even at lower levels, e.g., <1 mg/m^3) appears to result in airway inflammation and increased oxidative stress. Conversely, other modifications to the respiratory epithelium following formaldehyde exposure (e.g., at levels causing effects such as squamous metaplasia, which is generally observed in animals at ≥2.5 mg/m^3; see Section 3.2.4) could plausibly result in a decreased access of formaldehyde to receptors at trigeminal nerve endings. However, while the structure and function of the URT across species is similar,

interpretation of compensatory or adaptive changes within the human URT following long-term exposure based on findings in experimental animals is difficult to infer, and modification of sensory nerve signaling in the context of these important scenarios has, for the most part, not been directly tested. In addition, studies of related chemicals suggest that human sensitivity may also be dependent on demographic factors such as age, gender (women are generally more sensitive), and allergy status (Shusterman, 2007; Hummel et al., 2003), complicating an understanding of changes in sensitivity. While additional studies clarifying modifications to the sensitivity of this pathway with longer-term exposure or under different exposure scenarios would be useful, it is likely that rodents acutely exposed to ~0.2 mg/m^3 formaldehyde under normal conditions would exhibit sensory irritation, and exposed humans are expected to be more sensitive.

Table 3-3. Mechanistic evidence most informative to the occurrence of sensory irritation after formaldehyde inhalation

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
↑ URT Oxidative Stress	*High or Medium*	*Human*: Increased nasal epithelial M1dG adducts (oxidative stress and lipid peroxidation marker) (Bono et al., 2016): unknown duration (but likely years) at >0.066 mg/m^3	Direct and indirect evidence of elevated reactive oxygen species (ROS), possibly at low concentrations (e.g., at >0.066 mg/m^3; maximum of 0.444 mg/m^3) with prolonged human exposure	Moderate
		Animal: mRNA changes indicating increased stress-response proteins (Andersen et al., 2008): short-term exposure at ≥2.46 mg/m^3		
	Low	*Human*: Increased nasal lavage nitrites (Priha et al., 2004): acute (8-hr shift) exposure at 0.19 mg/m^3	Data suggest elevated oxidative stress at very low formaldehyde concentrations with acute and short-term exposure	
		Animal: Increased glutathione peroxidase and/or nonprotein sulfhydryl groups (Cassee and Feron, 1994; Cassee et al., 1996): short-term (3 d) duration at 3.94 and 4.43 mg/m^3, respectively		
TRPA1 Stimulation	*High or Medium*	*Human*: None	Indirect data identify TRPA1 as a molecular target for formaldehyde exposure-induced sensory effects	Moderate (data are primarily from acute or short-term exposure)
		Animal: Formaldehyde and related chemicals such as acrolein activate the trigeminal system in wild-type mice, but not TRPA1 knockout mice following acute exposure, at least at high exposure levels (Yonemitsu et al., 2013); taken together with the established role for TRPA1 in acrolein-induced sensory effects (e.g., (Bautista et al., 2006)), these data indirectly support a role for TRPA1 in sensory nerve-related changes following formaldehyde exposure		
	Low	*Human*: None	Indirect data identify TRPA1 as a molecular target of formaldehyde exposure with acute or short-term exposure; inhibitor studies demonstrate that downstream effects of sensory nerve stimulation depend on TRPA1 stimulation	
		Animal: Formaldehyde activates TRPA1 in in vitro and ex vivo models relevant to acute inhalation exposure of the URT and upper LRT (Mcnamara et al., 2007; Luo et al., 2013), and is well established in in vivo models using formalin as a pain stimulus (not a focus of this review); inhibition of TRPA1 channels localized to sensory nerve endings reduces formaldehyde		

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
		exposure-induced nerve currents in rat trachea (Luo et al., 2013) and immune-related responses in mice (Wu et al., 2013; Lu et al., 2005) with short-term (2- or 4-week) exposure at 1 or 3 mg/m^3		
Trigeminal Nerve Stimulation	*High or Medium*	Human: None	Increased activity of trigeminal nerve afferents at <0.5 mg/m^3 following acute exposure in anesthetized rats	Robust (data are primarily from acute exposure)
		Animal: Increased afferent nerve activity (Tsubone and Kawata, 1991): acute duration exposure resulted in ~20% at 0.62 mg/m^3 and ~50% at 2.21 mg/m^3; (Kulle and Cooper, 1975): acute exposure (threshold detection at 25 seconds) at 0.31 mg/m^3		
	Low	*Human*: None	Supportive indirect evidence from ex vivo and in vitro experiments	
		Animal: Indirect evidence: with acute exposure, dose-dependent increase in nerve currents and Cl^- release in intact rat trachea (Luo et al., 2013), and stimulation using in vitro neuronal preparations (Mcnamara et al., 2007; Kunkler et al., 2011)		

Summary of Inferences Regarding Mode of Action

Robust and moderate evidence for important mechanistic events identifies stimulation of the trigeminal nerve as the dominant MOA. This MOA is assumed to be relevant to sensory irritant effects in humans based on similarities in the systems mediating the identified MOA across species. The identified MOA highlights large variations in sensitivity across individuals, depending on features such as tissue health and physiology, including altered mucociliary function in the nasal cavity, that could influence the stimulation of key receptors (e.g., TRPA1).

Evidence Integration Summary

Symptoms of sensory irritation were consistently reported by studies of formaldehyde exposure in multiple exposure settings, and both prevalence and severity of symptoms increased with the level of exposure. Sensory irritation is an acute phenomenon, and symptoms resolve when exposure is removed (Sauder et al., 1986; Andersen, 1979; Andersen and Molhave, 1983). Irritation of the eyes was reported to occur at lower concentrations compared to irritation of the nose or throat (Mueller et al., 2013; Lang et al., 2008). The irritant effects of formaldehyde on the eyes and URT were reported by several controlled human exposure studies that evaluated responses among healthy or asthmatic volunteers using relatively high formaldehyde concentrations (0.12 and 3.7 mg/m^3) during rest or exercise. In addition to subjective reports, some investigators evaluated objective measures, including eye blink frequency, conjunctival redness, and nasal flow and resistance (Mueller et al., 2013; Lang et al., 2008; Andersen, 1979; Andersen and Molhave, 1983). Eye blink frequency was increased at exposure levels above those where subjective symptoms were reported. Symptoms of sensory irritation also were documented in the epidemiological literature among residential and occupational populations, and students exposed in anatomy classes. Exposed

groups described eye, nose, and throat symptoms with formaldehyde exposure, including itching, stinging, burning, and watering eyes; sneezing and rhinitis; sore or dry throat; and coughing. Average formaldehyde concentrations for exposed populations were 0.9 mg/m^3 (median) among anatomy students (Kriebel et al., 1993), > 0.3 mg/m^3 among occupational groups (Neghab et al., 2011; Horvath et al., 1988; Holmström and Wilhelmsson, 1988), and 0.2 mg/m^3 and lower among residential populations (Zhai et al., 2013; Liu et al., 1991; Hanrahan et al., 1984). A statistical exposure-response relationship for the prevalence of eye irritation or burning eyes was described using regression models in some studies (Liu et al., 1991; Kulle et al., 1987; Kriebel et al., 1993; Kriebel et al., 2001; Horvath et al., 1988; Hanrahan et al., 1984). Alternative explanations for these symptoms can be ruled out since there is strong evidence from controlled human exposure studies and residential studies, with exposure-response trends that were adjusted for potential confounders, including age, gender, and smoking. Coexposures in homes, such as that from terpenes, phenol, and acetaldehyde, which are emitted from wood products, carpets and wall coverings, and combustion, were present at lower levels compared to those of formaldehyde. Sensory irritation also was reported among groups in exposure settings without those coexposures (e.g., controlled human exposure studies, anatomy labs). NO_2, which is emitted from gas stoves, has not been correlated with formaldehyde levels in homes (Mullen et al., 2015).

The magnitude or severity of symptoms does not appear to worsen over periods of prolonged exposure, and some studies have observed decreases over observation periods lasting a few weeks. However, change in responses over time has been examined in only a few studies. Notably, controlled human exposure studies involving occupationally exposed individuals did not observe responses that were less sensitive than those among subjects with no occupational exposure, suggesting that the response persists even with prolonged exposure. Controlled human exposure studies that examined change in response during exposures at relatively high levels (>1 mg/m^3) reported higher symptom scores initially with subsequent declines suggestive of acclimation during exposure (Schachter et al., 1986; Green et al., 1987; Andersen and Molhave, 1983). However, at lower concentrations (0.3 and 0.5 mg/m^3), the initiation of symptoms was delayed, and symptom severity continued to increase during the exposure period (Andersen and Molhave, 1983). Overall, these few studies suggest that some acclimatization may occur over a few hours at higher concentrations; however, this phenomenon may not be apparent when concentrations are lower (<1 mg/m^3).

Stimulation by formaldehyde of sensory nerve endings, predominantly in the URT (but also possibly in the eyes) and presumably involving activation of TRPA1 ion channels on C fibers of the trigeminal nerve, is likely to be the dominant MOA for the observed effects on sensory irritation. It is expected that differences in tissue anatomy and respiratory health status would be strong modifiers of this MOA.

In conclusion, studies in humans provide *robust* evidence based on the controlled human exposure studies and observational epidemiology studies, *robust* evidence exists supporting an

effect in animals (this phenomenon is well described and accepted across a range of experimental species), and there is an established MOA based on mechanistic evidence in animals (the identified MOA is interpreted to be operant in humans). Overall, the **evidence demonstrates** that inhalation of formaldehyde causes sensory irritation in humans, given sufficient exposure conditions. The primary support for this conclusion is based on well-conducted residential studies with mean formaldehyde concentrations >0.05 mg/m^3 (range 0.01 to approximately 1.0 mg/m^3) and controlled human exposure studies testing responses to concentrations 0.1 mg/m^3 and above (see Table 3-4).

Table 3-4. Evidence integration summary for effects of formaldehyde inhalation on sensory irritation

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Human	*Consistency and Study Confidence*	• Four *medium* confidence studies of symptom prevalence (eye, nose, throat) among adults and children in residential settings (mean >0.05 mg/m^3 formaldehyde, range 0.01 to approximately 1.0 mg/m^3) • Consistent findings from several studies involving acute controlled exposure • Consistent findings in studies with longitudinal designs (e.g., occupational, panel studies of medical students)		*Robust* Based primarily on consistent and dose-dependent findings across residential, controlled acute exposure, and longitudinal studies	The **evidence demonstrates** that formaldehyde inhalation causes sensory irritation in humans given sufficient exposure conditions[a] Primarily based on *robust* human evidence from well-conducted residential studies with mean formaldehyde concentrations >0.05 mg/m^3 and controlled human exposure studies testing ≥0.1 mg/m^3. Strong supporting evidence exists, including established mechanistic understanding *Potential susceptibility*: Potentially large variations in sensitivity are expected, depending primarily on differences in nasal health (including allergy or inflammatory status) and underlying physiology, but also age and sex
	Strength and Precision	N/A			
	Dose-Response	• Consistent and clear exposure-response trends in numerous studies			
	Coherence	• Different manifestations of irritation, including various symptoms and objective measures, were observed			
	Biological Plausibility	No directly relevant human mechanistic studies were found			
Animal	Although animal studies were not formally evaluated, formaldehyde inhalation-induced sensory irritation in rodents is a well-documented phenomenon (see Appendix C.2)			*Robust*	

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
	Biological Plausibility	• Understanding of the MOA underlying the development of sensory irritation following formaldehyde inhalation is primarily based on experimental studies in animals		Inferred as a well-defined phenomenon with established biological understanding	
Other inferences	• *Relevance to humans*: The effect was observed in humans (*robust* evidence) • *MOA*: Robust and moderate evidence for mechanistic events from animal studies identifies stimulation of the trigeminal nerve as the dominant MOA. This is assumed to be relevant to humans based on similarities in systems mediating the identified MOA across species • *Other*: This effect does not appear to worsen with longer exposure durations, although some uncertainties with that judgment remain				

N/A = indicates the factor was not applicable to (i.e., did not influence) the judgment drawn.

[a]The "sufficient exposure conditions" are more fully evaluated and defined through dose-response analysis in Section 5.1.

3.2.2. Pulmonary Function

This section describes research on formaldehyde inhalation and pulmonary function effects in experimental and observational studies in humans. The study selection criteria (PECO) included studies of pulmonary function responses to any exposure duration including long term occupational or continuous residential exposure, episodic exposures during anatomy classes, or controlled human exposure studies for a few hours. EPA focused the hazard evaluation on exposure settings most relevant to the dose-response assessment and derivation of a RfC for chronic duration exposure scenarios. These studies include occupational studies of workers with long-term exposure (typically, years), residential or school exposures to adults or children, and episodic (weekly) exposures to medical students in anatomy classes followed over a period of months. Studies of acute- and short-term exposure scenarios did not provide a clear indication of effects on pulmonary function and these results are summarized in the appendix (see Appendix C.5.1 for controlled human exposure studies and Appendix C.5.2 for studies of workers or medical students and pulmonary function changes across a work shift or over a dissection lab). Animal studies of analogous endpoints were not included in the hazard evaluation because there were few directly relevant studies in the peer-reviewed literature and the extensive literature on these endpoints in humans was considered adequate to draw a hazard conclusion.

The review of the epidemiological literature provides evidence that long-term formaldehyde exposure is associated with declines in pulmonary function, including forced expiratory volume (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and expiratory flow rates. Pre-shift pulmonary function was lower in highly exposed occupational groups employed at exposed jobs for long durations compared to their nonexposed or lesser-exposed comparison groups. The few longitudinal studies found evidence of declines in some measures in excess of that expected from aging, although the duration of follow-up and individual variation combined with small group sizes may have resulted in lack of associations with other measures. Panel studies of anatomy students also provide evidence that formaldehyde exposure during dissections results in declining pulmonary function over time. There are few studies of residential exposure; however, a clear exposure-response relationship in children was reported by a well-conducted residential study with most household concentrations <0.045 mg/m^3 (Krzyzanowski et al., 1990). There is mechanistic support, primarily from studies in animals, for the biological plausibility of formaldehyde exposure-induced effects on decreased pulmonary function, although a definitive MOA(s) has not been fully defined. Overall, the most relevant mechanistic evidence (predominantly evidence interpreted as moderate or robust) included inflammatory structural alterations and eosinophil increases in the lower airways that appear to be at least partially related to indirect activation of sensory nerve endings. However, the initial cellular or tissue modifications that ultimately lead to these later events are not understood, and given the limitations of the available studies, it is unclear whether and to what extent certain events would be triggered with chronic, low-level exposure. Although there is an expectation that other important mechanistic events

would be identified with additional study, the available data were interpreted to provide reasonable support for the biological plausibility of the observed associations and to identify what is likely to be an incomplete mechanism by which formaldehyde inhalation could cause decreased pulmonary function.

Spirometric measures are used along with other diagnostic criteria in the evaluation of asthma and chronic obstructive pulmonary disease in individuals. While a group mean decrement in any pulmonary function measure does not indicate that the prevalence of these respiratory diseases has increased, EPA considered a decrease in mean values to suggest a shift toward a decline in the respiratory health status of the population. Poor pulmonary function, as well as a decrease in pulmonary function, is an important health endpoint associated with the development of chronic respiratory disease, coronary heart disease, and mortality (Young et al., 2007; Sorlie et al., 1989; Sin et al., 2005; Schunemann et al., 2000; Schroeder et al., 2003; Menezes et al., 2014; Clayton et al., 2014). The American Thoracic Society evaluated the clinical significance of small average declines in pulmonary function observed in a population in response to air pollutants and concluded that although the magnitude of the observed declines may not be clinically relevant to an individual, a shift in the population distribution toward lower pulmonary function, assuming the association is causal, may have a large impact on public health (ATS, 2000).

Overall, based on *moderate* human evidence from observational epidemiology studies, with corresponding *slight* evidence for an effect in animals based on mechanistic studies supporting biological plausibility, the **evidence indicates** that long-term inhalation of formaldehyde likely causes decreased pulmonary function in humans given sufficient exposure conditions. The primary support for this conclusion includes a study of children and adults in a residential setting (mean, 0.03 mg/m^3, maximum 0.17 mg/m^3) and numerous studies of workers with long-term exposure to >0.2 mg/m^3.

Human Studies

The synthesis of pulmonary function first discusses studies of long-term exposures among occupational groups or residential populations of adults and children. Then, panel studies of students in anatomy labs with episodic exposure over a period of weeks or months are discussed. Evidence tables for each exposure setting (see Tables 3-5 through 3-8) are organized by level of confidence in the study's results and then descending publication year. The table summarizing the studies of occupational exposure are organized first by study design (cross-sectional, longitudinal), then by confidence in study results and descending publication year. Eleven of the studies that met the PECO criteria were considered *not informative* after evaluation (Tanveer et al., 1995; Sripaiboonkij et al., 2009; Pourmahabadian et al., 2006; Ostojić et al., 2006; Mohammad `pour and Maleki, 2011; Milton et al., 1996; Marks et al., 2010; Kilburn et al., 1985; Kilburn et al., 1989a; Imbus and Tochilin, 1988; Gamble et al., 1976). The study evaluations are included in Appendix B.3.3. Generally, in the included studies of formaldehyde exposure and effects on pulmonary function, groups exposed to formaldehyde during the course of their jobs experienced TWA

concentrations above 0.2 mg/m^3 with intermittent peaks above 1 mg/m^3 (see Table 3-5). Students meeting once or twice a week in anatomy labs experienced fluctuating concentrations during dissections averaging between 0.1 and >1.0 mg/m^3 (see Table 3-8). Formaldehyde concentrations in residential or primary school settings were much lower, continuous, and less variable (<0.1 mg/m^3) (see Tables 3-6 and 3-7).

Occupational exposure

Overall, the set of occupational studies indicates that inhalation of formaldehyde over long periods at work is associated with deficits in measures of pulmonary function. With only a few exceptions, average values for FEV_1, FVC, and FEF measured before a work shift at the beginning of the work week were lower among exposed workers than average values in their referent groups (see Table 3-5). The occupational groups under study were exposed to high average formaldehyde concentrations (≥0.2 mg/m^3) in a variety of industries, including funeral homes (embalming), wood products (plywood, cabinetry), chemical products (formaldehyde resins), and manufacturing. Employees had worked at these jobs for at least 5 years, and in a few studies, for more than 10 years. While a few studies conducted longitudinal analyses (Nunn et al., 1990; Löfstedt et al., 2011; Alexandersson and Hedenstierna, 1989), most of the occupational studies were cross-sectional in design, recruiting only current employees (Schoenberg and Mitchell, 1975; Neghab et al., 2011; Malaka and Kodama, 1990; Löfstedt et al., 2009; Levine et al., 1984b; Khamgaonkar and Fulare, 1991; Horvath et al., 1988; Holmström and Wilhelmsson, 1988; Herbert et al., 1994; Alexandersson et al., 1982; Alexandersson, 1988; Alexandersson and Hedenstierna, 1988). In general, when only current employees are recruited for a cross-sectional study of an exposure that causes symptoms, there is a possibility that former workers may have left their jobs to reduce their exposure (lead time bias, healthy worker survival effect). Further, for studies that recruited from among those present on the day of the study, if employees were not present because of symptoms related to their formaldehyde exposure, attenuated effect estimates may have been observed (Alexandersson et al., 1982; Alexandersson, 1988; Alexandersson and Hedenstierna, 1988). Additional limitations also were identified that could result in attenuated risk estimates, which are noted in the evidence summary table (see Table 3-5). Despite their decreased sensitivity, most studies observed deficits in pre-shift pulmonary function associated with formaldehyde exposure, which increased EPA's confidence in their findings. Moreover, an increase in pulmonary function deficits with increasing cumulative exposure was reported in a study of woodworkers with area formaldehyde levels ranging from 0.27–4.28 mg/m^3 (Malaka and Kodama, 1990).

Figure 3-5 presents forest plots of the difference in mean FEV_1, FVC, and FEF_{25-75} between exposed and referent groups for 10 study results reported by 9 publications. Mean FEV_1 in exposed groups was consistently lower than their un- or lesser-exposed referent group across all industries, ranging from -3.6 to -9.5 percent in wood products workers, -1.7 to –12.2 percent in chemical manufacture workers, and –1.5 percent in embalmers. While no difference in mean FVC (%) was found by a few of the studies, and a higher mean was reported by a small study, most of the

comparisons indicate that exposed groups had lower mean values compared to their respective referent group ranging from –2.0 to -8.1 percent in wood products workers and -6.6 to -13.9 percent in chemical manufacture workers. A set of four studies of wood products workers reported consistently lower mean FEF_{25-75} compared to their unexposed referent groups ranging from –2.0 to –10.4 percent. Studies that reported only the absolute values or used a different analysis could not be plotted (Levine et al., 1984b; Khamgaonkar and Fulare, 1991; Herbert et al., 1994). All reported deficits in pulmonary function measures among exposed groups with varying degrees of precision.

In general, the studies of formaldehyde exposure in wood products industries reported the highest average and peak concentrations (TWA 0.4–1.0 mg/m^3, maximum 1.3–4.3 mg/m^3) (Malaka and Kodama, 1990; Horvath et al., 1988; Alexandersson et al., 1982; Alexandersson, 1988; Alexandersson and Hedenstierna, 1988), although levels were reported to be lower in two studies (minimum, 0.1 and 0.05 mg/m^3; maximum, 0.3 and 0.5 mg/m^3) (Holmström and Wilhelmsson, 1988; Herbert et al., 1994). Average concentrations in the chemical industries generally were lower and less variable, although there was variation between industries. Average concentrations in a melamine resin factory were 1.0 ± 0.49 mg/m^3 (Neghab et al., 2011) in contrast with 0.1 mg/m^3 (range 0.01–0.4 mg/m^3) among Hot Box foundry workers (Neghab et al., 2011). Differences in exposure levels between studies of these highly and variably exposed occupational groups do not clearly explain differences in the magnitude of deficits observed among exposed groups compared to their referent.

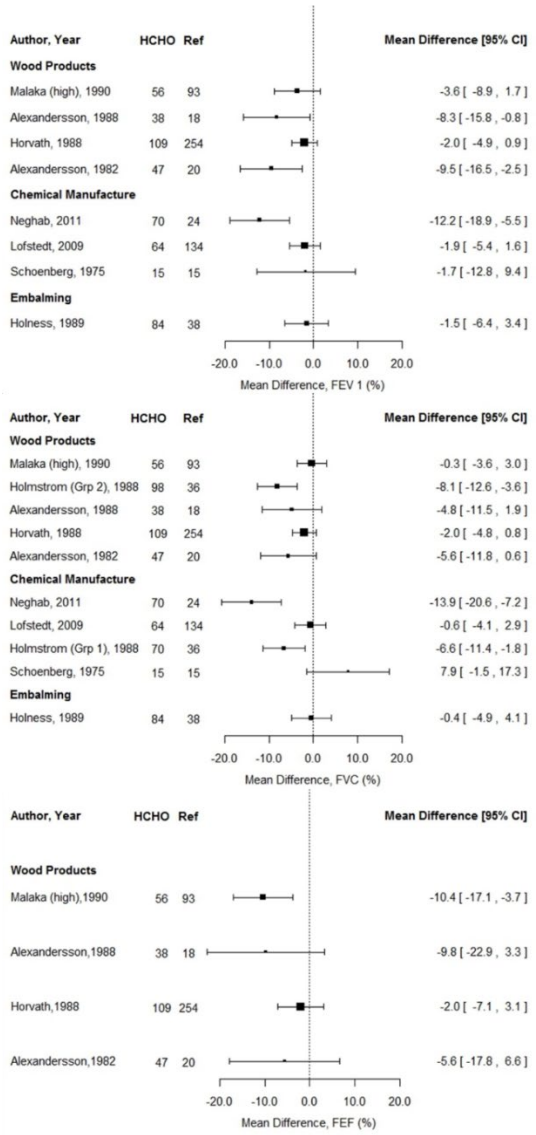


Figure 3-5. Forest plots depicting mean difference in pre-shift pulmonary function (percentage predicted) between exposed and comparison groups for FEV_1, FVC, and FEF.

The plots show the author and year, number of exposed (HCHO) and unexposed referents (Ref), and the mean difference in preshift values (%) between exposed and referents. The plots include results from six studies that reported the percentage of predicted normal function accounting for age, gender, and height, and three studies that reported mean absolute values and mean reference values for exposed and referent groups from which the percentage of the reference group could be calculated (Holmström and Wilhelmsson, 1988; Alexandersson et al., 1982; Alexandersson, 1988; Alexandersson and Hedenstierna, 1988). The forest plot compares the mean difference between all exposed and referent groups when available, although one study reported appropriate data only for subgroups [e.g., low, and high exposure categories; (Malaka and Kodama, 1990)]. The average of the standard deviations for a spirometric parameter specific to an exposure group, weighted by the size of the referent group, was used when no statistics from the individual study were available (Holmström and Wilhelmsson, 1988; Alexandersson et al., 1982; Alexandersson, 1988; Alexandersson and Hedenstierna, 1988).

In addition to accounting for age, gender, and height, most of the studies adjusted for smoking in their statistical analyses or otherwise addressed potential confounding by smoking. (Nunn et al., 1990; Neghab et al., 2011; Malaka and Kodama, 1990; Löfstedt et al., 2011; Levine et al., 1984b; Horvath et al., 1988; Holness and Nethercott, 1989; Holmström and Wilhelmsson, 1988; Herbert et al., 1994; Alexandersson and Hedenstierna, 1989).

The studies evaluated three types of occupational settings—wood products industries, chemical production, and mortuaries—and employees in these industries were exposed to other chemical and physical agents that may co-occur with formaldehyde. Other common exposures in the wood products industry can include phenols and other solvents contained in resins and glues, terpenes, and dust, while embalming fluids include methanol. Phenol and terpenes are not expected to have strong effects on pulmonary function, particularly at the concentrations reported by the studies. However, occupational exposure to high concentrations of wood dust (>2 mg/m^3) has been associated with reductions in pulmonary function (Mandryk et al., 2000). Many of the studies of wood products workers reported measurements for dust, terpenes, and phenols, stating that levels were a fraction of occupational exposure limits. Studies that either adjusted for dust levels or compared effects in formaldehyde-exposed groups with and without dust exposure did not find an independent effect by dust (Malaka and Kodama, 1990; Holmström and Wilhelmsson, 1988). The chemical industries included manufacture of formaldehyde products such as formaldehyde-phenol or formaldehyde-melamine resins and may involve exposures to phenols, other alcohols, VOCs, and other compounds, some of which may affect pulmonary function. However, since a pattern of reduction in pulmonary function was observed across several different exposure settings, all involving high formaldehyde exposure (TWA concentrations above 0.2 mg/m^3 with intermittent peaks above 1 mg/m^3), confounding by a coexposure becomes less likely to be an alternative explanation for the observed associations.

Three studies conducted longitudinal analyses of small groups of workers with continued exposure over 4–6 years (Nunn et al., 1990; Löfstedt et al., 2011; Alexandersson and Hedenstierna, 1989). All three longitudinal studies measured FEV1 and reported no change in the cohorts over the study period. However, Nunn et al (1990), a study of workers at a formaldehyde-urea resin manufacturing factory reported that among exposed nonsmokers, the annual decline was −45 mL/year (95% CI −28, −62 mL/year), which is 50% greater than the expected rate of age-related decline in FEV1 in nonsmokers (-29 mL/year), (Redlich et al., 2014; Lee and Fry, 2010). The annual decline among unexposed nonsmokers in this study was −29 mL/year, consistent with the expected rate of decline with age. In addition, Alexandersson and Hedenstierna (1989) reported a decline in FEF25−75 at a TWA concentration of 0.42−0.5 mg/m3. FEF25−75 percentage among the carpentry workers declined by −168 ± 46 mL/second (10.1 L/minute) for each year of exposure over a 5-year period ($p < 0.001$). There was a larger decrease among nonsmokers compared to smokers (−212 mL/sec/year and −60 mL/sec/year, respectively). The annual decrease was corrected for aging and reference pulmonary function spirometry values. The number of years that participants

were followed by the three studies, 4–6 years, is the minimum length of time considered adequate to observe changes (Redlich et al., 2014). Given the large amount of within-person variability in these measures when assessed over time, these studies would have had limited sensitivity to detect a small longitudinal change. Further, information in the reports for the three studies indicated a potential differential loss to follow-up of exposed individuals who may have changed jobs or left the industry because of the irritation effect of formaldehyde. Despite the low sensitivity of these studies, declines in FEV1 and FEF25−75 over time were reported.

Duration of work in an exposed job was associated with decreased pulmonary function values in two studies (Schoenberg and Mitchell, 1975; Neghab et al., 2011), but not others (Horvath et al., 1988; Holmström and Wilhelmsson, 1988; Alexandersson et al., 1982). These analyses controlled for age, height, gender, and cigarette smoking. One study examined associations with cumulative exposure (ppm-years) and observed reductions in pulmonary function measures (FEV_1, FEV_1/FVC, and FEF_{25-75}) among male employees at a plywood company who had worked an average of 6–7 years (Malaka and Kodama, 1990). In addition to other relevant covariates, this analysis controlled for cigarette smoking and dust levels in the regression model. Another study among wood products employees reported no association with a cumulative exposure measure, but did not present the results quantitatively (Holmström and Wilhelmsson, 1988).

Table 3-5. Formaldehyde effects on pulmonary function in occupational settings

Study and design	Results
Cross-sectional studies	
Reference: Horvath et al. (1988) Cross-sectional study, Wisconsin. **Population:** 109 exposed (workers at a particleboard and molded products operation, 68.6% of all exposed), average age 37.4 ± 11.7 years, 57% males; 53.2% current and former smokers, average work duration in exposed: 10.3 years (1–20 years). 254 unexposed (workers from nearby food processing facilities; average age 34.2 ± 10.6 years, 44% male). 53.1% current and former smokers. **Exposure:** 8-hour TWA measured using personal passive monitors on the day of the exam (LOD 0.15 mg/m^3). Area levels measured with an active sampling train (impingers). TWA 0.69 ppm, range 0.17–2.93 ppm (0.85 mg/m^3, range 0.21–3.60 mg/m^3),[a] and 0.05 ppm, range 0.03–0.12 ppm (0.062 mg/m^3, range 0.037–0.15 mg/m^3)[b] in the exposed and unexposed industries, respectively. Other exposures in exposed: Respirable particulates (PEL 5 mg/m^3): median 0.11 mg/m^3; phenol (PEL 5 ppm): mean 0.15 ppm; carbon monoxide (PEL 50 ppm): mean 7.35 ppm; sodium hydroxide (PEL 2 mg/m^3): 0.4–0.21 mg/m^3; nitrogen dioxide: ND; acrolein: ND.	**Comparison of mean preshift pulmonary function (percentage predicted (SD))** Exposed / Referent FEV_1 (L): 103 (13) / 105 (13) FVC (L): 105 (12) / 107 (13) FEV_1/FVC: 96 (8) / 95 (8) PEFR (L/sec): 100 (23) / 103 (22) FEF_{25-75} (L/sec): 83 (22) / 85 (25) FEF_{25} (L/sec): 6.91 (2.12) / 6.73 (1.98) FEF_{50} (L/sec): 4.5 (1.46) / 4.38 (1.43) FEF_{75} (L/sec): 1.63 (0.8) / 1.66 (0.77) $p > 0.05$ Exposure group was not associated with baseline absolute values in multiple linear regression models. Work duration was not associated with preshift pulmonary function.

Study and design	Results
Methods: Spirometry (volumetric) before and after the work shift. Pulmonary function (ATS methods) as percentage of predicted normal compared between exposed and unexposed (unpaired *t*-test); multiple linear regression of baseline absolute values by exposure group, adjusting for age, height, sex, and smoking. **Evaluation:**[a] *High* confidence	FEV_1, forced expiratory volume in 1second; FVC, forced vital capacity; PEFR, peak expiratory flow rate; FEF, forced expiratory flow; $FEF_{25, 50, 75}$ indicate flow expiratory flow rates at 25%, 50%, and 75% of FVC, respectively.
Reference: Neghab et al. (2011) Cross-sectional study, Iran. **Population:** 70 male workers at a local melamine-formaldehyde resin-producing factory with current exposure to formaldehyde and ≥2 years work history (mean age 38.2 ± 8.4 years, work duration 13.2 ± 7.8 years, 24.3% smokers). 24 healthy males from the same industry and comparable socioeconomic and demographic status, and no present or former formaldehyde or other exposure to respiratory irritants. 100% participation (mean age 40.0 ± 8.2 years, work duration 14.5 ± 8.1 years, 25% smokers). **Exposure:** Area samples (*N* = 7) in seven workshops with exposure and one area sample in office area (sampling in different time points and shifts). Sampling time 40 minutes. Exposed mean formaldehyde: 0.78 ± 0.4 ppm (0.96 ± 0.49 mg/m^3)[b]; referent: not detected. **Methods:** Pulmonary function tests (Vitalograph COMPACT), ATS methods) before and at the end of the work shift on the first working day of week, percentage predicted. Group comparisons and cross-shift difference among exposed, and multiple linear regression analysis of pulmonary function comparing exposed and referent adjusting for smoking, age, weight, height. **Evaluation:**[a] *Medium* confidence (↓) Potential for healthy survivor bias with attenuation in measure of association.	**Percentage predicted pulmonary function (mean (SD))** Exposed Preshift (*N* = 70) / Referent (*N* = 24) VC: 77.9 (12.0)[a] / 99.3 (21.0) FVC: 86.6 (14.5)[a] / 100.5 (14.5) FEV_1: 86.6 (14.4)[a] / 98.8 (14.6) FEV_1/FVC: 100.2 (8.8) / 98.8 (5.3) PEF: 90.9 (15.9) / 89.8 (31.2) [a]Difference between exposed and referent, $p < 0.025$ **Difference in pulmonary function between exposure groups** Regression coefficients (percentage difference; SD provided by author; *p*-value): VC −21.43 (3.48) ($p = 0.001$) FVC −13.88 (3.44) ($p = 0.001$) FEV_1 −12.23 (3.42) ($p = 0.001$) **Change in pulmonary function per year work duration** Regression coefficients (unit change/year): VC −0.1 ($p = 0.315$) FVC −0.43 ($p = 0.02$) FEV_1 −0.375 ($p = 0.035$) FEV_1/FVC −0.1 ($p = 0.225$) PEF −0.28 ($p = 0.2$) VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; PEF, peak expiratory flow.
Reference: (Herbert et al., 1994) Cross-sectional study, Canada. **Population:** 99 oriented strand board workers (exposed, 98% participation), mean age 35.4 years, 51.5% smokers; work duration 5.1 years; 165 oil/gas field plant workers (not exposed to formaldehyde or oil and gas vapors) from same geographic	**Preshift pulmonary function (mean) by exposure group** OSB / Oilfield FEV_1 (mL): 4.203 / 4.223 FVC (mL): 5.364 / 5.257

Study and design	Results
area (82% participation), mean age 34.9 years, 27.9% smokers, work duration 10 years. Excluded 14 workers in referent with hydrogen sulfide exposure. **Exposure:** TWA formaldehyde and dust concentrations at OSB plant based on 21 hours of continuous sampling in the breathing zone at five work sites on 2 separate days. Formaldehyde range: 0.07–0.27 ppm (0.09–0.33 mg/m^3),[b] dust mean: 0.27 mg/m^3, 2.5 µm diameter. **Methods:** Spirometric testing (volumetric, best of five satisfactory maneuvers) at start of work shift and after 6 hours (ATS guidelines). Analysis ANCOVA controlling for age, height, and smoking. **Evaluation:**[a] *Medium* confidence (↓) Potential for healthy survivor bias with attenuation in measure of association. Possible irritant exposure in referent.	FEV_1/FVC (%) 78.6[a] 80.3[a] [a]$p = 0.028$ **Risk of airway obstruction (FEV_1/FVC < 75%) by smoking category (*N* = number below criteria)** Nonsmokers (17) Odds Ratio 1.68 95% CI 0.54, 5.25 Exsmokers (15) 1.08 0.32, 3.64 Current (25) 2.98 1.10, 8.07
Reference: Khamgaonkar and Fulare (1991) Cross-sectional study, India. **Population:** 74 individuals working in anatomy and histopathology departments at three colleges and exposed to formaldehyde. Selected every 2nd person from occupational list. Comparison group matched by age and sex (*N* = 74) (individuals not working in laboratories with formaldehyde). Comparable for mean height and weight. Excluded persons with a history of pulmonary disease before their present occupation. **Exposure:** Multiple 30-minute area samples collected in the breathing zone in both the exposed (*N* = 43) and unexposed (*N* = 18) areas. Mean (SD) exposed 1.00 ppm (0.556), range 0.036–2.27 ppm (1.23 mg/m^3 (0.68), range 0.044–2.79 mg/m^3).[b] Referent 0.102 ppm (0.115), range 0–0.52 ppm (0.125 mg/m^3 (0.141) range ND–0.64 mg/m^3).[b] **Methods:** Pulmonary function tests on a subset of 37 exposed and 37 comparison individuals on a Monday morning after days of no exposure. **Evaluation:**[a] *Medium* confidence (↓) Possible exposures in referent that affect pulmonary function; exposure to formaldehyde in referent labs.	**Mean pulmonary function values by exposure group** FVC (L) Exposed (*N* = 37) 2.18 Referent (*N* = 37) 2.63[a] MMEFR (L/sec) 1.55 2.71[b] FEV_1 (%) 60.68 78.74[a] [a]$p < 0.01$, [b]$p < 0.05$ FVC, forced vital capacity; MMEFR, maximum mid-expiratory flow rate; FEV_1, forced expiratory volume in 1 second.
Reference: Malaka and Kodama (1990) Cross-sectional study, Indonesia. **Population:** Male employees at plywood company. Exposed workers (*N* = 93) randomly selected with stratification by smoking status and work duration (<5 and ≥5 years; 93% participation), mean age 26.6 years, work duration 6.2 ± 2.4 years; unexposed group (*N* = 93) matched for age, ethnicity, and smoking status (53%), mean age 28.8 years, similar in height, work duration 6.7 ± 2.3 years, worked in areas where formaldehyde was not used, and had no previous or	**Mean baseline spirometric values (adjusted for dust) (SD)** Exposed Referent FEV_1/FVC (%) 84.7 (6.5) 86.9 (4.9)[a] FEV_1 (L) 2.78 (0.41) 2.82 (0.30)[a] FVC (L) 3.28 (0.44) 3.37 (0.36) $FEF_{25–75\%}$ (L/sec) 3.04 (0.76) 3.44 (0.78)[a] [a]$p < 0.005$

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>current exposure to formaldehyde based on occupational histories; 93% participation rate.
Exposure: Area sampling and personal monitoring. Average exposed 0.9 ppm (1.1 mg/m^3),[b] range 0.22–3.48 ppm (0.27–4.28 mg/m^3)[b]; calculated by EPA from weighted average of area specific averages in Table 2 in the paper; referent 0.003–0.07 ppm (0.0037–0.09 mg/m^3).[b]
Cumulative exposure measure developed using area concentrations and duration in current job (mean 6.29 ppm-year, SD 2.72). Categorized into none (*N* = 93), low (<5 ppm-year) (*N* = 37), and high (≥5 ppm-year) (*N* = 56).
Other exposures: average total dust 1.35 mg/m^3, average respirable dust 0.6 mg/m^3.
Methods: Baseline (Monday) and cross-shift spirometric measurements (volumetric) followed ATS methods.
Pulmonary function (percentage of expected function) by category of cumulative exposure analyzed using analysis of covariance. Stepwise regression of pulmonary function on cumulative formaldehyde (continuous) adjusted for age, height, weight, cigarettes/day, and dust.
Evaluation:[a]
Medium confidence (↓)
Potential for healthy survivor bias with attenuation in measure of association.</td><td>**Multiple regression model of pulmonary function**[a]
<table><tr><th></th><th>β(per ppm-year FA)</th></tr><tr><td>FEV_1/FVC (%)</td><td>−0.347[b]</td></tr><tr><td>FEV_1 (L)</td><td>−0.015[b]</td></tr><tr><td>FVC (L)</td><td>NS</td></tr><tr><td>$FEF_{25–75}$ (L/sec)</td><td>−0.043[b]</td></tr></table>[a]adjusted for age, height, weight, cigarettes/day, and dust.
[b]$p < 0.05$

Mean pulmonary function (percentage predicted) (SD) by Categories of Cumulative Exposure
<table><tr><th></th><th>None</th><th>Low</th><th>High</th></tr><tr><td>FEV_1</td><td>94.4 (20.0)</td><td>87.4 (10.2)</td><td>90.8 (12.7)</td></tr><tr><td>FVC</td><td>92.0 (9.2)</td><td>87.1 (8.4)</td><td>91.7 (10.4)</td></tr><tr><td>FEV_1/FVC</td><td>86.9 (4.9)</td><td>85.3 (6.4)</td><td>84.4 (6.5)</td></tr><tr><td>$FEF_{25–75}$</td><td>90.4 (20.0)</td><td>79.5 (18.2)</td><td>80.0 (20.1)</td></tr></table>
Dust was not associated with any pulmonary function measures.</td></tr>
<tr><td>**Reference:** Holness and Nethercott (1989)
Cross-sectional study of funeral workers, Canada.
Population: 67 currently active embalmers and 17 formerly active, recruited through a list of funeral homes from a district funeral directors association (86.6% participation). Average work duration 10 years. Unexposed group (*N* = 38) recruited from large service organization and paid student volunteers.
Exposure: Average concentration from two area samples (impingers), measured during embalming procedures lasting from 30 to 180 minutes, 0.36 ± 0.19 ppm, range 0.08–0.81 ppm (0.44 ± 0.23 mg/m^3, range 0.10–1.0 mg/m^3).[b]
Unexposed average concentration: 0.02 ppm (0.025 mg/m^3).[b]
Methods: Information on symptoms, past and family medical history, and work practices by questionnaire.
Spirometry (volumetric) tests on 22 embalmers before and after embalming procedure and on 13 referents 2–3 hours after first test.
Pulmonary function (percentage predicted) compared using multiple regression, correcting for age, height, and pack-years smoked.
Evaluation:[a]
Medium confidence</td><td>**Comparisons of baseline pulmonary function (percentage predicted) (SD)**
<table><tr><th></th><th>Exposed (*N* = 84)</th><th>Unexposed (*N* = 38)</th></tr><tr><td>FVC</td><td>100.5 (12.3)</td><td>100.9 (11.5)</td></tr><tr><td>FEV_1</td><td>99.2 (12.9)</td><td>100.7 (12.9)</td></tr><tr><td>FEV_1/FVC</td><td>98.4 (7.9)</td><td>99.4 (8.7)</td></tr><tr><td>FEF_{50}</td><td>104.8 (29.7)</td><td>110.3 (34.5)</td></tr><tr><td>FEF_{75}</td><td>76.2 (32.9)</td><td>86.6 (36.0)</td></tr><tr><td></td><td>Active (*N* = 67)</td><td>Inactive (*N* = 17)</td></tr><tr><td>FVC</td><td>100.7 (12.2)</td><td>95.8 (12.0)[a]</td></tr><tr><td>FEV_1</td><td>100.8 (12.19)</td><td>93.1 (14.1)[b]</td></tr><tr><td>FEV_1/FVC</td><td>98.9 (7.8)</td><td>96.6 (8.0)</td></tr><tr><td>FEF_{50}</td><td>107.5 (28.7)</td><td>94.1 (32.3)</td></tr><tr><td>FEF_{75}</td><td>80.8 (33.1)</td><td>57.1 (24.7)</td></tr></table>[a]$p = 0.0385$, [b]$p = 0.0652$</td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Differences in source populations for exposed and referent groups lead to uncertainty in comparability, with no consideration of potential confounding.</td><td></td></tr>
<tr><td>Reference: Alexandersson and Hedenstierna (1988); Alexandersson (1988)
Cross-sectional study, carpentry shop, Sweden.
Population: 38 exposed employees working with acid-hardening lacquers for the previous 12 months [mean age (SD): 34 (10) years, mean duration employment 7.8 years] and at work on the study day. 18 referent employees at the same company (mean age [SD] 37 [9] years). Asthmatics excluded.
Exposure: Personal exposure monitored during three to four 15-minute periods during the workday. No formaldehyde measurements reported for referent group.
TWA 0.40 mg/m^3, range: 0.12–1.32 mg/m^3. Peak concentration (15 minute) 0.70 mg/m^3, range 0.14–2.6 mg/m^3.
Additional measurements of solvents and dust (4 hr)—considered very low compared to Swedish threshold limit values.
Methods: Spirometry (volumetric) on Monday after 2 days unexposed and again at end of shift on second day. Half of referent employees tested before, and half tested after, shift. Compared difference from sex, age, and height matched reference values.
Evaluation:[a]
Medium confidence (↓)
Potential for healthy survivor bias with attenuation in measure of association. Small sample size in referent.</td><td>Pulmonary function before work on Monday (Mean difference from reference values)
<table><tr><th></th><th>Exposed (N = 38)</th><th>Referent (N = 18)</th></tr><tr><td></td><td>Difference (SD)</td><td>Difference (SD)</td></tr><tr><td>FVC (L)</td><td>−0.24 (0.64)*</td><td>0.03 (0.65)</td></tr><tr><td>FEV_1 (L)</td><td>−0.21 (0.51)**</td><td>0.15 (0.42)</td></tr><tr><td>FEV%</td><td>−0.7 (6.7)</td><td>1.8 (5.3)</td></tr><tr><td>$FEV_{25–75}$ (L/sec)</td><td>−0.10 (0.98)</td><td>0.31 (0.76)</td></tr></table>*p < 0.05; **p < 0.01

Difference from reference values greater among nonsmokers than smokers.</td></tr>
<tr><td>Reference: Holmström and Wilhelmsson (1988)
Cross-sectional study, Sweden.
Population: 3 study groups: 70 individuals (87% male) in formaldehyde products group (mean age 36.9 years); 100 furniture workers exposed to formaldehyde and wood dust (93% males, mean age 40.5 years). Comparison group, 36 persons (56% male, mean age 39.9 years), primarily local government clerks. 100% participation. Mean duration of employment 10.4 years for exposed and 11.4 years for referent group.
Exposure: Mean formaldehyde in 1985.
Group 1: mean 0.26 ± 0.17 mg/m^3, range 0.05–0.5 mg/m^3, Dust ≤1 mg/m^3.
Group 2: mean 0.25 ± 0.05 mg/m^3, range 0.2–0.3 mg/m^3, dust 1.65 ± 1.06 mg/m^3.
Referent: mean 0.09 mg/m^3.
Data on formaldehyde concentrations available 1979–1984 and from 1 to 2 hours personal sampling in breathing zone at different workstations in 1985.
Mean annual exposure estimated for each participant from start of employment; dose-years.</td><td>Pulmonary function values compared to expected by exposure group
<table><tr><th></th><th>FA exposed (N = 70)</th><th>FA-dust exposed (N = 98)</th><th>Referent (N = 36)</th></tr><tr><td>FVC</td><td></td><td></td><td></td></tr><tr><td>Observed</td><td>4.979[a]</td><td>4.929[a]</td><td>4.539</td></tr><tr><td>Expected</td><td>5.556</td><td>5.593</td><td>4.718</td></tr><tr><td>FEV%</td><td></td><td></td><td></td></tr><tr><td>Observed</td><td>80.8</td><td>78.3</td><td>81.4</td></tr><tr><td>Expected</td><td>80.6</td><td>79.5</td><td>80.7</td></tr></table>[a]paired t-test comparing observed to expected, p < 0.001.

No correlation of FVC with cumulative formaldehyde dose or years of service >5 years.</td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Other exposures (phenol, ammonia, epichlorhydrin, methanol, ethanol) <1% of occupational exposure limit.
Methods: Spirometric measures analyzed as percentage of expected normal based on age, sex, smoking, height, and weight.
Evaluation:[a]
Medium confidence (↓)
Potential for healthy survivor bias with attenuation in measure of association. Comparison groups selected from different source populations.</td><td></td></tr>
<tr><td>**Reference:** Levine et al. (1984b)
Cross-sectional study, USA, 1978.
Population: 105 white, male morticians attending postgraduate course (94% participation).
Exposure: # embalmings.
Exposure index: rank ordering of the total # embalmings; divided into categories of low and high exposure based on # bodies embalmed, matched on age (within 3 years).
Methods: Completed self-reported respiratory disease questionnaire (ATS) and detailed occupational history; pulmonary function testing (volumetric spirometer) (*N* = 99), analysis of 90 with complete data after excluding pipe and cigar smokers.
Evaluation:[a]
Medium confidence
Uncertainty regarding assignment of exposure rank.</td><td>**Change in pulmonary function per unit exposure rank (*N* = 90)**
<table><tr><th>Variable</th><th>Exposure Rank</th></tr><tr><td>FVC (L)</td><td>+0.0003</td></tr><tr><td>FEV_1 (L)</td><td>−0.0001</td></tr><tr><td>FEV_1/FVC</td><td>+0.0019</td></tr><tr><td>$FEF_{25–75}$ (L/s)</td><td>−0.0016</td></tr><tr><td>$FEF_{25–75}$/FVC</td><td>−0.0002</td></tr><tr><td>Rank FVC/predicted</td><td>−0.0547</td></tr><tr><td>Rank FEV_1/predicted</td><td>+0.0229</td></tr><tr><td>$FEF_{25–75}$/predicted</td><td>−0.0676</td></tr></table>Coefficients were not statistically significant ($p > 0.05$).
Multiple regression equations adjusted for age, height, number of pack-years, and exposure index.

Comparison of pulmonary function by exposure group (low, high) in nonsmokers (*N* = 24); mean (SE)
<table><tr><th>Measure</th><th>Low</th><th>High</th></tr><tr><td>FVC (L)</td><td>4.69 (0.22)</td><td>4.56 (0.32)</td></tr><tr><td>FVC % predicted</td><td>100.5 (3.1)</td><td>98.9 (3.4)</td></tr><tr><td>FEV_1 (L)</td><td>3.80 (0.22)</td><td>3.64 (0.27)</td></tr><tr><td>FEV_1 % predicted</td><td>108.9 (3.3)</td><td>105.5 (4.1)</td></tr><tr><td>FEV_1/FVC</td><td>0.807 (0.02)</td><td>0.797 (0.02)</td></tr><tr><td>$FEF_{25–75}$ (L/sec)</td><td>4.28 (0.48)</td><td>3.88 (0.49)</td></tr><tr><td>$FEF_{25–75}$ % predicted</td><td>117.9 (8.8)</td><td>110.5 (11.7)</td></tr></table>Groups matched on age, similar in height
Group comparisons, $p > 0.05$</td></tr>
<tr><td>**Reference:** Alexandersson et al. (1982)
Cross-sectional study, Sweden.</td><td>**Comparisons of pre-shift mean pulmonary**</td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Population: 47 exposed carpentry workers employed at the plant for >1 year and at work on study day (mean age 35 years, mean duration 5.9 years) and 20 unexposed employees. No asthmatics were included.
Exposure: TWA concentration, measured using personal sampling over a working day, 0.47 mg/m^3 (range 0.05–1.62 mg/m^3).
Other exposures: Terpenes: range ND–9 mg/m^3; dust (all particle sizes) mean 0.5 mg/m^3 (range 0.3–0.7 mg/m^3).
Methods: Spirometric measurements (volumetric, ATS methods) Monday morning preshift and after work for exposed. Pulmonary function was measured in the unexposed in the morning or the afternoon. Statistical analysis of preshift values and cross-shift change, two-tailed Student’s t-test. Linear regression of association with duration of employment.
Evaluation:[a]
Medium confidence (↓)
Potential for healthy survivor bias with attenuation in measure of association. P-values were reported.</td><td>function (SD)
<table><tr><th></th><th>Exposed (N = 47)</th><th>Referent (N = 20)</th></tr><tr><td>FVC (L)</td><td>5.73 (0.14)</td><td>6.0 (0.2)</td></tr><tr><td>FEV_1 (L)</td><td>4.52 (0.12)[a]</td><td>4.86 (0.15)</td></tr><tr><td>FEV%</td><td>79.2 (1.0)</td><td>80.7 (1.32)</td></tr><tr><td>MMF (L/sec)</td><td>4.94 (0.2)</td><td>5.08 (0.31)</td></tr><tr><td>CV%</td><td>16.7 (1.07)</td><td>17.1 (1.5)</td></tr></table>[a]Difference from reference value, p = 0.08

No association with duration of employment (quantitative results not presented).</td></tr>
<tr><td>Reference: Schoenberg and Mitchell (1975)
Cross-sectional study, USA.
Population: Employees using formaldehyde-phenol resin in the filter acrylic wool filter department of a filter manufacturing plant.
Exposed production line workers and supervisors, N = 63 (94% of recruited); younger age and cigarette smoking (packs/year) less among present line group compared to never on-line.
Exposure: Measurements taken by insurance company during same month; 0.5–1 mg/m^3.
3 breathing zone samples, 10.6–16.3 mg/m^3.
Exposure groups
Present line, N = 40
Previous line, N = 8
Never-on-line, N = 15
Some in never-on-line had some exposure.
Other exposures:
Phenol, four breathing zone samples, 7–10 mg/m^3.
Methods: Standardized questionnaire, pulmonary function measured before and after shift on Monday and Friday (pneumotachometer); 5 maneuvers, average of best two used to calculate values; compared to predicted based on age, height, and gender.
Evaluation:[a]
Medium confidence (↓)
Potential for healthy survivor bias with attenuation in measure of association. Multiple exposures: formaldehyde, phenol. Phenol is an irritant but may not be associated with pulmonary function at these levels. Small sample size.</td><td>Monday preshift pulmonary function by exposure duration (mean, SEM)
<table><tr><th></th><th>Never (N = 15)</th><th><1 year (N = 15)</th><th>1–4 years (N = 10)</th><th>>5 years (N = 15)</th></tr><tr><td>FVC[a]</td><td>104.3 (2.9)</td><td>103.7 (2.9)</td><td>108.8 (2.7)</td><td>112.2 (3.8)</td></tr><tr><td>FEV_1[a]</td><td>98.9 (3.6)</td><td>100.7 (3.1)</td><td>99.6 (3.5)</td><td>97.2 (4.4)</td></tr><tr><td>FEV_1/FVC, %[b]</td><td>79.4 (1.3)</td><td>79.9 (1.4)</td><td>74.1 (2.2)</td><td>71.2 (2.6)[c]</td></tr><tr><td>$MEF_{50\%}$/FVC, %[b]</td><td>90.3 (4.0)</td><td>87.1 (6.1)</td><td>73.6 (8.4)</td><td>64.0 (6.2)[d]</td></tr></table>[a]Percentage predicted
[b]Standardized to cigarette consumption of 15 pack-years
[c]Different from never-on-line group (p < 0.05)
[d]Different from never-on-line group (p < 0.005)</td></tr>
<tr><td>Reference: Main and Hogan (1983)</td><td>Mean pulmonary function (percentage</td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Cross-sectional study, USA.
Population: 21 exposed individuals working in two mobile trailers for 34 months (mean age 38 ± 9 years, 76% male, 19% nonsmokers).
18 referent individuals who did not work in the trailers (mean age 30 ± 6 years, 50% male, 22% nonsmokers).
Exposure: Three 1-hour area samples using impingers taken on four occasions (August, September, December, April) always on a Monday. At least one sample from each office in both trailers. Concentration range 0.12 to 1.6 ppm (0.15−1.97 mg/m^3).[b]
Methods: Volumetric spirometer, percentage predicted FEV_1 and FVC stratified by smoking status (unadjusted group means compared using t-tests).
Evaluation:[a]
Low confidence
Comparison groups selected from different sources (possible unmeasured confounding), ETS in referent; small sample size (low sensitivity).</td><td>**predicted)**
<table><tr><th></th><th>Exposed (*N* = 14)</th><th>Unexposed (*N* = 17)</th></tr><tr><td>FEV_1</td><td>98</td><td>99</td></tr><tr><td>FVC</td><td>94</td><td>97</td></tr><tr><td>FEF_{50}</td><td>93</td><td>90</td></tr><tr><td>FEF_{75}</td><td>69</td><td>70</td></tr><tr><td>%Δ FEF_{50}</td><td>55</td><td>43</td></tr></table></td></tr>
<tr><th colspan="2">Longitudinal studies</th></tr>
<tr><td>**Reference:** Nunn et al. (1990)
Prospective study at chemical factory manufacturing urea formaldehyde resin, Duxford, England.
Population: Exposed: 164 workers, aged 25 or older, exposed to free formaldehyde in 1980; 29% <35 years, 46% current smokers, 22% employed >22 years; referent: 129 workers from bonded structures division at same factory in 1980; 39% <35 years, 45% current smokers, 4% employed >22 years. Followed over 6 years (1980−1985).
Exposure: Area samples (1−6 hours) periodically, 1979 and 1985, and personal sampling for representative exposed workers, 1985 to 1987. Exposure prior to 1976 based on subjective determinations and knowledge of process changes and industrial hygiene measures. Pre-1979 levels estimated as low, medium, and high, corresponding to an 8-hour day. TWA of 0.1−0.5 ppm (0.12−0.62 mg/m^3),[b] 0.6−2.0 ppm (0.74−2.46 mg/m^3),[b] and >2 ppm, respectively.
Other exposures: Records examined for random sample of 20 per group; more exposure to asbestos, carbon and glass fibers, siliceous fillers, aliphatic amines in referent group; both groups exposed to phenol and urea formaldehyde resin (not free formaldehyde).
Methods: Data on FEV_1 and FVC (volumetric spirometer) highest of two readings within 5% of each other) obtained from routine annual health screenings conducted by the same nurse throughout the study period. Follow-up complete for 76% of exposed and 74% of unexposed. FEV_1 values adjusted for height (FEV_1/height^3), regressed on time of screening visit for each worker, adjusted for age in 1980, smoking status in 1980, and at</td><td>**Decline in FEV_1 with age by smoking history (mean slope, mL/year (95% CI)**
<table><tr><th>Smoking status</th><th>Exposed</th><th>*N*</th><th>Unexposed</th><th>*N*</th></tr><tr><td>Never</td><td>−45 (−28, −62)</td><td>26</td><td>−29 (−7, −51)</td><td>13</td></tr><tr><td>Ex-smoker</td><td>−33 (−20, −46)</td><td>34</td><td>−40 (−26, −54)</td><td>31</td></tr><tr><td>Current</td><td>−46 (−33, −59)</td><td>57</td><td>−46 (−32, −61)</td><td>36</td></tr><tr><td>Total</td><td>−42 (−34, −51)</td><td>117</td><td>−41 (−32, −50)</td><td>80</td></tr></table>
Among those lost to follow-up, FEV_1 was less than predicted among 75% of 12 exposed and 33% of 27 referent compared to 36% of 117 exposed and 45% of 80 referent followed.</td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>final assessment, maximum and mean exposure, assessment level, and total duration of exposure.
Evaluation:[a]
Medium confidence (↓)
Concern for selection bias: loss to follow-up higher among exposed with low pulmonary function compared to referent; referent exposed to other potential irritants.</td><td></td></tr>
<tr><td>Reference: Alexandersson and Hedenstierna (1989)
Prospective occupational study, follow-up of Alexandersson et al. (1982), Sweden.
Population: 47 exposed cabinetry workers and 20 unexposed workers examined in 1980, 34 exposed and 18 unexposed were examined again in 1984. Of the 47 originally exposed, 13 had been reassigned to other unexposed jobs. Average exposure duration among exposed and transferred workers: 11 years.
Exposure: Personal monitoring during 3 or 4 15-minute periods during workday.
TWA 0.42 ± 0.27 mg/m^3 in 1980 and 0.50 ± 0.12 mg/m^3 in 1984. Other exposures: terpenes ND; respirable dust: mean 0.1 ± 0.2 mg/m^3.
Methods: Spirometric measures (volumetric, ATS methods) compared with reference values for sex, age, height, and weight. 5-year change corrected for age-dependent change. Results presented by smoking status.
Evaluation:[a]
Medium confidence (↓)
Potential for healthy survivor bias with attenuation in measure of association; small sample.</td><td>Annual change (1980–1984) in exposed, mean (SD)
<table><tr><th></th><th>Smokers (N = 10)</th><th>Nonsmokers (N = 11)</th><th>All (N = 21)</th></tr><tr><td>FVC (mL/year)</td><td>−15 (24)</td><td>−10 (26)</td><td>−12 (16)</td></tr><tr><td>FEV_1 (mL/year)</td><td>−15 (21)</td><td>−31 (20)</td><td>−24 (20)</td></tr><tr><td>FEV_1/FVC (%/year)</td><td>−0.1 (0.4)</td><td>−0.4 (0.2)[a]</td><td>−0.3 (0.3)</td></tr><tr><td>$FEF_{25–75}$ (mL/s/year)</td><td>−60 (69)</td><td>−212 (66)[a]</td><td>−168 (46)[a]</td></tr><tr><td>CV% (%/year)</td><td>−0.6 (0.3)</td><td>0.2 (0.4)</td><td>−0.2 (0.3)</td></tr></table>[a] $p < 0.001$, compared to predicted normal
Pulmonary function was unchanged among referent group.
Pulmonary function was correlated with formaldehyde concentration in unadjusted regression analysis.
Pulmonary function improved after a 4-week holiday.</td></tr>
<tr><td>Reference: Löfstedt et al. (2011)
Prospective study; follow-up of Löfstedt et al. (2009), Sweden.
Population: One of four foundries opted out of follow-up, plus 39 individuals (14 exposed workers and 25 referents) were lost to follow-up. 25 of 64 workers from 2009 study involved with Hot Box method; 55 of 134 referents from 2009 study working outside core-production and die-casting halls; not exposed to chemicals. Prevalence of childhood allergy lower in exposed than in referent in 2005 (4 vs. 31%, $p < 0.05$); higher prevalence of nasal symptoms among referent in 2005.
Exposure: Formaldehyde, isocyanic acid, and methyl isocyanate measurements on same day as spirometry.
Monoisocyanates: Mean of 4 to 5 15-minute samples
Formaldehyde: sampling over entire shift
Individual exposure estimated for 2001 and 2005 (mg/m^3); levels 50% lower in 2005 (mean, range).

2001 0.098 (0.094) 0.014–0.44</td><td>Decreased across shift pulmonary function reported in 2001 was correlated with decreased preshift pulmonary function in 2005.
VC $r = 0.51$, FEV $r = 0.57$, $p < 0.05$

Preshift value and change in pulmonary function (percentage predicted), 2001–2005
<table><tr><th></th><th colspan="2">2001</th><th colspan="2">2001–2005</th></tr><tr><th></th><th>Mean (SD)</th><th>Mean (SD)</th><th>Range</th></tr><tr><td>VC</td><td></td><td></td><td></td></tr><tr><td>Exposed</td><td>93.3 (12.1)</td><td>−0.8 (4.2)</td><td>−11.2–6.5</td></tr><tr><td>Referent</td><td>93.9 (10.8)</td><td>−0.4 (3.8)</td><td>−11.0–5.9</td></tr><tr><td>FEV_1</td><td></td><td></td><td></td></tr><tr><td>Exposed</td><td>94.4 (11.6)</td><td>−1.3 (5.5)</td><td>−14.0–8.8</td></tr></table></td></tr>
</table>

Study and design	Results
2005 0.045 (0.043) 0.01–0.19 Correlation low between formaldehyde and either methyl isocyanate (r = −0.20) or isocyanic acid (r = 0.09); 61% of exposed were coremakers where formaldehyde levels were highest and isocyanate levels were lower. **Methods:** Pulmonary function by spirometry (volumetric) using ATS guidelines. Pre- and postshift after 2 days with no exposure. Percentage predicted using Swedish reference. Regression analysis of formaldehyde adjusted for MIC, smoking, and childhood allergy. **Evaluation:**[a] *Low* confidence Limited sample size to detect small changes between 2001 and 2005; concern for survivor bias; coexposure to methyl isocyanate and isocyanic acid in exposed—unable to differentiate for comparisons of change from 2001 to 2005.	Referent 96.3 (11.6) 0.3 (5.3) −13.8–10.3 Across shift change was not different between exposure groups (data not provided). No association of formaldehyde with change in pulmonary function at follow-up in regression analysis (data not provided).

Within each grouping by study type, organized by study confidence, then descending publication year. Results for *low* confidence studies are shaded gray.

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.3).

Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

[b]Concentrations reported by authors as ppm or ppb converted to mg/m^3.

Exposure in residences or school

Adults

Results among four studies of residential exposure among adults are difficult to compare because different methods were used to assess pulmonary function and two of the studies did not report results quantitatively (Norback et al., 1995; Broder et al., 1988c) (see Table 3-6). A cross-sectional study of residential formaldehyde exposure in a large, representative sample in Arizona observed a dose-dependent decline in PEFR among adult smokers at formaldehyde concentrations between 0.049 and 0.172 mg/m^3, but not among the group as a whole (Krzyzanowski et al., 1990). Another study among elderly nursing home residents observed an elevated risk of low pulmonary function (defined as values falling in the lower 20% of the distribution) in association with formaldehyde concentrations above the median level measured in each nursing home (Bentayeb et al., 2015). The overall median and range of formaldehyde concentrations was 0.007 mg/m^3 and 0.001–0.021 mg/m^3, respectively, but the concentrations associated with elevated risks varied according to the median in each nursing home. Two additional studies that assessed effects of formaldehyde exposure on pulmonary function in primarily adult residential populations exposed to concentrations between 0.009 and 0.279 mg/m^3 reported no associations, although the outcomes evaluated by each study were not directly comparable (Norback et al., 1995; Broder et al., 1988c).

The study by Krzyzanowski et al. (1990), which used the most thorough exposure-assessment protocol and included repeated measurements of PEFR (thus enhancing the ability to detect an association at the lower concentrations found in the homes) was interpreted with *high* confidence. The stability of the formaldehyde measurements over the two one-week sampling periods, some of which were separated by weeks or seasons, was confirmed by the authors (Quackenboss et al., 1989a; Quackenboss et al., 1989c) and reasonably represents exposures in the homes during the previous weeks and months (i.e., the etiologically relevant exposure window for pulmonary function status). Of the residential studies, only Krzyzanowski et al. (1990) examined effect modification by smoking status. Confidence in the regression results by Norbäck et al. (1995) is *low* because most of the measured formaldehyde concentrations were less than the LOD and the sensitivity of the study was low. Overall, results from the small set of studies suggest that participants 15 years of age and older did not experience declines in pulmonary function at average formaldehyde levels less than 0.05 mg/m^3 (Krzyzanowski et al., 1990), however, declines may be experienced at lower concentrations among susceptible individuals (e.g., elderly, smokers) (Krzyzanowski et al., 1990; Bentayeb et al., 2015).

Table 3-6. Formaldehyde effects on pulmonary function among adults in residential settings

Study and design	Results	
Reference: Krzyzanowski et al. (1990);Quackenboss et al. (1989c); (Quackenboss et al., 1989a) Cross-sectional study, Arizona, USA. **Population:** A stratified random sample of 202 households of municipal employees, selected based on information about potential exposure (age of housing) and potential susceptibility obtained from an initial screening questionnaire. Households with children aged 5−15 years (613 adults and 298 children) were eligible for inclusion. Mean age: >15 years old: 37 years, percentage male: 43.4%, percentage white: 70.4%, 24.4% current smokers. Asthma prevalence: >15 years old: 12.9%. **Exposure:** Sampling: two one-week samples (a subset in multiple seasons) from each individual's kitchen, living area, and bedroom using passive sampling tubes (sensitivity 12 µg/m^3 for 1 week, 15% accuracy). Average formaldehyde concentration, 26 ppb [0.032 mg/m^3],[b] maximum 140 ppb, [0.172 mg/m^3].[b] The majority of subjects (83%) lived in homes with 2-week average concentrations below 40 ppb [0.049 mg/m^3].[b] **Methods:** Trained subjects measured peak expiratory flow rates (PEFRs) using Mini-Wright peak flow meters four times daily, in the morning, at noon, in the early evening, and before bed, for 2 weeks. The largest of three test results was recorded for each test period. Evening and morning values were used in analysis. Analysis of PEFR in relation to indoor formaldehyde concentration, random effects model adjusting for asthma status, smoking status, SES, NO_2 levels, episodes of acute respiratory illness, and time of day. Analysis performed separately for ages younger and older than 15 years. **Evaluation:**[a] *High* confidence	**Change in PEFR in L/min in relation to indoor formaldehyde, ages >15 years. (*N* = 526; 8,463 observations); β (SE)**	
	Formaldehyde (household mean)	0.09 (0.27)
	Morning formaldehyde (vs. bedtime)	−5.9 (1.1) [a]
	Bedroom formaldehyde × morning	−0.07 (0.04)[b]
	Morning × smoking	−7.4 (2.6)[a]
	Bedroom formaldehyde × morning × smoking	0.59 (0.13)[a]
	Bedroom formaldehyde^2 × morning × smoking	−0.007 (0.001)[a]
	Constant	491.7 (8.5)
	[a]$p < 0.05$, [b]$0.05 < p < 0.10$	
	In adults, only the morning PEFR values were affected by formaldehyde concentrations. Smoking status was shown to affect the relationship between PEFR and formaldehyde exposure.	

Study and design	Results
Reference: Bentayeb et al. (2015) Cross-sectional study, 2009–2011; 7 European countries. **Population:** 600 elderly residents (20 randomly selected per home) permanently living in randomly selected nursing homes (8 per city) in selected city in seven countries. Exclusion criteria stated (neurological or psychiatric disorders), 71.8% female, 62.8% ≥80 years old, 35% active smokers, 13.8% passive smoking. **Exposure:** Measurements in common room; 1-week samples; also measured particulates, NO_2, ozone, temperature, humidity and CO_2; range of 1-week averages 0.001–0.021 mg/m^3, median 0.006 mg/m^3; categorical (low and high) based on median concentration in each nursing home. **Methods:** Assessed by same team in all countries; medical visit and standardized questionnaire (European Community Respiratory Health Survey); lifetime COPD (ever told by doctor; spirometry (ATS/European Respiratory Society guidelines), percentage predicted. General estimating equations analysis, accounting for correlations within nursing homes; adjusted OR (95% CI) for risk of values <20% of distribution; stratification by presence of ventilation. **Evaluation:**[a] *Medium* confidence Confounding by coexposures was not assessed; median concentrations which defined low and high exposure categories were not reported.	**Association of formaldehyde (cutpoint median in the nursing home) with pulmonary function < 20% of distribution among elderly nursing home residents** aOR[a] 95% CI FEV_1 1.12 0.97–1.28 FVC 1.16 1.06–1.28 FEV_1/FVC < 70% 0.46 0.12–1.66 [a]aOR: adjusted OR Stratification by poor (*n* = 436) or adequate (*n* = 105) ventilation. FEV_1 aOR (95% CI), 2.65 (1.29, 5.45).
Reference: Broder et al. (1988b, 1988c); Broder et al. (1988a) Cross-sectional study, February 1983–March 1984, Toronto, Canada. **Population:** 1,726 occupants from 517 households with urea formaldehyde foam insulation (UFFI) identified from registry maintained by Urea Formaldehyde Foam Insulation Information and Coordination Centre, Consumer and Corporate Affairs, Canada (50% male, mean age 40 years, 80% over 16 years, 18% current smokers). 231 referent households (*n* = 720) selected at random from streets adjacent to UFFI households (49% male, mean age 35 years, 20% current smokers). Interviewers and respondents were not blinded with respect to the focus of the study or the presence of UFFI insulation. **Exposure:** Formaldehyde sampling 5 hours on 2 successive days in central hallway, all bedrooms and in yard. Inside: referent 0.035 ppm, range 0.006–0.112 ppm [0.043 mg/m^3, range 0.007–0.138 mg/m^3].[b] 90% 0.061; UFFI 0.043 ppm, range 0.007–0.227 [0.053 mg/m^3, range 0.009–0.279 mg/m^3],[b] 90% 0.073 ppm. Outside: referent 0.005 ppm, UFFI 0.005 ppm. Carbon dioxide sampled in central hallway and in yard (as indication of ventilation). **Methods:** Questionnaire on symptoms and household characteristics, spirometry (minimum of three satisfactory tests, recorded largest value). Testing on ages 10 years and older. Statistical comparisons by group and within group (multiple linear regression), adjusted for date of examination, gender, age, race, height, smoking, total hours spent in house per week. **Evaluation:**[a] *Medium* confidence For within group analyses: Results not presented for formaldehyde. Between group analysis: Small exposure contrast between exposure groups	Formaldehyde concentration within group was not associated with pulmonary function in multiple regression models (quantitative results not presented). Between-group comparisons were not informative for formaldehyde associations because formaldehyde concentrations were comparable.
Reference: Norback et al. (1995) Cross-sectional study, Uppsala, Sweden. **Population:** 88 men and women (47 with asthma symptoms and 41 without) who agreed to participate (57%) from a group of 154 eligible randomly selected	FEV1 mean percentage predicted (SD): 106% (13%). PEF mean variability (range): 5% (1–18%).

Study and design	Results
from 488 preliminary subjects from general population of Uppsala in 1990, aged 20–44 years. Mean duration in homes 6 years (range 0.5–31 years). **Exposure:** Field measurements: October 1991–April 1992. Formaldehyde (one 2-hour sample) and guanine (house dust mites) in the bedroom at pillow height. Room temperature, air humidity, VOCs, respirable dust, and CO_2 in living room and bedroom. Formaldehyde mean (range): 29 (<5–110 µg/m^3) in homes of those with nocturnal breathlessness. 17 (<5–60 µg/m^3) in homes without symptoms. Formaldehyde and VOCs concentrations were correlated and could not be evaluated in same regression model (no data presented). **Methods**: Structured interview, spirometry (*N* = 82), blinded to exposure. FEV_1 spirometry, percentage predicted, multiple regression model, Kendall's rank correlation test. **Evaluation:**[a] *Low* confidence Exposure: Sampling period less than one day. Low sensitivity, most exposed to concentration <LOQ; study population selected for high prevalence of asthma symptoms; correlated coexposure: VOCs.	FEV1 percentage predicted, and PEF variability (during the day) were not associated with log-transformed formaldehyde concentration using Kendall's rank correlation test (data not presented).

Organized by study confidence, then descending publication year. Results for *low* confidence studies are shaded gray.
[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.3). Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
[b]Concentrations reported by authors as ppm or ppb converted to mg/m^3.

Children

A cross-sectional study of residential formaldehyde exposure in a large (298 children), population-based sample observed a linear relationship between increased formaldehyde exposure and lower peak expiratory flow rate (PEFR) averaged over 12 days among children aged 5 to 15 years exposed to average concentrations of 0.032 mg/m^3 (26 ppb) (Krzyzanowski et al., 1990). Earlier reports showing preliminary results provided details about the methods used to sample formaldehyde concentrations and the stability of one-week averages separated in time. Formaldehyde concentrations measured during consecutive one-week sampling periods were compared to one-week averages separated by one or more weeks, including different seasons, in a subset of households Quackenboss et al. (1989c); (Quackenboss et al., 1989a). While correlation between the consecutive averages was higher than averages separated in time (consecutive weeks correlation coefficient = 0.9, R^2 = 0.85; separated weeks R^2 = 0.69, n=16), week to week differences were not statistically significantly different from zero indicating stability over time. These data support the conclusion that the average of two-week measurements represented stable formaldehyde levels present in the households over an extended period during the previous weeks and months (i.e., the etiologically relevant period for this outcome)(Krzyzanowski et al., 1990).

Since no trend was observed in the PEFR values over the 12 days of measurements, the 12-day average of PEFR in an individual was concluded to represent the current average pulmonary function for the children at the time of the study and the association with formaldehyde concentrations averaged over two one-week sampling periods was judged to indicate a "persistent"

effect of formaldehyde exposure. As presented in Figure 3-6, the investigators reported a statistically significant decrease of −1.28 ± 0.46 L/minute in PEFR per ppb household mean formaldehyde. The figure shows the incremental decrement in PEFR measured at bedtime versus morning and shows differences in the morning among asthmatics and nonasthmatics. Asthmatic children (15.8% of the total) showed a steeper decline in PEFR in the morning at formaldehyde concentrations less than 0.049 mg/m^3 (40 ppb). The analysis of multiple PEFR measurements resulted in an increased statistical power to detect an association at the lower formaldehyde levels present in the homes. Environmental tobacco smoke and NO_2 exposure, as well as socioeconomic status, were not confounders of the association between formaldehyde exposure and PEFR in the children.

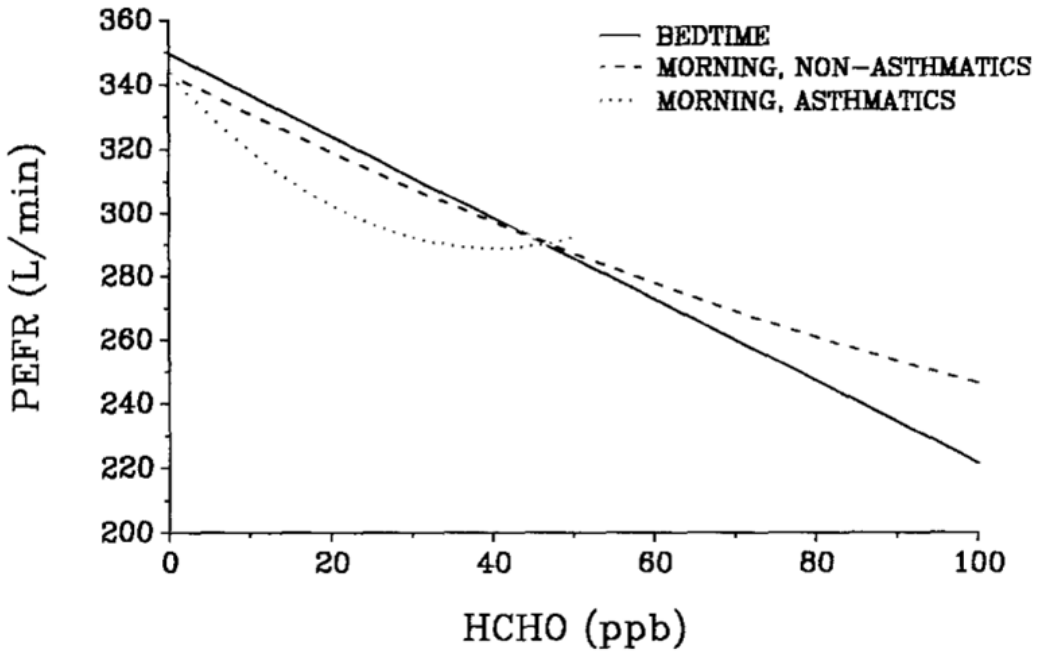


Figure 3-6. Association of PEFR measured at bedtime and in the morning with household mean formaldehyde concentration among children less than 15 years of age (Krzyzanowski et al., 1990).

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Two other studies among children evaluated exposure to formaldehyde at home (Franklin et al., 2000) and at school (Wallner et al., 2012). The range of formaldehyde concentrations was similar to those in the homes evaluated by Krzyzanowski et al. (1990). While no associations were reported for FVC or FEV_1 by either of the two studies that evaluated these measures (Wallner et al., 2012; Franklin et al., 2000), Wallner et al. (2012) also measured maximal expiratory flow at 50 or 75% of FVC (MEF_{50} and MEF_{75}) and observed an approximate 3% decrease per standard deviation

increase in formaldehyde concentration measured in elementary school classrooms. Several pollutants were evaluated by this study, and a few also were associated with MEF_{75}. These pollutants, benzylbutylphthalate and polybrominated diphenylether congeners, both measured in dust, would be expected to originate from different sources than formaldehyde, and therefore, were not likely to be highly correlated with formaldehyde in air. The exposure contrast in the homes evaluated by Franklin et al. (2000) was relatively small, limiting the ability of the study to detect an association with formaldehyde. The interquartile range was 0.011–0.035 mg/m^3, and concentrations between 0.062 and 0.107 mg/m^3, the range in the higher exposure group, were found only in 10 homes.

The studies of formaldehyde exposure in homes and schools are limited in their sensitivity to detect a small reduction in pulmonary function associated with formaldehyde exposure at concentrations below 0.1 mg/m^3 (see Table 3-7). However, a methodologically robust (*high* confidence) study reported an association with lower average peak expiratory flow rate (PEFR) measured multiple times per day over a 12-day period in this concentration range (Krzyzanowski et al., 1990). These findings are supported by lower levels of MEF_{50} and MEF_{75} (but not other measures) in association with increasing formaldehyde concentration in a separate *medium* confidence study (Wallner et al., 2012).

Table 3-7. Formaldehyde effects on pulmonary function among children in residential or school settings

Study and design	Results
Reference: Krzyzanowski et al. (1990); Quackenboss et al. (1989c); Quackenboss et al. (1989a) Cross-sectional study, Arizona. **Population:** A stratified random sample of 202 households of municipal employees, selected based on information about potential exposure (age of housing) and potential susceptibility obtained from an initial screening questionnaire. Households with children aged 5–15 years (613 adults and 298 children) were eligible for inclusion. Mean age: <15: 9.3 years, percentage male: <15: 50.2%, percentage white: <15: 67.3%, Asthma prevalence: <15: 15.8%. **Exposure:** Sampling: two 1-week samples (a subset in multiple seasons) from each individual's kitchen, living area, and bedroom using passive sampling tubes (sensitivity 12 µg/m^3 for 1 week). Average concentration, 26 ppb [0.032 mg/m^3],[b] maximum 140 ppb, (0.172 mg/m^3).[b] The majority of subjects (83%) lived in homes with 2-week average concentrations below 40 ppb (0.049 mg/m^3).[b] **Methods:** Trained subjects measured peak expiratory flow rates (PEFRs) using Mini-Wright peak flow meters four times daily, in the	**Change in PEFR (L/min) in relation to indoor formaldehyde, random effects longitudinal model, ages ≤15 (*N* = 208; 3,021 observations)** Factor — b (SE) Formaldehyde (household mean, ppb) — −1.28 (0.46)[a] Morning formaldehyde (vs. bedtime) — −6.1 (3.0)[a] Bedroom formaldehyde *morning — 0.09 (0.15) Bedroom formaldehyde squared *morning — 0.0031 (0.0015)[a] Morning*asthma — 4.59 (9.60) Bedroom formaldehyde*morning*asthma — −1.45 (0.53)[a] Bedroom formaldehyde squared *morning*asthma — 0.031 (0.006)[a] Constant — 349.6 (13.2)

Study and design	Results
morning, at noon, in the early evening, and before bed, for 2 weeks. The largest of three test results was recorded for each daily test period (e.g., morning, bedtime). Evening and morning values were used in analysis. Analysis of PEFR in relation to indoor formaldehyde concentration, random effects longitudinal model including morning and bedtime formaldehyde concentration, adjusting for asthma status, smoking status, environmental tobacco smoke, socioeconomic status, NO_2 levels, episodes of acute respiratory illness, and time of day. Analysis performed separately for ages younger and older than 15 years. **Evaluation:**[a] *High* confidence	[a]$p < 0.05$, [b]$0.05 < p < 0.10$ PEFR decreased in children as formaldehyde concentrations increased with a difference noted between the measurements taken in the morning vs. bedtime. The morning PEFR was further decreased in children with asthma.
Reference: Wallner et al. (2012) Cross-sectional study; Austria. **Population:** 433 children (aged 6–10 years) with spirometry of 596 eligible (72.7%) in two classrooms each at 9 of 19 schools that volunteered to participate in study (50% male). 53% of the children were exposed to environmental tobacco smoke at home. **Exposure:** Pollutant measurements for 252 agents: 2 samples in each classroom, 1 per season (autumn, spring). Formaldehyde: 24-hour sampling period, all values > LOQ 34 chemicals selected for statistical analysis were those with substantial variation across schools based on an arbitrarily selected criterion (ratio of between-school variance to the pooled within-school variance >4). **Methods:** Questionnaire completed by parents, spirometry assessed at school between 8:30 am and 12:30 pm by trained technician, ATS protocol except 6-second minimum exhalation time (not feasible in children). Values expressed as percentage of reference based on age, gender, height, and weight. Regression of log-transformed values on mean concentration of chemical adjusted for education and occupation of parents, urban/rural residence, and # smokers at home. No adjustment of statistical significance criterion for multiple comparisons (exploratory). **Evaluation:**[a] *Medium* confidence No adjustment for coexposures in classroom that were also associated with pulmonary function, but correlation not anticipated.	Percentage change in pulmonary function (95% CI) per 1 SD change in formaldehyde concentration | | % Change | 95% CI | |---|---|---| | FVC[a] | −0.94 | −3.29, 1.35 | | FEV_1[a] | −2.16 | −4.80, 0.41 | | MEF_{75}[b] | −3.31 | −6.6, −0.08 | | MEF_{50} | −2.60 | −4.31, −0.91 | [a]Associations with ethylbenzene, *m*-, *p*-xylene, and *o*-xylene in air, tris (1,3-dichlor-2-propyl)-phosphate in particulate matter, and benzylbutylphthalate (FEV_1 only) and polybrominated diphenylether congeners in dust were statistically significant. [b]Associations with benzylbutylphthalate and polybrominated diphenylether congeners in dust also were statistically significant.
Reference: Franklin et al. (2000) Cross-sectional study, Australia.	Mean pulmonary function (SD) by exposure group[a] | | <50 ppb | ≥50 ppb |

Study and design	Results
Population: 224 healthy children (116 girls, 108 boys) with no current or history of upper or lower respiratory tract disease based on responses to respiratory health questionnaire and household inventory distributed through local primary schools. Age provided by author: <50 ppb, 9.5 years (SD 1.6); ≥50 ppb, 9.2 years (SD 1.9). **Exposure:** 3 to 4-day passive samples collected in the child's bedroom and the main living area of the house, average of both rooms; 214 homes. TWA categorized into two groups: <50 ppb (0.062 mg/m^3)[b] and ≥50 ppb (10 homes). Additional information from author: Mean (SD): 20.1 ppb (15.6) (0.025 mg/m^3)[a]; range ND−86.6 ppb (ND−0.107 mg/m^3)[b]. Median (IQR): 15.6 ppb (0.019 mg/m^3)[a] (range 9.2−28.1) (0.011−0.035 mg/m^3).[b] **Methods:** Clinical respiratory measures obtained at children's hospital. Measured spirometry (ATS guidelines), exhaled nitric oxide (eNO), and skin prick tests for seven common allergens. **Evaluation:**[a] *Medium* confidence Limited exposure contrast; few subjects in high exposure group.	FVC (L) 2.21 (0.55) 2.18 (0.46) Percentage predicted 99.1 (10.2) 101.4 (7.3) FEV_1 1.89 (0.46) 1.83 (0.24) Percentage predicted 96.3 (11.1) 97.2 (5.4) FEV/FVC (%) 89.1 (9.2) 93.1 (11.3) [a]Not reported; data provided to EPA by author; percentage predicted based on age, sex, and height. eNO levels by exposure category HCHO (ppb) eNO (ppb) Range ≥50 15.5 10.5−22.9 <50 8.7[a] 7.9−9.6 [a]p = 0.002, linear regression adjusted for age, atopic status.

Organized by study confidence, then descending publication year.
[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.3).
Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
[b]Concentrations reported by authors as ppm or ppb converted to mg/m^3.

Panel studies of changes in pulmonary function among anatomy/pathology students

Three panel studies examined pulmonary function changes over the course of 10 weeks, 12 weeks, and 7 months among anatomy students exposed to formaldehyde, with average concentrations ranging from 0.12 to 6.2 mg/m^3 intermittently [once or twice a week: (Uba et al., 1989; Kriebel et al., 1993; Kriebel et al., 2001); see Table 3-8]. The primary source of formaldehyde exposure in the laboratory air was formalin, a preservative composed of a mixture of formaldehyde (37%) and methanol (14%). Methanol is not expected to be associated with pulmonary function deficits and would not be a strong confounder in these studies (U.S. EPA, 2013). One study that measured pulmonary function using spirometry did not observe statistically significant declines over 7 months (Uba et al., 1989). Two studies by the same research group using repeated peak expiratory flow measures taken by students trained in the procedure at multiple points during the lab sessions suggested a dose-dependent average decline in PEF over 2 to several weeks related to concentration averaged over the entire duration, as well as reductions during dissections (Kriebel et al., 1993; Kriebel et al., 2001). Cumulative exposure (ppm-minutes) summed over all previous weeks was not a significant predictor of changes in pulmonary function. The measurement of multiple measures of PEF per student in the studies by (Kriebel et al., 1993; Kriebel et al., 2001) increased the precision of the mean value and, consequently, the statistical power to detect a significant change. Evidence from these panel studies provides support that formaldehyde exposure during anatomy labs results in pulmonary function declines over several weeks duration, although interpretation of the analyses by both Kriebel et al. and Uba et al. is complicated by the consideration that class attendance as well as formaldehyde concentrations decreased over the semester in the studies (Uba et al., 1989; Kriebel et al., 2001).

Table 3-8. Formaldehyde effects on pulmonary function in panel studies among anatomy or pathology students

Study and design	Results		
Reference: Uba et al. (1989) Panel study, California **Population:** 96 medical students (72.5% participation) during a 7-month anatomy class meeting twice a week for 4 hours. Mean age: 24.3 years, 88% white, 73.8% male, nonsmokers, 12 asthmatics. **Exposure:** Personal sampling monitors (impingers) in the breathing zone, 32 samples during different class periods in 7-month period. Short-term samples (*N* = 16) for peak concentrations during dissection. Range of TWA formaldehyde: below LOD (0.05 ppm) to 0.93 ppm (0.06 to 1.14 mg/m^3)[a] Monthly averages in September, October, and May: 0.6, 0.8, and 0.1 ppm (0.74, 0.98, and 0.12 mg/m^3),[a] respectively. Peak concentrations: During dissection: mean 1.9 ppm	**Pulmonary function by test day (mean ± SD) (*N* = 96)**		
	Before exposure (Day 1)	FVC (L)	5.246 ± 1.025
		FEV_1 (L)	4.379 ± 0.846
		$FEF_{25–75}$ (L/sec)	4.492 ± 1.216
		FEV_1/FVC	0.835
	2 Weeks	FVC (L)	5.277 ± 1.027
		FEV_1 (L)	4.409 ± 0.824
		$FEF_{25–75}$ (L/sec)	4.484 ± 1.151
		FEV_1/FVC	0.836
	7 months	FVC (L)	5.308 ± 1.027

(2.3 mg/m^3),[a] range 0.1 to 5.0 ppm (0.12 to 6.1 mg/m^3),[a] observing dissection: mean 1.2 ppm (1.5 mg/m^3)[a] range 0.2 to 2.0 ppm (0.25 to 2.5 mg/m^3)[a] **Methods:** Pre- (noon) and postlab spirometric measures (ATS methods) taken before the class began, after the first 2 weeks, and after 7 months. Analyzed using repeated measures ANOVA, adjusted for sex. **Evaluation:**[a] *High* confidence	FEV_1 (L) 4.399 ± 0.823 FEF_{25-75} (L/sec) 4.392 ± 1.198 FEV_1/FVC 0.829
Reference: Kriebel et al. (2001) Panel study, USA **Population:** 51 gross anatomy students (out of 54 total) during a 12-week class meeting once per week for 2.5 hours. Mean age: 24.9 years, 23.7% male, two current smokers, four with history of asthma. **Exposure:** Continuous monitoring in six homogenous sampling zones (LOD = 0.05 ppm). 12-minute work-zone concentrations calculated per student using sampling data and recorded work locations. Geometric mean concentration: 0.7 ppm (0.9 mg/m^3)[a] (GSD: 2.13 ppm). Peak 12-min concentration: 10.91 ppm (13.4 mg/m^3).[a] Average concentration: 1.1 ppm (1.35 mg/m^3)[a] (SD = 0.56 ppm). Concentrations decreased over 12-week semester. **Methods:** Spirometry (FEV_1, FVC) using ATS criteria before 1st exposure and during 10th week. Pre- and post-lab PEF measurements obtained for at least 1 week for 38 students. PEF as fraction of value before 1st lab session; individual pre-lab and cross-lab change data analyzed together in relation to recent, average, and cumulative formaldehyde in single generalized estimating equations model. Generalized estimating equations regression adjusted for cold on lab day. **Evaluation:**[a] *Medium* confidence (↓) Attrition and declining concentration over course—bias to healthy individuals and toward null	Exposure metrics: Recent exposure = mean concentration during 2.5-hour lab; cumulative exposure = ppm-minutes for all previous weeks; past average exposure: Cumulative exposure divided by total number of minutes of exposure. **PEF as fraction of baseline (before 1st lab) (L/s per ppm)** Recent exposure: ß (SE) −1.05 (0.33), *p*-value 0.002 Recent exposure *ln(week): ß (SE) 0.69 (0.24), *p*-value 0.004 Past average exposure: ß (SE) −0.52 (0.30), *p*-value 0.08 Cold on lab day: ß (SE) −1.67 (0.41), *p*-value 0.001 No association with cumulative exposure. Pulmonary function among asthmatics not different.
Reference: Kriebel et al. (1993) Panel study, USA **Population:** 24 clinical anatomy students (out of 25 total) during a 10-week anatomy class meeting once a week for 3 hours. Mean age 26, 42% male, 1 current smoker, five reported history of asthma. **Exposure:** Personal samples in the breathing zone, 1−1.5 hours sampling periods. Formaldehyde concentration geometric mean: 0.73 ppm (0.9 mg/m^3),[a] GSD 1.22; range: 0.49−0.93 ppm (0.6−1.14 mg/m^3); 8 samples. No trend in concentrations over semester.	**PEF (L/min) during course (mean ± SD) (*n* = 20)** Weeks 1−2: PEF (L/min) 538.9 (86.9) Weeks 9−10[a]: PEF (L/min) 529.4 (88.4) Weeks 24−25: PEF (L/min) 536.6 (86.2) [a]End of course. Decrement over 10-week course,

Pentachlorophenol: ND (LOD = 83 µg/m^3). **Methods:** PEF measured by trained students pre- and postlab and 1–3 times during lab using Mini-Wright peak flowmeters. Mean absolute value (SD) pre- and cross-lab change in pulmonary function analyzed in separate models using multivariate linear models, including asthma, asthma × week, eye and nose or throat symptoms. **Evaluation:**[a] *Medium* confidence Limited sample size	β = −2.7 ± 1.1 L/min per week; p = 0.01, Model included asthma, asthma × week, eye symptoms, nose symptoms.

Organized by study confidence, then descending publication year.

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.3). Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Summary of Human Evidence Synthesis Judgments on Pulmonary Function

The following factors, in particular the observed dose-dependence, were influential to the synthesis judgment that the human studies of long-term (months to years) formaldehyde exposure provide *moderate* evidence of formaldehyde exposure-induced decrements in pulmonary function.

- *Consistency and Study Confidence*: The majority of the numerous *high* and *medium* confidence studies reported consistent decrements in pulmonary function in relation to formaldehyde exposure; in different settings including occupational, residential and anatomy labs. Associations with pulmonary function deficits were found in occupational studies with longitudinal designs as well as cross-sectional analyses. Although one panel study among anatomy students did not report declines related to formaldehyde exposure, evidence from two panel studies conducted by one investigator group provides support that formaldehyde exposure during anatomy labs results in pulmonary function declines over several weeks duration.
- There was less consistency across studies for deficits in individual measures of pulmonary function (e.g., FEV_1, FVC or FEF_{25-75}).
- *Dose-Response*: Demonstrated exposure-response trends were observed in four *high* or *medium* confidence studies. In addition, well-conducted studies of individuals likely to be more susceptible to these effects (e.g., children; persons with asthma, elderly) showed that these effects occurred in these persons at lower formaldehyde levels (<0.05 mg/m^3) in analyses that ruled out confounding by smoking status, environmental tobacco smoke and NO_2 exposure.
- *Strength and Precision*: Decrements in FEV_1, FVC or FEF_{25-75} of 3% or greater were reported by several studies, although many analyses were imprecise which reduces certainty to a limited extent.

In addition to the judgment above, a general inference can be drawn based on the human studies. Specifically, children and individuals with compromised respiratory health are likely to be more sensitive to the effects of formaldehyde inhalation on pulmonary function.

Animal Studies

Summary of Animal Evidence Synthesis Judgments

Animal studies of apical pulmonary function endpoints were not formally evaluated (see Section 2.2.3). However, the mode of action information (discussed below) describing how formaldehyde inhalation might result in decrements in pulmonary function is primarily based on experimental studies in animals, which supports the biological plausibility of such effects and, by itself, is interpreted to provide *slight* animal evidence for effects on pulmonary function.

Evidence on Mode of Action

Although an MOA for formaldehyde-related effects on pulmonary function remains incompletely defined, it is likely that it involves the indirect activation of sensory nerve endings in the lower respiratory tract (LRT), increases in airway eosinophils, or both (see Figure 3-7). Moderate evidence exists for the mechanistic changes that could be directly related to decrements in pulmonary function (e.g., inflammatory changes in airway structure), and moderate or robust evidence supports the linkages between events in this pathway. However, the initial cellular or tissue modifications that ultimately lead to these later events are not completely understood and given the limitations of the available studies (see Appendix B.3.6), it is unclear whether certain events would be triggered at low-exposure levels. It is also possible that structural and functional changes in the upper respiratory tract (URT) might contribute to decreased pulmonary function; however, these possibilities are considered unlikely to be significant drivers of these effects (see additional discussion below). Overall, the airway inflammatory changes in the LRT, which may be at least partially related to indirect activation of sensory nerve endings, is judged as likely to be an incomplete mechanism by which formaldehyde inhalation could cause decreased pulmonary function. As the mechanistic event(s) critical to understanding the observed relationship remain unknown, including how sensory nerve endings in the LRT might be stimulated without distribution of inhaled formaldehyde to the LRT, it is expected that important insights would be gained from additional studies, particularly those testing longer exposure durations. Although much of the mechanistic support is from studies in experimental animals, it is expected that related mechanisms are operant in exposed humans and could contribute to the consistent decrements in pulmonary function observed in the available epidemiology studies. Variation in sensitivity is likely to be affected by underlying respiratory health status and the exposure history of the individuals, including exposure to known allergens.

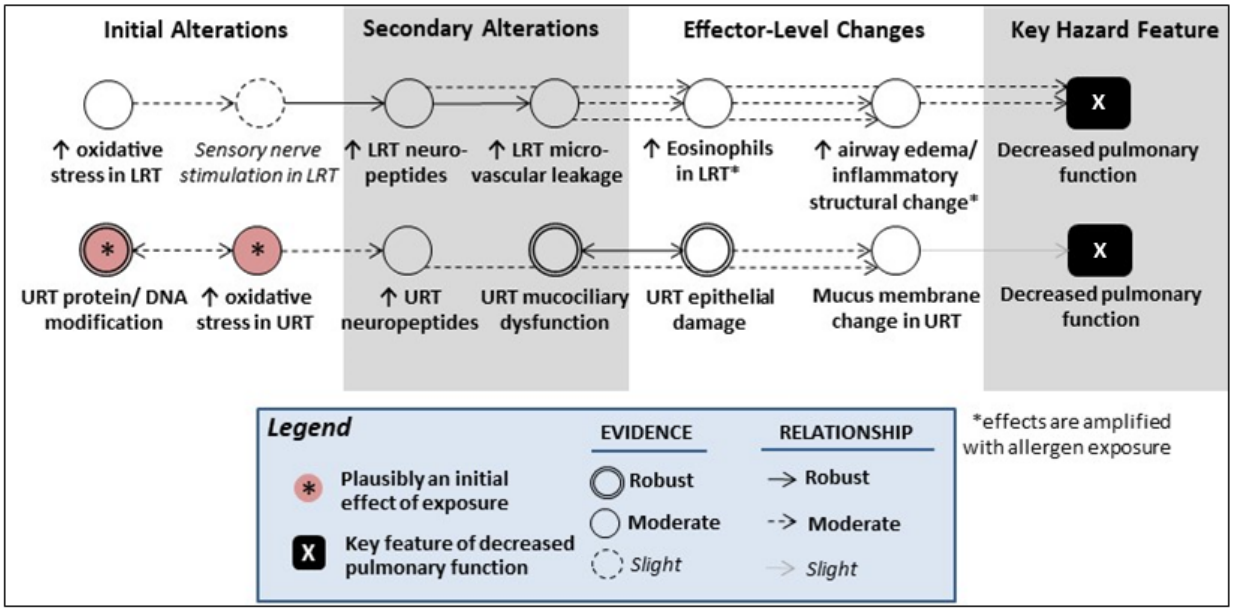


Figure 3-7. Possible mechanistic associations between formaldehyde exposure and decreased pulmonary function.

An evaluation of the formaldehyde exposure-specific mechanistic evidence informing the potential for formaldehyde exposure to cause respiratory health effects (see Table 3-9 and Appendix C.7) identified these sequences of mechanistic events as those most directly relevant to interpreting effects on pulmonary function. Evidence of airway inflammatory changes, including eosinophil, is considered as likely to represent an incomplete mechanism by which formaldehyde inhalation could cause decreased pulmonary function, although whether certain events occur at lower exposure levels is unclear, and other unexplored mechanistic events are expected to contribute. URT modifications, primarily structural changes (bottom pathway), may also contribute; however, this is not interpreted as likely to be a significant contributing mechanism.

The most plausible support for a mechanism(s) that explains the observed decreases in pulmonary function includes evidence of increased airway eosinophils and other immunogenic changes that could be attributed to sensory nerve activation in the LRT (presumably, the vagus nerve) of exposed rodents, although the potential involvement of LRT sensory nerve stimulation is poorly studied (i.e., slight evidence). It is expected that LRT sensory nerve activation would be reliant on a secondary response to TRP channel-activating stimuli increased in the LRT via indirect mechanisms, such as increased LRT oxidative stress or inflammatory mediators, or both, released from activated immune cells. This response is unlikely to result from direct stimulation of the nerve by inhaled formaldehyde or in response to cellular damage, as inhaled formaldehyde is unlikely to reach the LRT in appreciable amounts and overt epithelial damage in the LRT is not supported by the available evidence (see Appendix A.5.6). While it might also be explained by a central

trigeminal-to-vagal neural reflex response to irritation of the URT (i.e., a "nasobronchial" reflex[17]), the existence of this reflex in humans is debated and a clear scientific consensus does not exist (Togias, 1999, 2004; Sahin-Yilmaz and Naclerio, 2011; Giavina-Bianchi et al., 2016).

Stimulation of sensory nerve endings can cause a localized release of neuropeptides. Accordingly, moderate evidence supports that formaldehyde exposure results in increased LRT neuropeptides, including substance P, typically at formaldehyde concentrations ≥2.5 mg/m^3, with coherent moderate evidence for rapid activation of the primary receptor for substance P, the neurokinin (NK1) receptor, after acute exposure to higher formaldehyde levels. Further, the activation of the substance P pathway has been experimentally linked to formaldehyde-induced leakage of the LRT microvasculature. Airway edema and related inflammatory structural changes (i.e., in airway bronchi), which have been reported in experimental animals following short-term formaldehyde exposures ranging from >0.3 to >3 mg/m^3 and which appear to be exacerbated by prior allergen exposure, may represent consequences of increased microvascular leakage and inflammation (see below). To date, potential experimental linkages between these structural changes and sensory nerve stimulation or substance P signaling have not been studied after formaldehyde exposure. Similarly, while these changes could lead to an increased permeability to bronchoconstrictors such as histamine, and while substance P itself can increase the responsiveness of airway smooth muscle, these endpoints were generally unexamined in the available studies. Any or all of these immunogenic changes could plausibly contribute to airway narrowing or obstruction and affect pulmonary function, although airway obstruction would generally be expected to require much higher exposure levels or effects that cumulate over an extended period of time. Importantly, however, the majority of the evidence available to inform these immunogenic changes is from studies of short-term exposure.

Substance P and NK1R signaling has been implicated in establishing the successful recruitment and adhesion of eosinophils to inflamed airways, and it can promote immune cell survival and activation through the release of cytokines and chemokines (Mashaghi et al., 2016). Moderate evidence for an association between formaldehyde exposure and increases in LRT eosinophils was identified, including amplification of the response of these cells in rodents previously exposed to allergens. Considering the evidence in the respiratory tract, a generalized increase in airway eosinophils after formaldehyde exposure is supported by robust evidence. Increased airway eosinophils have been reported following exposure of laboratory rodents for several weeks at effective concentrations above 0.5 mg/m^3, with increases generally not being observed following acute exposure. Recruitment of eosinophils to the airways might be related to the moderate evidence for LRT markers of oxidative stress, as eosinophils can release toxic mediators, including lipid-active factors and reactive oxygen species (again noting that it is

[17]Note: neural reflexes involving afferent and efferent activity of the vagus nerve (e.g., across different LRT regions), some of which may involve C fibers and TRP channels, are better established (Mazzone and Undem, 2016).

considered more likely that any oxidative stress increases would result from changes in inflammatory factors and immune cells in the LRT, rather than LRT epithelial damage). However, the activation characteristics of the recruited airway eosinophils, including factors released, have not been defined, preventing a more complete understanding of whether and how these cells might decrease pulmonary function in these contexts.

As noted above, modifications to the URT respiratory epithelium could also result in changes that might indirectly affect pulmonary function. Such modifications include potential effects on immunological functions, such as an altered release of secreted factors from damaged epithelial cells, or effects on structural functions (e.g., modified clearance or barrier processes due to dysfunction of the mucociliary apparatus or cell type transitions or narrowing of upper airways due to inflammation or proliferation). If increased URT cytokines or other soluble mediators were to reach the LRT, they could contribute to decreased pulmonary function through airway hyperreactivity or hypersensitivity to challenges such as allergen exposure (Hulsmann and Dejongste, 1996). However, it is expected that most immune factors released from URT respiratory epithelial cells are tightly controlled and locally acting, and that modest increases would be unlikely to have significant effects on the lower airways and lungs. Similarly, it is reasonable to presume that physical modifications to the URT would need to be severe to cause a noticeable change in function, which would not be expected with typical exposure scenarios. Direct, formaldehyde-specific examinations of any such associations between the robust evidence for structural URT changes and LRT effects were not identified, further limiting the interpretation of this potential association.

While evidence for some events at low formaldehyde levels (e.g., <1 mg/m^3) exists, some of the more convincing associations have only been tested at high formaldehyde concentrations. Additionally, the supporting mechanistic evidence is generally from studies of short-term (i.e., days to weeks) exposure. Therefore, the relevance and sensitivity of the proposed mechanistic pathways to chronic, low-level exposure scenarios is uncertain. It is also presumed that several important mechanistic events are currently unidentified. In particular, the initial effects of formaldehyde exposure that lead to the LRT changes remain undefined, although speculative, untested scenarios explaining the associations can be hypothesized based on the data available. Similarly, no explanation exists for the observed exaggerated effects on some mechanistic events following prior allergen exposure. Overall, however, although a definitive MOA has not been fully identified, several contributing mechanistic events interpreted with moderate or robust evidence appear to impact pulmonary function and, taken together, these data provide support for the biological plausibility of formaldehyde exposure-induced decreases in pulmonary function (see Table 3-9).

Table 3-9. Mechanistic evidence most informative to the occurrence of decreased pulmonary function after formaldehyde inhalation

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
Modifications in the nose and upper airways				
Modification of biological macro-molecules (see Appendix C.1 and C.3 on ADME and Genotoxicity for additional detail)	*High or Medium*	*Human*: No direct evidence [note: binding of formaldehyde to albumin and other soluble proteins in human mucus has been demonstrated in vitro, e.g., (Bogdanffy et al., 1987)]; hemoglobin adducts are observable after months-to-years exposure at ~0.2 mg/m^3 (Bono et al., 2012).	Consistent with its known chemistry, formaldehyde can modify cellular macromolecules, including DNA, and interact with soluble factors such as albumin and glutathione, after exposure to low levels (e.g., <0.5 mg/m^3) across a wide range of exposure durations.	Robust
		Animal: Multiple animal studies testing various exposure durations demonstrate that inhaled formaldehyde can bind and modify biological macromolecules, which is consistent with the known biological reactivity of formaldehyde; evidence includes increased DNA-protein crosslinks (DPXs), hydroxymethyl (hm) DNA adducts, and reactions with glutathione [e.g., increased DPXs are observed at ≥0.37 mg/m^3 (Casanova et al., 1989)]; and hmDNA adducts and protein adducts are observed at ≥0.86 mg/m^3 (Lu et al., 2010a; Lu et al., 2011; Edrissi et al., 2013b).		
	Low	N/A: Sufficient information for 'robust' from *high or medium* confidence studies.		
Impaired mucociliary function (see Appendix C.7 for additional detail and discussion)	*High or Medium*	*Human*: Decreased mucus flow at ≥0.3 mg/m^3 after acute exposure and pathological changes in mucociliary clearance in workers at mean exposed levels of 0.25–0.26 mg/m^3 after chronic exposure (Holmström and Wilhelmsson, 1988; Andersen and Molhave, 1983).	Decreased mucus flow and ciliary beat, and impaired clearance, in humans and rats at ≥0.25 and ≥2.5 mg/m^3, respectively (observed across exposure durations), eventually leading to cilia loss.	Robust
		Animal: Mucociliary function was generally unaffected at <0.57 mg/m^3 after short-term exposure, with minor changes noted at the next exposure level, around 2.5 mg/m^3; robust changes were observed at the next highest concentrations tested, ≥7.27 mg/m^3 after acute or short-term exposure; there was a general lack of recovery with longer exposure duration (e.g., (Morgan et al., 1986a; Morgan et al., 1986c; Monticello et al., 1989); see Appendix C.7 and B.3.6).		
	Low	*Human*: Increases in ciliary activity at 1.23 mg/m^3 in dissociated human nasal epithelial cells (Wang et al., 2014b), with decreased ciliary beating frequency in human epithelial cells at ≥3.46 mg/m^3 (Wang et al., 2014b; Schafer et al., 1999): in vitro, acute exposure.	Suggestive of decreased ciliary beat and ciliastasis at ≥5 mg/m^3 in humans and animals with acute exposure, and ciliary damage at ≥0.5 mg/m^3 with short-term exposure; usually preceded by initial effects including slight increases in activity.	
		Animal: Ciliastasis and mucostasis after acute exposure in vitro (Morgan et al., 1984): frog palates at ≥5.36 mg/m^3 (with early activity increases, even at 1.69 mg/m^3); structural cilia changes were also observed (Monteiro-Riviere and Popp, 1986): short-term exposure at ≥0.5 mg/m^3; and (Abreu et al., 2016): acute exposure at 0.25, but not 1.2–3.7 mg/m^3.		
Structural change in URT	*High*	*Human*: Membrane hypertrophy, atrophy, rhinitis (Lyapina et al., 2004): chronic (years) exposure at 0.87 mg/m^3.	Mucus membrane damage and swelling in humans at	Moderate (particularly

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
mucus membrane or nasal obstruction		*Animal*: None	0.87 mg/m^3 with chronic exposure.	in persons with nasal damage)
	Low	*Human*: Data suggest increased mucosal swelling, nasal obstruction or rhinitis in workers by (Holmström and Wilhelmsson, 1988): chronic exposure at 0.26 mg/m^3, and (Norback et al., 2000): short-term exposure at ≤0.016 mg/m^3, which did not increase in severity with longer exposure; increased mucosal swelling was also noted in symptomatic nasal distress patients, but not healthy controls (Falk et al., 1994): acute (2-hr) exposure at ≥0.073 mg/m^3.	Observations at ≤0.26 mg/m^3 in humans or at >3.5 mg/m^3 in rats support data from the chronic duration study and suggest increased acute vulnerability of people with a prior nasal condition.	
		Animal: Rhinitis and necrosis in rats after acute or short-term exposure, generally at ≥3.5 mg/m^3 (see Appendix C.6 and C.7).		
URT epithelial damage or dysfunction (see Section 3.2.4 for additional detail)	*High or Medium*	*Human*: Indirect data indicating epithelial damage, including loss of ciliated cells, in occupational studies at 0.1 to >2 mg/m^3 (Holmström and Wilhelmsson, 1988; Holmstrom et al., 1989c; Edling et al., 1987a, 1988; Ballarin et al., 1992), with some equivocal findings (Boysen et al., 1990); however, these histopathological symptom scores included hyperplasia and metaplasia, which complicate interpretation.	Duration-dependent epithelial damage, typically at ≥2.5 mg/m^3 in subchronic or chronic rat studies, and with supportive indirect findings from human studies at 0.1–0.2 mg/m^3, generally correlates with inhibited mucociliary activity.	Robust
		Animal: Increased epithelial damage and related nasal lesions [e.g., (Andersen et al., 2010)]: duration dependent, typically ≥2.46 mg/m^3 in subchronic and chronic studies, with general correlation with inhibited mucociliary activity; goblet cell loss noted in monkeys (Monticello et al., 1989): short-term (1 week) exposure at 7.38 mg/m^3; indirect evidence mRNA or miRNA changes associated with apoptosis (Rager et al., 2013; Rager et al., 2014): short-term (2-d in macques or 28-d in rats) exposure at ≥2.46 mg/m^3.		
	Low	*Human*: None	Studies suggest that nasal epithelial damage is increased, even in short-term studies, at ≥2.5 mg/m^3.	
		Animal: Goblet cell damage and decreased junctional proteins between epithelial cells in rats (Arican et al., 2009): subchronic (12-week) exposure at 18.5 mg/m^3; mRNA changes in DNA repair genes in rats (Andersen et al., 2010): short-term (1-week) exposure, but not longer (4- to 13-week) durations at ≥12.3 mg/m^3; rhinitis and necrosis in rats after acute or short-term (1- to 3-d) exposure at ≥3.94 or 4.43 mg/m^3.		
↑ URT oxidative stress	*See Section 3.2.1* for a description of the direct and indirect evidence of elevated reactive oxygen species (ROS) in the URT, possibly at very low concentrations (e.g., at >0.066 mg/m^3) with prolonged exposure.			Moderate

Endpoint		Endpoint-specific findings and confidence	Summary of evidence	Conclusion
↑ **Neuro-peptide release**	*High or Medium*	*Human*: None *Animal*: Increased substance P **in plasma** in mice (Fujimaki et al., 2004b): subchronic exposure at 2.46 mg/m^3; microvascular leakage in rats (Ito et al., 1996): acute exposure to 18.45 mg/m^3; this was inhibited by NK1 receptor antagonists (note: substance P binds NK1R).	Indirect evidence after subchronic exposure in a mouse study at 2.46 mg/m^3; Indirect evidence for acute activation of the receptor for substance P in rats at >18 mg/m^3.	Moderate (for ↑ neuro-peptides) Moderate (for NK1R stimulation) (note: relevant to both URT and LRT)
	Low	*Human*: Substance P in nasal lavage (**in URT**) is increased in human volunteers with ocular exposure (He et al., 2005): 4-d (5-min/d) exposure at 3 mg/m^3, not 1 mg/m^3. *Animal*: **In URT** models, formaldehyde stimulates release of calcitonin gene-related protein (CGRP) in in vitro models relevant to inhalation exposure of the URT (Kunkler et al., 2011); experiments using the related chemical, acrolein, suggest this is TRPA1-mediated (Kunkler et al., 2011). **In LRT** models, inhibition of substance P receptor (NK1R) inhibited formaldehyde-induced currents in isolated rat trachea (Luo et al., 2013); increased substance P and CGRP in mouse BAL, both amplified with ovalbumin (OVA) sensitization, and both involved TRP activation (Wu et al., 2013): short-term exposure at 3 mg/m^3.	Data suggest formaldehyde activates TRP channels on sensory neurons, leading to release of CGRP and substance P, with acute or short-term exposure at >1 mg/m^3. An inhibitor study in isolated rat LRT tissue provides evidence of NK1R involvement, although the relevant inhalation exposure levels are unknown.	
Nasal cellular inflammatory response	*High or Medium*	*Human*: None *Animal*: Increased inflammatory response, mostly neutrophils but also mention of lymphocytes and other inflammatory cells (e.g., assumed monocytes, basophils and eosinophils) (Monticello et al., 1989): short-term (1- or 6-week) exposure at 7.38 mg/m^3; "inflammatory cell" infiltration (Andersen et al., 2008): acute or short-term (1-d to 3-week) exposure at 7.38 mg/m^3; miRNA changes associated with inflammation in rats and nonhuman primates (Rager et al., 2013; Rager et al., 2014): short-term (1- or 4- week, with some miRNA changes reversible with 1-week recovery) exposure at 2.46 mg/m^3; in rats, 35 formaldehyde-responsive transcripts in the nose known to be related to immune cells indirectly indicated increases in granulocytes (i.e., eosinophil and neutrophil markers) and lymphocyte changes (Andersen et al., 2010): short-term (1-week, but not ≥4-week) exposure at ≥12.3 mg/m^3.	Cellular infiltration observed by histology, primarily neutrophils, but indirectly supporting other immune cell infiltration, in short-term animal studies at 7.38 mg/m^3. Indirect evidence of increases in granulocytes (and possibly lymphocytes) at 2.46 mg/m^3 with short-term exposure.	Moderate (↑ granulo-cytes: neutrophils and eosinophils) (Note: data on lympho-cytes were indeterm-inate)
	Low	*Human*: N/C in nasal lavage cell counts, but increased total protein (Priha et al., 2004): occupationally exposed (8-hr shift) 0.19 mg/m^3; allergy-independent increased eosinophils, permeability (albumin index) and total protein in lavage (Pazdrak et al., 1993): acute (2-hr) exposure at 0.5 mg/m^3; increased eosinophils, leukocytes, and permeability (albumin index) in lavage (Krakowiak et al., 1998): acute (2-hr) exposure at 0.5 mg/m^3 (reversible); indirect evidence of eosinophil infiltration (increased	Suggestive of cellular inflammation, particularly eosinophils, at 0.5 mg/m^3 and indirect markers of eosinophil recruitment at lower levels in humans, following *acute* exposure; neutrophil inflammation observed at ≥6 mg/m^3 in	

Endpoint		Endpoint-specific findings and confidence	Summary of evidence	Conclusion
		markers: lysozyme and eosinophil cationic protein), but not neutrophils, at very low levels (Norback et al., 2000): <0.02 mg/m^3 for unknown duration (likely ≥months) in schools. *Animal*: Neutrophil inflammation (Monteiro-Riviere and Popp, 1986): short-term exposure at ≥6 mg/m^3.	rats with *short-term* exposure.	
Modifications in the lower airways				
↑ Lower respiratory tract (LRT) microvascular leakage	*High or Medium*	*Human*: None *Animal*: Increased in rats (Ito et al., 1996): acute exposure at ≥6.15 mg/m^3; note: inhibited at 18.45 mg/m^3 by NK1 receptor antagonist (note: substance P binds NK1R), but not histamine or bradykinin antagonists.	Demonstrated increased leakage from acute exposure ≥6.15 mg/m^3 in 1 study, which appears to be mediated by substance P.	Moderate (only examined in acute studies)
	Low	*Human*: None *Animal*: Transiently increased in rats (Kimura et al., 2010): acute exposure at ≥1.23 mg/m^3 (duration-independent); note: leakage blocked by inhibiting mast cells, but not blocking cyclooxygenases; indirect mechanistic data following injection of formalin into the trachea, causing leakage that appeared to be dependent on substance P release after stimulation of C-fiber afferents (Lundberg and Saria, 1983).	One study suggests acute exposure as low as 1.23 mg/m^3 induces microvascular leakage, although continued exposure appeared (at least in the near-term) to result in less leakage.	
↑ Airway edema or other inflammatory structural changes	*High or Medium*	*Human*: None *Animal*: Increased edema in lung bronchi, but not alveoli, without signs of inflammation in lower airways in guinea pigs (Riedel et al., 1996): 5 d at 0.31 mg/m^3, not at 0.16 mg/m^3.	Bronchial edema in one short-term study at 0.31 mg/m^3.	Moderate (may require high exposure levels or allergen sensitization to elicit pronounced changes)
	Low	*Human*: None *Animal*: Airway structural changes consistent with inflammation (e.g., wall thickening; cell infiltration) in mice (Jung et al., 2007), some evidence for which was slight (Wu et al., 2013; Liu et al., 2011a), and in mice and rats sensitized with OVA (Wu et al., 2013; Qiao et al., 2009; Liu et al., 2011a), but not in nonsensitized rats (Qiao et al., 2009): all 2- to 3-week exposure at ≥3 mg/m^3 [Note: most studied bronchial airways].	Airway structural changes with allergen sensitization in two species (and, to a lesser extent, without sensitization) with short-term exposure at ≥3 mg/m^3.	
LRT sensory nerve activation	*High or Medium*	*Human*: None *Animal*: None	No evidence to evaluate	Slight (levels required for potential activation are unknown; may involve TRPA1 binding)
	Low	*Human*: None *Animal*: With acute exposure, dose-dependent increase in nerve currents and Cl^- release in intact rat trachea (Luo et al., 2013), with supporting evidence of substance P and NK receptor involvement. Indirectly, increased substance P and CGRP were observed in mouse lung tissue, both were	A single acute rat study and indirect evidence from potentially related exposures suggest that lower airway sensory nerve afferents may be activated,	

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
		amplified with OVA, and both were dependent on TRP activation (Wu et al., 2013): short-term exposure at 3 mg/m^3. Note: the potential involvement of tracheobronchial reflexes, as is shown with direct LRT stimulation by irritants including cigarette smoke constituents and capsaicin (e.g., (Widdicombe, 1998)), may provide indirect support.	but the inhaled formaldehyde levels required for such potential activation have not been experimentally demonstrated.	

Endpoint		Endpoint-specific findings and confidence	Summary of evidence	Conclusion
↑ LRT oxidative stress	*High or Medium*	*Human*: Increased exhaled nitric oxide, a noninvasive marker of lower airway inflammation and oxidative stress, in healthy or asthmatic children (Franklin et al., 2000; Flamant-Hulin et al., 2010): unknown duration (likely months to years: classrooms or homes) at 0.04–0.06 mg/m^3, but not in elderly nursing home patients at lower levels (Bentayeb et al., 2015) for unknown duration (likely months to years) at 0.005–0.01 mg/m^3.	Increased biomarkers (indirect evidence) of oxidative stress in children at ≥0.04 mg/m^3, but not in elderly individuals at ≤0.01 mg/m^3 with prolonged (months–years) exposure, with indirect support from a subchronic rat study at >6 mg/m^3.	Moderate (observed in children at low levels: ~0.04 mg/m^3)
		Animal: Increased iron and zinc, indirect markers of potential oxidative stress, in lungs of male rats: 13 weeks at ≥6.15 mg/m^3 (Ozen et al., 2003).		
	Low	*Human*: None	Multiple studies in two species suggest elevated oxidative stress at ≥1 mg/m^3 with short-term exposure.	
		Animal: **In mice**: NO and NOS activity increased with 3 d exposure at 3 mg/m^3 (Yan et al., 2005), GSH levels decreased with 3-week exposure at ≥0.5 mg/m^3 (Ye et al., 2013b), and increased ROS or lipid peroxidation markers were observed with 3-week exposure at ≥1 mg/m^3 (Ye et al., 2013b) or 2-week exposure at ≥6.15 mg/m^3 (Jung et al., 2007), but decreased with acute exposure in one study (Matsuoka et al., 2010): 24-hr exposure at 0.12 mg/m^3. **In rats**: short-term studies at ≥12.3 mg/m^3 demonstrated increased total oxidant levels and decreased total antioxidant level (Aydin et al., 2014), increased lipid peroxidation markers and protein oxidation markers (Sul et al., 2007), and decreased gamma-glutamyl transpeptidase (indirect evidence) (Dinsdale et al., 1993).		
↑ LRT eosinophils[b] (see **Appendix C.7** for discussion of LRT evidence on other cell types and soluble factors)	*High or Medium*	*Human*: None	Increased after subchronic exposure to 2.5 mg/m^3 in mice coexposed to antigen.	Moderate (with short-term exposure at ≥0.5 mg/m^3; note: moderate evidence for increases in total BAL cells or total white blood cells, under similar conditions; see Appendix C.7)
		Animal: ↑ in rats at 2.5 mg/m^3 with coexposure to the antigen, ovalbumin (OVA) (Fujimaki et al., 2004b).		
	Low	*Human*: Two studies did not observe increases following acute exposure at 0.1 mg/m^3 ((Casset et al., 2007); note: trend toward ↑) and 0.5 mg/m^3 (Ezratty et al., 2007) with allergen coexposure (i.e., dust mite antigen; pollen).	Evidence of increases with short-term exposure (in general, at ≥0.5 mg/m^3) in both rats and mice; the data suggest that changes may not occur after acute exposure.	
		Animal: ↑ in four short-term studies of mice in the absence of antigen [12.3 mg/m^3; (Jung et al., 2007)], with antigen (>~12.3 mg/m^3 with house dust mite antigen; (Sadakane et al., 2002)[a]), or both with and without antigen (at 0.5–3 mg/m^3 ± OVA (Liu et al., 2011a), and at 3 mg/m^3 ± OVA (Wu et al., 2013)); ↑ in one short-term rat study at 0.5–3.1 mg/m^3 with OVA antigen (Qiao et al., 2009) One acute rat study did not observe effects at 6.2 mg/m^3 without antigen (Kimura et al., 2010).		

[a]Reported as 0.5% formaldehyde solution; concentration assumed to be >12.3 mg/m^3 (Sadakane et al., 2002).
[b]There was also slight evidence for increases in eosinophil attractant and adhesion factors (see Appendix C.7).

Summary of Inferences Regarding Mode of Action

Although a definitive MOA has not been fully identified, several contributing mechanistic events interpreted with moderate or robust evidence appear to impact pulmonary function and, taken together, these data provide support for the biological plausibility of formaldehyde exposure-induced decreases in pulmonary function. However, important gaps in understanding of the MOA exist and some of the most biologically relevant mechanistic findings have not been examined at lower formaldehyde concentrations (e.g., < 1 mg/m^3). In addition, several important mechanistic events have only been examined in longer-term, or conversely short-term studies, complicating interpretations of duration-dependence. Thus, notable uncertainties exist.

Evidence Integration Summary

Measures of pre-shift FEV1, FVC, FEV1/FVC, and expiratory flow rates were generally lower in highly exposed occupational groups compared to their nonexposed or lesser-exposed comparison groups. While the direction of the associations was generally consistent, some effect estimates were imprecise. The differences may be a result of individual variability, lower sensitivity in some studies to detect small mean differences or changes, or random variation. Another source of variation may be incomplete control for confounders (e.g., smoking, dust, other pollutant exposure), although some studies did adjust for these factors and still observed an independent association with formaldehyde, and associations were found among groups in different exposure settings. Evidence from two of three panel studies, both conducted by one investigator group, provides limited support that formaldehyde exposure during anatomy labs results in pulmonary function declines over several weeks duration.

Demonstrated exposure-response trends were observed in four *high* or *medium* confidence studies (Wallner et al., 2012; Malaka and Kodama, 1990; Krzyzanowski et al., 1990; Kriebel et al., 2001). An increase in pulmonary function deficits with increasing exposure was reported by a study of woodworkers with area formaldehyde levels ranging from 0.27–4.28 mg/m^3 (Malaka and Kodama, 1990). Dose dependent decreases in pulmonary function were observed among adults smokers and children who lived in mobile homes with average formaldehyde concentrations of 0.032 mg/m^3 and a maximum of 0.172 mg/m^3 (Krzyzanowski et al., 1990) and also by a study of pollutant exposures among school children (Wallner et al., 2012). Dose-dependent decreases in PEF also were observed among anatomy students exposed to an average formaldehyde concentration of 1.35 mg/m^3 with peak concentrations of 13.4 mg/m^3 (Kriebel et al., 2001).

Smoking, health status, and lifestage may increase sensitivity to inhaled formaldehyde. The limited number of population-based studies evaluating lower exposure levels indicates that while, in general, no associations were observed among adults as a whole, declines were reported for smokers and the elderly living in nursing homes. The study with the strongest design and methods found an association with declines in PEFR among adult smokers and increasing average formaldehyde concentration between 0.049 and 0.172 mg/m^3 (Krzyzanowski et al., 1990). In this

large, population-based sample, the investigators also observed a linear relationship between increased formaldehyde exposure and decreased peak expiratory flow rate (PEFR) among children exposed to average concentrations of 0.032 mg/m^3 (26 ppb), and a stronger response was observed among children with asthma. The stability of average exposure concentrations between sampling periods, some separated by weeks, was confirmed by the investigators, thus the high quality exposure assessment addressed the etiologically relevant time window for the evaluation of associations with ongoing pulmonary function status. The analyses controlled for other exposures including smoking status, environmental tobacco smoke and NO_2. This finding is supported by declines in some of the pulmonary function measures in a *medium* confidence study in schools (Wallner et al., 2012).

While there were very few studies in humans that inform potential biological mechanisms (i.e., several studies indirectly support inflammatory changes in the LRT), experimental evidence primarily from animal studies provides robust or moderate evidence of mechanistic changes that can be plausibly associated with effects on pulmonary function, including increases in airway eosinophils and other inflammatory airway changes that appear to be at least partially dependent on indirect activation of sensory nerve endings in the LRT. Taken together, the data provide what is likely to be an incomplete mechanism explaining how formaldehyde exposure might result in decreased pulmonary function. Uncertainties remain regarding the initial cellular or tissue modifications that ultimately lead to the observed mechanistic changes in the lower airways, and it is unclear whether certain events would be triggered with chronic, low-level exposure.

Overall, based on *moderate* human evidence from observational epidemiology studies, with corresponding *slight* evidence for an effect in animals based on mechanistic studies supporting biological plausibility, the **evidence indicates** that long-term inhalation of formaldehyde likely causes decreased pulmonary function in humans given sufficient exposure conditions. The primary support for this conclusion includes a study of children and adults in a residential setting (mean, 0.03 mg/m^3, maximum 0.17 mg/m^3) and several studies of workers with long-term exposure to >0.2 mg/m^3 (see Table 3-10).

Table 3-10. Evidence integration summary for effects of long-term (months to years) formaldehyde inhalation on pulmonary function

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis Judgment	Hazard determination
Human	*Consistency and Study Confidence*	• Numerous *high* and *medium* confidence studies show a pattern of lower mean pulmonary function in formaldehyde-exposed occupational groups compared to referent groups across a variety of exposure settings and countries, plus longitudinal declines in two occupational populations and a panel study of medical students. • A large, population-based study observed a linear relationship between increased formaldehyde exposure and decreased peak expiratory flow rate (PEFR) among children overall, with a stronger response among children with asthma. A study among school children also found deficits using a different measure.	• Null or equivocal associations were identified for some studies; these studies had limitations that may have contributed to lower sensitivity. • Some inconsistencies across studies were noted for specific PEF measures; possible explanations include random variation and low study sensitivity.	*Moderate* Based on consistency across exposure settings (residential, occupational) and study designs (cross-sectional, longitudinal), multiple observations of dose-dependent reductions and greater sensitivity among susceptible groups (children, asthmatics, adult smokers, elderly). Confidence is moderated by less consistent observations for individual pulmonary function measures across studies.	The **evidence indicates** that long-term inhalation of formaldehyde likely causes decreased pulmonary function in humans, given sufficient exposure conditions[a]. Primarily based on *moderate* human evidence from a study of children and adults in a residential setting (mean, 0.03 mg/m^3, maximum 0.17mg/m^3) and numerous studies of workers with long-term exposure to >0.2 mg/m^3 formaldehyde. *Potential Susceptibilities:* Variation in sensitivity is anticipated to depend on age and respiratory health (including smoking status), with the potential for children (particularly children with asthma) to be more sensitive.
	Strength and Precision	• One *high* and two *medium* confidence studies in residential and school populations indicate that susceptible individuals may experience reduced pulmonary function at lower average concentrations (<0.05 mg/m^3).	• Some of the observed decreases in pulmonary function were small in magnitude (< 1–2%). • Some of the differences between exposed and their referent groups in occupational studies were imprecise.		

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis Judgment	Hazard determination
	Dose-Response	• Concentration-related decrements in pulmonary function from four *high* and *medium* confidence adjusted analyses indicate an independent association for formaldehyde exposure.			
	Coherence	N/A			
	Biological Plausibility	• Some indirectly supportive mechanistic information from well-conducted human studies exists related to increased lower airway oxidative stress following exposures likely to span months to years.			
Animal	Animal studies of pulmonary function endpoints were not formally evaluated (see Section 2.2.3).			*Slight* Based on mode of action evidence from experimental animal studies.	
	Biological Plausibility	• Understanding of the partial MOA likely to underly the development of pulmonary function decrements following formaldehyde inhalation is primarily based on experimental studies in animals. Although uncertainties remain, this strong mechanistic evidence alone is considered to support an animal evidence synthesis judgment stronger than *indeterminate*.			
Other inferences	• *Relevance to humans*: The primary effect of interest was observed in humans (*moderate* evidence). • *MOA*: Not established, but likely to involve airway eosinophil increases and stimulation of airway sensory nerve endings. Specifically, robust and moderate evidence for several mechanistic events, primarily from experimental animal studies,				

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis Judgment	Hazard determination
	provides support for inflammatory changes in the lower airways, including eosinophil increases, which appear to be at least partially dependent on indirect stimulation of sensory nerve endings. While evidence exists for some changes in the range of 0.3−0.5 mg/m^3 with exposure for several weeks, some potential associations in the identified, incomplete MOA pathway have only been tested at higher (i.e., >1 mg/m^3) levels and with shorter-term exposures. This partial MOA is assumed to be relevant to humans based on similarities in systems mediating the identified MOA across species and some supportive findings for lower airway mechanistic changes in exposed humans.				

N/A = indicates the factor was not applicable to (i.e., did not influence) the judgment drawn.

[a]The "sufficient exposure conditions" are more fully evaluated and defined through dose-response analysis in Section 5.1.

3.2.3. Immune-mediated Conditions, Focusing on Allergies and Asthma

This section examines the evidence pertaining to the effect of formaldehyde exposure on immune-mediated responses, primarily in the respiratory system, focusing on allergy-related conditions (e.g., rhinitis, rhinoconjunctivitis, eczema), and asthma; sensitization related to dermal exposure is not a focus of this review. Lower respiratory tract conditions in infants and children up to 3 years in age, in particular wheezing episodes, are also examined as a separate endpoint. Experimental animal studies were ultimately concluded to be unsuitable models (i.e., *indeterminate*) for evaluating allergy-related conditions and asthma as apical outcomes (see discussion in *Immune-mediated Conditions, Focusing on Allergies and Asthma, in Animal Studies*). Studies examining respiratory immune function (i.e., the ability to respond to infection) are discussed within the wider context of potential mechanistic changes that might explain respiratory health hazards (see Appendix C.7 and discussion below in *Evidence on MOA*), rather than as an independent health hazard to be evaluated. The mechanistic studies considered most relevant to these health outcomes provided biological support for the immune-mediated conditions observed in humans, although complete and definitive MOAs could not be established and several changes thought to be important to the development or progression of asthma, in particular, were not identified. The few available studies on developmental immunotoxicity in animals (hypersensitivity studies) were *indeterminate* in regard to the information necessary to draw conclusions.

The general population studies in children (ages >= 5 years) and adults (ages 18 to 65 years) provided evidence of an association between formaldehyde exposure and prevalence of rhinitis, or rhinoconjunctivitis, with a relative risk of approximately 1.2 for formaldehyde exposures of around 0.04–0.06 mg/m^3. Although the effect size was small, these are relatively common conditions and could result in a large impact in the population. A stronger association (two-fold risk) was seen in the only study of eczema in adults. Eczema, while not indicative of an allergic respiratory response, is often associated with other allergic disorders, including those affecting the respiratory system [e.g., allergic rhinitis; (Weidinger and Novak, 2016a, b)], and it appears that some inhaled allergens may have the potential to exacerbate this condition (Morren et al., 1994; Mendell et al., 2011). The available general population studies also provided evidence of an association between formaldehyde exposure and the prevalence of current asthma, typically as determined by symptoms or medication use in the past 12 months, in studies with some exposures above 0.05 mg/m^3, but associations were not seen in settings with exposures below 0.05 mg/m^3. For the allergy-related outcomes and asthma, the study designs and outcome classification used in the *high* and *medium* confidence studies were considered to be appropriate by the two expert panels consulted by the EPA. The two studies examining asthma control or severity among children with asthma suggest associations may be seen at lower exposures (e.g., 0.04 mg/m^3) in this potentially susceptible population. Relatively strong associations were seen in studies examining prevalence of current asthma in relation to formaldehyde exposure in occupational settings (exposures above 0.10 mg/m^3). The mechanistic evidence supports that formaldehyde exposure

can induce bronchoconstriction and lead to the development of hyperresponsive airways,[18] particularly with allergen sensitization. These heightened responses may be due to a combination of potentially progressive changes, including neurogenic increases in tachykinins and eosinophil recruitment and activation in the lung. The mechanistic studies also provided consistent evidence that formaldehyde may stimulate a number of immunological and neurological processes related to asthmatic responses; however, a molecular understanding of how formaldehyde exposure favors asthmatic T-helper 2 (T_H2) responses has not been experimentally established.

Overall, based primarily on a *moderate* level of human evidence supporting an association from the available epidemiological studies, with corresponding *slight* evidence for an effect in animals based on mechanistic studies in animals supporting biological plausibility, the **evidence indicates** that inhalation of formaldehyde likely causes an increased risk of prevalent allergic conditions and prevalent asthma symptoms, as well as decreased control of asthma symptoms, given sufficient exposure conditions. The primary basis for this conclusion involves studies of occupational settings (>0.1 mg/m^3) and population studies where formaldehyde concentrations measured in schools and homes averaged between 0.05 and <0.1 mg/m^3.

Human Studies

In the following sections, the evidence regarding allergic conditions (symptoms, skin prick tests) from general population studies is discussed by age category (i.e., children, adults). For asthma, general population studies of asthma prevalence and degree of control among children and adults are discussed by exposure setting (general population, occupational). In addition, responses among asthmatics to acute exposure are described (controlled human exposure studies), followed by other respiratory conditions in infants and toddlers, and a discussion of factors that may increase susceptibility. As described in Section 2.3.4, these studies were evaluated and classified by confidence (see Appendix B.3.4 for documentation). The studies are summarized in tables for these outcomes that are ordered by age group, confidence in study results, and publication year.

Allergic conditions

The set of seven *high* and *medium* confidence general population studies of allergy-related conditions were conducted in school children in France (Annesi-Maesano et al., 2012), Romania (Neamtiu et al., 2019), Malaysia (Norbäck et al., 2017), Korea (Yon et al., 2019), and China Huang et al. (2017) and in adults in France (Billionnet et al., 2011) and Japan (Matsunaga et al., 2008). These studies provide evidence that formaldehyde exposure around 0.04 mg/m^3 and above is associated with an increased prevalence of rhinitis or rhinoconjunctivitis in children, with relative risks of approximately 1.2 (see Figure 3-8, Table 3-11). Two studies in children did not observe an

[18]Hyperresponsive airways (or hyperresponsiveness) represents a mechanistic event (supported by *robust* evidence) and a potential key feature of respiratory health hazards that is defined to encompass any of a range of relevant airway features, including hyperreactivity (exaggerated response) and hypersensitivity (lower dose to elicit response). See also Appendix C.7.

association with rhinitis at lower exposure levels (0.004–0. 027 mg/m^3) (Norbäck et al., 2017); Huang et al. (2017). The point estimates of the relative risks in two studies of rhinitis in adults covering a higher exposure range were also around 1.2, but these estimates were highly imprecise and so cannot be interpreted as strong support for an association (or for no association) in this older population (Matsunaga et al., 2008; Billionnet et al., 2011) (see Figure 3-8). Annesi-Maesano et al. (2012) examined more than two exposure groups in relation to rhinoconjunctivitis risk in children and observed the highest relative risk in the highest exposure group compared to the referent group, with weaker or no associations seen in the lower exposure categories; no other pollutants (e.g., NO_X, $PM_{2.5}$, acetaldehyde, acrolein, ETS) were associated with rhinoconjunctivitis in this study. Another school-based study reported associations with the prevalence of rhinitis (RR 1.207, 95% CI: 1.02,1.44) and with severity of rhinitis (RR 1.28, 95% CI: 1.07, 1.54) per 0.01 mg/m3 increase in formaldehyde at levels up to 0.066 mg/m^3 (Yon et al., 2019). A stronger association (RR 2.25, 95% CI: 1.01, 5.01) was seen in the only study of eczema in adults at exposures of 0.058 - 0.161 mg/m^3 compared to < 0.058 (midpoint approximately 0.033) mg/m^3 (Matsunaga et al., 2008). Neamtiu et al. observed a 3-fold increased risk (RR 3.23, 95% CI: 1.31, 8.00) for a combination of symptoms relating to eye, nose, and skin in children exposed to formaldehyde (Neamtiu et al., 2019). A relative risk of 1.4 for formaldehyde exposures above approximately 0.035 mg/m^3 and atopy based on skin prick tests was also seen in a study in children (Garrett et al., 1999), but not in the study by Palczynski et al. (1999) (see Table 3-12). Both of these were classified as *medium* confidence with respect to the results in children. The exposure range examined in Garrett et al. (1999) is wider than that in Palczynski et al. (1999), and the exposure measurement protocol (four 1-day samples in different seasons) was an additional strength of the study by Garrett et al. (1999). This study also reported associations between formaldehyde exposure and both wheal size and the number of positive skin prick tests (from a mean of approximately 1.5 in the lowest to 4.0 in the highest category of exposure). A limitation of the skin prick test studies was the uncertainty regarding the congruence between the exposure measure and the exposure during the relevant time window with respect to development of sensitization; EPA considered this to be of particular importance with respect to studies of skin prick tests in adults. In particular, all of the residences in the study by Palczynski et al. (1999) had been built 10 years prior to enrollment in the study, and sensitization may have occurred years before the exposure assessment, possibly when exposure levels were higher. A similar concern was raised for Garrett et al. (1999), as the authors did not report the age of the housing stock for participants and 74% of the children had lived in their homes at least 5 years.

Results from the two occupational studies were mixed (see Table 3-13). Both are considered *low* confidence based primarily on limitations of the outcome ascertainment used in these studies.

Because of the limitations noted above with respect to interpretation of skin prick tests, EPA has higher confidence in the studies of allergy-related conditions. Consistent results were

observed for various symptoms or combinations of symptoms across this set of studies in children at exposures around 0.05 mg/m^3 and above, and in the only study of eczema in adults comprising diverse populations. The pattern of exposure-response seen in the studies with sufficient sample size and range of exposure to examine these patterns suggests that formaldehyde exposure at levels seen in the general population studies can enhance the immune hypersensitivity response to allergens. The studies of allergy-related conditions are summarized in Figure 3-8.

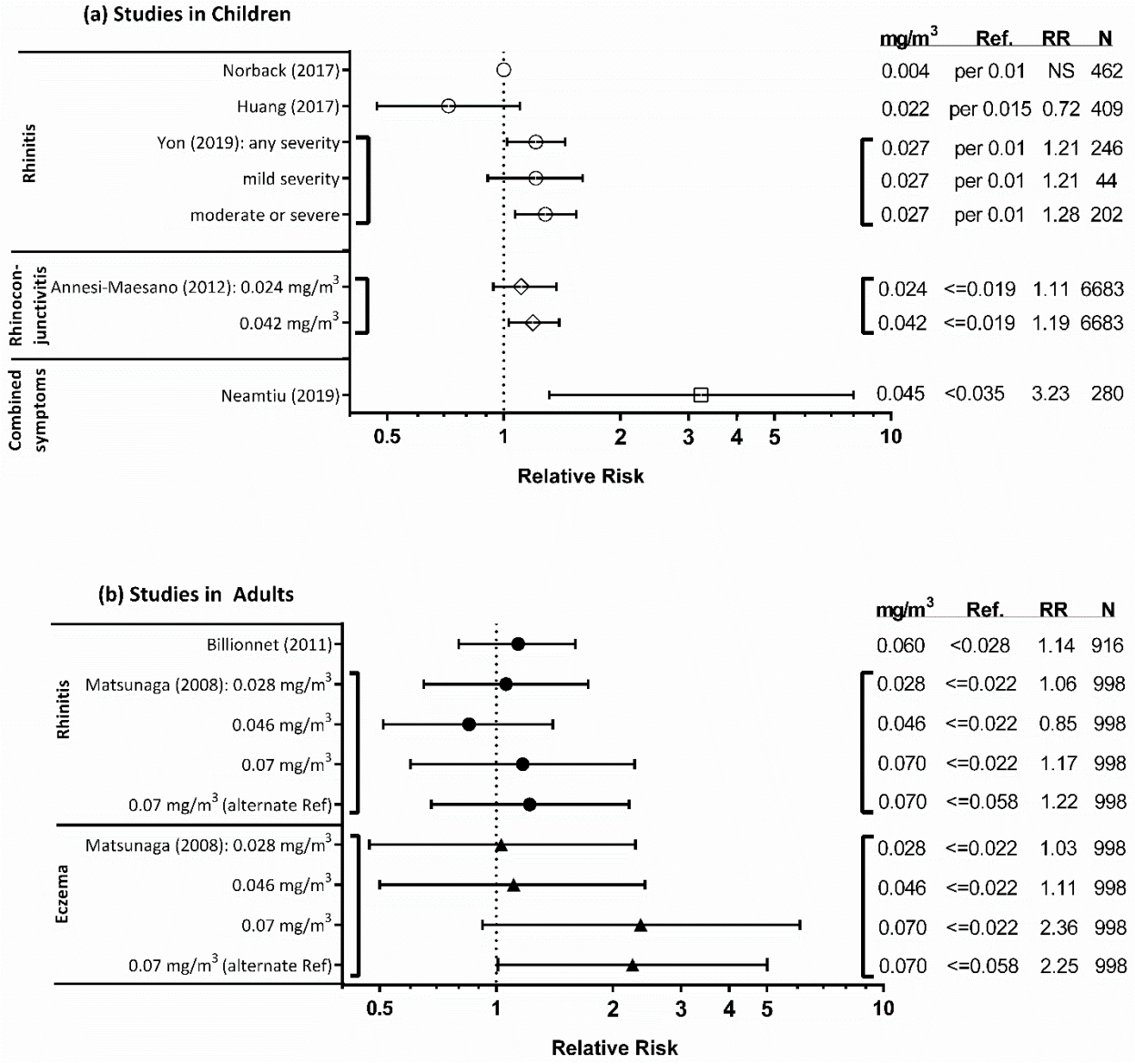


Figure 3-8. Relative risk estimates for prevalence of allergy-related conditions in children and adults in relation to formaldehyde in residential and school settings.

Results are depicted for rhinitis (circles), rhinoconjunctivitis (diamonds), eczema (triangles) and symptom combinations (squares). *High* and *medium* confidence studies are included in the figure. Open symbols are for studies in children (panel a); closed symbols are for studies in adults (panel b). NS = no quantitative results were available; however, Norback et al. (2017) reported no association. Mg/m^3 = for studies using categorical analysis, is approximate midpoint of formaldehyde levels calculated for the group being compared to the referent group. For studies using continuous analysis, different measures were available for the different studies; the 75th percentile was used for Huang et al. 2017; the mean + 1 SD was used for Yon et al. 2019; and the maximum value was used for Norback et al. 2017. Low, mid, and high refer to the relative formaldehyde levels; RR = relative risk. in studies with categorical analysis.

Table 3-11. History of allergy-related conditions in relation to formaldehyde exposure, by age group

Study and design[a]	Results	
	Nasal	**Dermatologic**
Children		
Annesi-Maesano et al. (2012) (France) **Design:** Prevalence study, *n* = 6,683, ages 9−10 years, participation rate 69%. Sampling from 108 schools, all classes of specified grade level per school. **Exposure:** 5-day samples in classrooms. Median (75th percentile) 0.027 (0.034) mg/m^3; maximum 0.055 mg/m^3; *(estimated from Figure 1 in paper).* **Outcome:** Based on ISAAC questionnaire, parent report, sneezing and runny nose, with itchy eyes, without a cold, in past 12 months. **Evaluation[a]:** *High* confidence	**Rhinoconjunctivitis** prevalence 11.8%, OR (95% CI) (adjusted) ≤0.0191 mg/m^3 1.0 (referent) >0.0191−0.0284 1.11 (0.94, 1.37) >0.0284−~0.055 1.19 (1.03, 1.39) *(Confidence intervals estimated from Figure 3 in paper)* Adjusted for age, gender, passive smoking, maternal and paternal history of asthma and allergic diseases.	Not examined
Yon et al. (2019) (Seongnam City, Korea) **Design**: Prevalence study, n = 427 school children recruited from 22 randomly selected classrooms at 11 elementary schools; 68.9% participation rate, ages 10–12 years. **Exposure:** Formaldehyde sampling in each classroom using monitors with pumps during the 1st and 2nd half of the school year. Mean 0.027 ± 0.0077 mg/m^3; as high as 0.06 mg/m^3 in some classrooms. Duration and sampling methods were not described. **Outcome:** Rhinitis definition: presence of characteristic symptoms and /or signs during the previous 12 months using ISAAC questionnaire. Rhinitis severity: low, moderate, severe, using Allergic Rhinitis and Its Impact in Asthma guidelines. **Evaluation:** *Medium* confidence Uncertainty regarding validation of ISAAC in this population; uncertainty regarding exposure measurement period and other protocol details.	**Rhinitis prevalence**: 57.6%, n = 246 OR (95% CI) per 0.010 mg/m^3 1.21 (1.02, 1.44) adjusted for age, sex, environmental tobacco smoke exposure, and physician-diagnosed allergic rhinitis in parents. **Rhinitis severity** Control: n = 181, Reference Mild: n = 44, 1.21 (0.91, 1.60) Moderate/ Severe: n = 202, 1.28 (1.07, 1.54) OR (95% CI) per 0.010 mg/m^3 p_{trend} = 0.011 [Results represented by authors were in units of per 1 µg/m^3 increase; EPA converted these to per 0.01 mg/m^3 increase to facilitate comparison with other studies]	

Study and design[a]	Results	
	Nasal	**Dermatologic**
Neamtiu et al. (2019) (Romania) **Design:** Prevalence study; n = 281 89.7% participation rate. Sampling from five primary schools in one county, 3 classrooms per school. **Exposure:** 5-day samples in each classroom. Median (75th percentile) 0.035 (0.045) mg/m^3, maximum = 0.066 mg/m^3. **Outcome:** Allergy-like symptoms in the past week based on ISAAC questionnaire, as skin conditions (e.g., rash, itch, eczema), eye disorders (e.g., red, dry, swollen, itching, or burning eyes, or sensation of "sand in the eyes," and rhinitis symptoms (e.g., itching nose, sneezes, and/or stuffy or blocked nose. **Evaluation[a]** *Medium* confidence Outcome definition for allergy-like symptoms using ISAAC questionnaire included combined symptoms of rhinitis (nose), eye, and skin conditions (rash, itch, and eczema), which could mask an effect in one of these categories. Skin condition question not specific for eczema.	**Allergy-like symptoms (eyes, nose and skin)** OR (95% CI), above compared to below median (0.035 mg/m^3): 3.23 (1.31, 8.00). Logistic regression model adjusted for age, gender, NO_2, CO, CO_2, temperature, relative humidity, ventilation rate, and tobacco smoke exposure for the past week.	
Norbäck et al. (2017) (Malaysia) **Design**: Prevalence study, n = 462 randomly selected children recruited from 8 randomly selected schools (15 students in each of 4 randomly selected classes per school). 96% participation rate. Mean age 14 years (range 14–16 years), 48% male. **Exposure:** Formaldehyde sampled continuously over 7 days in each classroom using diffusion samplers. Samplers placed 2 meters above floor, methods described. Mean concentrations formaldehyde indoor 0.0042 mg/m^3(SD not reported), max 0.018 mg/m^3, 100% samples above the detection limit. Outside 0.005 mg/m^3, max 0.0060 mg/m^3, 100% samples above the detection limit.	**Rhinitis,** weekly symptoms during previous 3 months. Prevalence 18.8%. No association with formaldehyde in initial model; quantitative results were not reported. Initial stepwise multiple logistic regression model included indoor exposures (CO_2, NO_2, formaldehyde and VOC), personal factors (sex, race, current smoking, atopy, parental asthma/allergy) and home environment factors (ETS, dampness/mold, recent indoor painting), total amount of dust in the classroom and the concentration of endotoxin, and ergosterol in vacuumed dust.	

Study and design[a]	Results	
	Nasal	Dermatologic
Outcome: Rhinitis defined by two questions combined regarding nasal catarrh or nasal congestion in standardized questionnaire. Cases defined by reporting symptoms weekly over a 3-month period. **Evaluation[a]:** *Medium* confidence Results for rhinitis were reported as "not statistically significant" without providing quantitative effect estimates. Very low indoor formaldehyde concentrations.		
Huang et al. (2017) (Shanghai, China) **Design:** Case-control study, n = 409 children, aged 5–10 years, who were participants in a previous cross-sectional study (2011–2012) selected from 88 kindergartens located in 6 Shanghai districts. Eligible children lived in homes not renovated in prior two years and agreed to home inspection during March 2013-December 2014. **Exposure**: Formaldehyde sampling in child's bedroom, 24 hours, in breathing zone (detection range: 0.012-0.08 mg/m^3). Mean (± SD) concentration (mg/m^3), 24-hr 0.0215 ± 0.0130; 75th percentile 0.0275 mg/m^3 Range 0.006–0.060 mg/m^3, 3 homes above. **Outcome:** Rhinitis and eczema in past 12 months using selected questions from translated ISAAC questionnaire. **Evaluation[a]**: **Rhinitis:** *Medium* confidence Participation rate unclear, and potentially differential with respect to exposure and disease status. **Eczema:** *Low* confidence See above, and uncertainty regarding validation of truncated version of ISAAC questionnaire for eczema in this population.	**Current rhinitis** 41.4% OR (95% CI) per IQR (0.0152 mg/m^3) 0.72 (0.47, 1.10). Logistic regression adjusted for age, sex, family history of atopy, family annual income, household (ETS), early and current household dampness-related exposures, early antibiotics exposure, early home decoration, and the inspection season. **Current eczema 13**.4% OR (95% CI) per IQR (15.2 µg/m^3) 0.75 (0.41, 1.39).	

Study and design[a]	Results	
	Nasal	**Dermatologic**
Isa et al. (2020) (Malaysia) **Design:** Prevalence study; n = 470, participation rate not reported. 8 randomly selected schools (4 urban, 4 suburban), randomly selected students from 4 classes (Form two, aged 14 years) during August-November 2018 & February 2019. **Exposure:** One-hour samples in four classes during class session. Median (IQR) Urban: 0.0132 (0.0093) mg/m^3, Suburban: 0.0031 (0.0052) mg/m^3 (reported as mg/m^3 but likely µg/m^3). **Outcome:** Allergy information and symptoms within defined period using ECRHS and ISAAC questionnaires. Allergic symptoms in last 12 months: rhinitis, skin allergy. **Evaluation:** Low confidence Uncertainty in exposure concentrations and distribution given short sampling duration; very low concentrations in half the schools.	**Rhinitis** in last 12 months 55.5% OR (95% CI) per 10 units formaldehyde (reported as mg/m^3 but likely µg/m^3). 1.10 (1.03, 1.17) Adjusted for atopy, parental asthma/allergy, and NO_2.	**Skin allergy** in last 12 months 14.5% OR (95% CI) per 10 units formaldehyde (reported as mg/m^3 but likely µg/m^3). 2.41 (0.96, 6.07) Adjusted for atopy, sex, doctor's diagnosed asthma, parental asthma/ allergy and urban/suburban location; not modeled further because this result was considered not statistically significant, Stronger association seen with NO_2 and PM_{10} but no model presented with formaldehyde and these other exposures.
Hsu et al. (2012) (Taiwan) **Design:** Case-control study, *n* = 48 allergic rhinitis cases, 36 eczema cases 42 controls, recruited through kindergartens and day care centers, ages 3−9 years at enrollment. Participation rate (clinic exam and home measures) approximately 5% of potential cases and controls (but differential at various steps). **Exposure:** 2-hour household sample (probably bedroom; converted from ppb) Median (25th, 75th percentile): Controls 0.017 (0.005, 0.030) mg/m^3 **Outcome:** Initial screening through parent report of history (ages 2−6) with confirmation (1−3 years later) by clinical examination. **Evaluation[a]:** *Low* confidence Low and differential (at various steps) participation rate. Short exposure sampling period and no information on protocol.	**Allergic rhinitis** Formaldehyde concentrations lower in cases than in controls: (*n*) Median (25th, 75th percentile) mg/m^3 Controls (42) 0.017 (0.005, 0.030) Allergic rhinitis (48) 0.005 (0.005, 0.020) (p = 0.02) Mann-Whitney nonparametric test	**Eczema** Formaldehyde concentrations lower in cases than in controls: (*n*) Median (25th, 75th percentile) mg/m^3 Controls (42) 0.017 (0.005, 0.030) Eczema (36) 0.006 (0.005, 0.018) (p = 0.07) Mann-Whitney nonparametric test

Study and design[a]	Results	
	Nasal	**Dermatologic**
Choi et al. (2009) (Korea) **Design:** Case-control study, *n* = 50 atopic dermatitis cases, 28 controls, recruited through university outpatient clinic; recruitment procedures not described. Mean age (SD) 15.4 years (3.4) and 16.2 years (4.1) in atopic dermatitis cases and controls, respectively. Housing age and type: cases 58% <3 years old and 72% apartments; controls 29% <3 years old and 50% apartments. Location: 44 and 21% near road for cases and controls, respectively. **Exposure:** Household sample (sampling period not reported, but closed windows and use of duplicates). Geometric mean, 25th, and 75th percentiles in controls: 0.043 (0.024, 0.115) mg/m^3. 92% above LOD. **Outcome:** Atopic dermatitis based on medical history, skin prick test and IgE (criteria not provided). **Evaluation[a]:** *Low* confidence Selection and recruitment process not reported; sampling period not reported and specific criteria for case definition not reported; potential confounders not addressed (age and type of housing and location differed between cases and controls, as measure of socioeconomic status). Limited analysis.	Not examined	**Formaldehyde levels (mg/m^3):** Cases: Geometric mean 0.100; 75th percentile 0.220 Controls: Geometric mean 0.043; 75th percentile 0.115 $p < 0.01$
Smedje and Norback (2001) (Sweden) **Design:** Prospective (incidence) nested case-control study, children, 1,258 without asthma at baseline, 88 incident cases of pollen allergy and 50 incident cases of pet allergy in 4-year follow-up; 78% participation in follow-up, mean age 10.3 years at baseline. School-based sample; 1st, 4th, and 7th grades. **Exposure:** Two 4-hour samples in 2–5 classrooms per school; measured in 1993 (*n* = 98) and 1995 (*n* = 101). mean 0.008 mg/m^3, geometric mean 0.004 mg/m^3 (min, max) (<0.005, 0.072) mg/m^3, 54% of 1993 samples	**Allergies** (incidence) RR (95% CI) per 0.010 mg/m^3, Pollen allergy: 1.3 (0.95, 1.7) Pet allergy: 1.1 (0.7, 1.7) Adjusted for sex, age, history of atopy, smoking.	Not examined

Study and design[a]	Results	
	Nasal	**Dermatologic**
and 24% of 1995 samples below detection limit (0.005 mg/m^3); median among those above detection limit = 0.010 mg/m^3. Individual student values based on average of 1993 and 1995 classrooms (<0.005 to 0.042 mg/m^3). **Outcome:** Parent report, hay fever/pollen allergy or pet dander allergy. **Evaluation[a]:** *Low* confidence Exposure measures in only 2 of the 4 years and 2/3 of the students left the school more than a year before follow-up; uncertainty about distribution; relatively high percentage <LOD. Confounding by other exposures not fully addressed but pattern of results differed among the exposures examined. **Related References:** Smedje et al. (1997).		
Adults		
Billionnet et al. (2011) (France) **Design:** Prevalence study, *n* = 916 adults from 490 dwellings (drawn from nationally representative sample; 13.6% participation rate), median age 44 (15–89); 48% men. **Exposure:** 1-week sample in bedroom Median, 75th percentile (minimum, maximum) 0.0194, 0.028 (0.013, 0.0863) mg/m^3. **Outcome:** ISAAC questionnaire; wheezing, running or blocked nose without cold or respiratory infection, in past 12 months. **Evaluation[a]:** *Medium* confidence Low participation rate but potential for differential participation (by formaldehyde exposure and disease status) uncertain.	**Rhinitis** prevalence 38.3% OR (95% CI), above vs. below 75th percentile: 0.028 to 0.0863 vs. <0.028 mg/m^3 1.14 (0.8, 1.6) Adjusted for age, gender, smoking, education, relative humidity, time of survey, pets, mold, outdoor pollution measures.	Not examined
Matsunaga et al. (2008) (Osaka, Japan) **Design:** Prevalence study. Adults, *n* = 998 women, median 17th week of pregnancy, median age ~30. Recruited through obstetric clinics and public health nurses.	**Allergic rhinitis** (14.0% prevalence) mg/m^3 — *n* — OR — (95% CI) <0.022 — 298 — 1.0 — (referent) 0.022–0.033 — 299 — 1.06 — (0.65, 1.73) 0.034–0.057 — 301 — 0.85 — (0.51, 1.40) 0.058– — 100 — 1.17 — (0.60, 2.28)	**Atopic eczema** (5.7% prevalence) mg/m^3 — *n* — OR — (95% CI) <0.022 — 298 — 1.0 — (referent) 0.022–0.033 — 299 — 1.03 — (0.47, 2.29) 0.034–0.057 — 301 — 1.11 — (0.50, 2.42) 0.058–0.161 — 100 — 2.36 — (0.92, 6.09) (trend *p*-value) — (0.08)

Study and design[a]	Results	
	Nasal	**Dermatologic**
Participation rate 17% of pregnant women in the area. **Exposure:** 24-hour personal sample (converted from ppb). Median 0.030, maximum 0.161 mg/m^3. Cutpoints based on 30th, 60th, and 90th percentiles (<0.022, 0.022–0.033, 0.034–0.57, and ≥0.058 mg/m^3). **Outcome:** Self-report, treatment for allergic rhinitis or atopic eczema in past 12 months. **Evaluation[a]:** *Medium* confidence Low participation rate but potential for differential participation (by formaldehyde exposure and disease status) uncertain. Some uncertainty pertaining to sensitivity and specificity of outcome assessment.	0.161 (trend *p*-value) (0.91) 0.058–0.161 vs. <0.058 1.22 (0.68, 2.20) Adjusted for age, gestation, parity, family history (of asthma, atopic eczema, allergic rhinitis), smoking status, current passive smoking at home and work, mold in kitchen, indoor domestic pets, dust mite antigen level, family income, education, and season. (Midpoint of highest quartile estimated as 0.07 mg/m^3 based on personal communication (Matsunaga, 2012))	0.058–0.161 vs. <0.058 2.25 (1.01, 5.01) per 0.0123 mg/m^3 1.16 (0.99, 1.35) Adjusted for same factors as allergic rhinitis analysis. Additional analyses examined effect modification by family history of asthma, atopic eczema, or allergic rhinitis, see Figure 3-11 in this report. (Midpoint of highest quartile estimated as 0.07 mg/m^3 based on personal communication (Matsunaga, 2012)).

Within each age group, organized by study confidence, then descending publication year. Results for *low* confidence studies are shaded gray.

Abbreviations: ISAAC = International study of Asthma and Allergies in Children; ECRHS = European Community Respiratory Health Survey.

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.4).

Table 3-12. Skin prick tests in relation to formaldehyde exposure, by age group

Study and design	Results
Children	
Garrett et al. (1999) (Australia) **Design:** Prevalence study, *n* = 145 (57 asthma cases, 88 controls; combined for this analysis; some cases and controls from same household; three excluded for total *n* = 145), ages 7–14 (mean 10.2) years. **Exposure:** 4-day (one per season) measures in home (bedroom, living room, kitchens, outdoors). 74% of the children had lived in the house for at least 5 years; 34% for entire life. Median (maximum) 0.0158 (0.139) mg/m^3. **Outcome:** Atopy based on skin prick tests to 12 allergens (cat, dog, grass mix #7, Bermuda grass, house dust, two dust mite, five fungi). **Evaluation[a]:** *Medium* confidence (↓) Uncertainty about effect of recruitment process and ability to fully address household correlation of cases and controls; could result in attenuated effect estimate.	**Atopy** prevalence: 88/145 = 0.61 Exposure (mg/m^3) — *N* — Proportion with atopy <0.020 — 30 — 0.33 0.020–0.050 — 75 — 0.64 > 0.050–0.139 — 40 — 0.75 (trend *p*-value) — (<0.001) per 0.020 mg/m^3 increase OR 1.42 (0.99, 2.04) Odds ratio, adjusted for parental asthma history, sex; other factors examined (passive smoke, pets, indoor NO_2, fungal spores, house dust mite allergens). (Similar trend seen based on bedroom measure: prevalence 0.50, 0.59, 0.74, trend *p* = 0.06.) Exposure (mg/m^3) — *N* — Number of allergens[a] — Wheal size[a] <0.020 — 30 — 1.3 — 0.5 0.020–0.050 — 75 — 3.4 — 1.0 > 0.050–0.139 — 40 — 3.9 — 1.3 (trend *p*-value) — (0.004) — (0.002) [a]Estimated from Figure 1 (Garrett et al., 1999)
Children and adults (stratified)	
Palczynski et al. (1999) (Poland) **Design:** Prevalence study, *n* = 278 adults ages 16–65 years; *n* = 186 children ages 5–16 years from 120 households with children (random selection from 10-year-old apartment houses). Participation rate not reported. **Exposure:** 24-hour household sample (area not specified) Mean (±SD) (minimum, maximum) 0.026 (±0.011) (0.002, 0.067) mg/m^3; 2% >0.050. **Outcome:** Allergy based on skin prick tests (SPT) to allergens (dust, dust mites, feathers, grasses) **Evaluation[a]** **Children:** *Medium* confidence Not informative above 0.050 mg/m^3 because of sample size (≤5). **Adults:** *Low* confidence Uncertainty about time window of exposure measurement for skin prick test results (greater uncertainty in adults than in children). Not informative above 0.050 mg/m^3 because of sample size (≤5).	Positive Skin Prick Test (%) — (*n*) — IgE (>100 kU/L) (%) Children <0.025 mg/m^3 — (101) — 34.7 — 37.6 0.025–0.050 — (82) — 28.0 — 32.9 0.051–0.067 — (4) — 25.0 — 25.0 Adults <0.025 mg/m^3 — (142) — 29.6 — 26.1 0.025–0.050 — (131) — 28.2 — 25.6 0.051–0.067 — (5) — 60.3 — 40.0 Additional analyses demonstrated effect modification by environmental tobacco smoke, see Table 3-20 in this report.

Results classified as *low* confidence are shaded gray.

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.4). Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Table 3-13. Allergy symptoms or skin prick tests in relation to formaldehyde exposure in workers

Study and design	Results
Allergy symptoms	
Fransman et al. (2003) (New Zealand) **Design:** Prevalence study. Plywood mill workers, *n* = 112. Participation rate 66%. Mean age 34.5 years, 71% men, mean duration 4.7 years. **Exposure:** Personal samples (15-minute samples) in jobs held by 49 workers: (*n*), geometric mean (±geometric standard deviation) (mg/m^3). all (22) 0.080 (3.0) dryers (14) 0.070 (3.2) (one outlier) pressing (5) 0.160 (2.7) other areas 0.030–0.040 mg/m^3 (at or near detection limit) Total inhalable dust (full-shift personal samples): geometric mean 0.7 mg/m^3. **Outcome:** Self-report, allergy symptoms based on sensitivity to house dust, food, animals, or grasses/plants. **Evaluation[a]:** *Low* confidence Uncertain impact of outcome classification (inclusion of food allergies) and uncertainty regarding details of analysis. Selection out of the exposed work force of "affecteds" possible in this type of prevalence study. "Low" exposure group exposed to levels of formaldehyde up to 0.080 mg/m^3.	**Allergy symptoms** prevalence Low (<0.080 mg/m^3, *n* = 38) 31.6% High (>0.080 mg/m^3; *n* = 11) 45.5% OR (95% CI) (>0.080 vs. <0080 mg/m^3): 2.4 (0.5, 11.8) Adjusted for age, sex, ethnicity, smoking. Internal comparison by exposure category limited to the 49 workers with same job titles as those with the 22 air sample measurements. Dust not related to high formaldehyde exposure. Not clear if these specific symptoms were or were not related to other exposures (e.g., endotoxin).
Skin prick tests	
Herbert et al. (1994) (Canada) **Design:** Prevalence study. Oriented strand board manufacturing (*n* = 99). Comparison group (*n* = 165) oil field workers, not exposed to gas or vapors. Participation rate 98% in workers, 82% in comparison group. Mean age ~35 years in both groups. **Exposure:** 21 hours continuous area sampling, 2 consecutive days Saw line, debarking: 0.090–0.160 mg/m^3 Postheat, press conveyor, packaging, storage: 0.200–0.290 mg/m^3 Preheat conveyor: 0. 330 mg/m^3 Total dust: mean 0.27 mg/m^3, median aerodynamic equivalent diameter = 2.5 µm. **Outcome:** Atopy based on skin prick test to six allergens (wheat, rye, *Alternaria*, cat, house dust, birch; four of these are common allergens in this area). **Evaluation[a]:** *Low* confidence Selection out of the exposed work force of "affecteds" possible in this type of prevalence study. Uncertainty about exposures in referent group. Uncertainty about time window of exposure measurement with respect to skin prick test results in adults	**Atopy** prevalence not reported OR (95% CI) 0.75 (0.40, 1.35) Dust exposure considered low; not included in analysis.

Results classified as *low* confidence are shaded gray.

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.4). Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Asthma

Asthma affects approximately 5–10% of the U.S. population, and results in a significant individual and societal burden in terms of morbidity, health care costs, and indirect costs [e.g., due to absences from work (Shenolikar et al., 2011; Bahadori et al., 2009)]. The potential for formaldehyde to induce or exacerbate asthma symptoms has been described in occupational settings in reports spanning several decades (see for example, (Popa et al., 1969; Nordman et al.,

1985)). Characterization of this risk on a population level requires more extensive evaluation. Epidemiological studies have investigated potential associations between formaldehyde and asthma in children and adults using formaldehyde measurements conducted in occupational, residential, and school-based settings. The outcomes studied include the incidence of asthma (i.e., the number of people newly diagnosed with asthma in a period of time), [19] prevalence of current asthma (typically ascertained through a set of questions pertaining to symptoms or medication use over a period of time, e.g., past 12 months), and asthma control (typically ascertained through a larger set of symptoms, medication, and medical care use over a shorter period of time, e.g., 2–4 weeks). Asthma control pertains to the extent to which symptoms can be reduced or eliminated with medication. The prevalence of current asthma includes newly diagnosed patients, as well as previously diagnosed patients who are experiencing the expression (and thus the costs and burden) of this condition. EPA considered "ever had asthma" to be of limited use in this review, as the formaldehyde measures available do not reflect cumulative exposures that could be related to cumulative risk, and thus EPA did not include results using the definition, "ever had asthma." However, there were a small number of studies where asthma was not defined clearly but study details appeared to indicate that the definition was not "ever had asthma"; these were included but the limitation was noted. Altered lung function in people with asthma, examined in acute controlled exposure studies, is also discussed in this section, although these acute, high exposure scenarios are of less direct relevance to the question of risks of chronic exposures.

Asthma prevalence studies

The collection of studies evaluated associations between formaldehyde exposure and prevalence of current asthma, as determined by symptoms or medication use in the past 12 months. Based on advice from the expert panel consulted by the EPA, this type of questionnaire-based outcome classification used in a cross-sectional design was considered to be an appropriate choice for studies of exposures that could affect the occurrence of asthma episodes. The five *medium* or *high* confidence studies in homes or schools with relatively low exposures (<0.05 mg/m^3, most from approximately 0.02 to 0.04 mg/m^3) reported relative risks around 1.0 (ranging from 0.72 to 1.14; see Tables 3-14 and 3-15, Figure 3-9). This set of studies included a variety of designs and populations; the school-based studies are large (from 1,014 to 6,683 total participants). The case definition of wheezing during the past year used by Venn et al. (2003) is interpreted to be relevant to a definition of current asthma as used in this assessment since 88% of the cases also reported using a reliever inhaler in the past year.

19 Only one incidence study was found in the literature search (Smedje and Norback, 2001); this study was classified as a *low* confidence study because only two formaldehyde measures were taken over the four-year period, and 2/3 of the students left the school before the follow-up evaluation which added to the uncertainty in the relevance of the exposure measure. The evidence from this study was not considered in the synthesis; the study details are presented in Table 3-14 and characterized as a *low* confidence study.

Seven *medium* confidence general population studies in children or adults where a proportion of the study sample had exposures of 0.05–0.1 mg/m^3 (e.g., the 75th percentile was > 0.05 mg/m^3) were available (see Tables 3-14 and 3-15; Figure 3-9). A hospital-based case-control study of children (mean age 10 years) examined prevalent asthma using the ISAAC questionnaire followed by spirometry results (an FEV_1 increase of 15% in response to β-agonist inhalation) (Liu et al., 2018). The authors reported an association with formaldehyde levels based on a regression analysis using quartiles of formaldehyde concentration (OR = 2.736, 95% CI: 1.098, 5.516). Exposure levels in the highest quartile ranged from 0.05 to 0.14 mg/m^3. In a school-based study in Romania, an OR of 2.7 (95% CI: 1.04, 6.97) was seen for asthma symptoms occurring in the past week, a less sensitive and specific outcome compared to "current asthma," comparing children exposed to formaldehyde at levels of 0.035 to 0.066 mg/m^3 to the referent group of < 0.035 mg/m^3 (Neamtiu et al., 2019). Results from a school-based study in Portugal reported an OR of 1.19 (95% CI: 0.60, 2.39) for formaldehyde levels above versus below the median (0.0225 mg/m^3); the 75th percentile in that study was 0.0646 mg/m^3 (Branco et al., 2020). Two other studies with relatively high exposures included both children and adults (Zhai et al., 2013; Krzyzanowski et al., 1990), and each provides evidence of a greater susceptibility in children. Both studies compared effects in groups exposed to levels approximately 0.08 mg/m^3 or above to lower exposed groups; a limitation of the Krzyzanowski et al. (1990) analysis is the relatively small number in the highest exposure group (n = 21), possibly contributing to the imprecision of the effect estimate for that group. Two other *medium* confidence studies with exposures above 0.05 mg/m^3 were conducted only in adults (Matsunaga et al., 2008; Billionnet et al., 2011). Billionnet et al. (2011) compared the asthma outcome for subjects exposed to exposures greater than the 75th percentile of 0.028 mg/m^3 to those exposed to less than the 75th percentile. While most of the study population was exposed to lower concentrations, a portion were exposed to concentrations as high as 0.09 mg/m^3, which likely influenced the observed RR of 1.4. In the study by Matsunaga et al. (2008) the point estimates were below 1.0 for exposure groups < 0.050 mg/m^3 but was 2.65 in the highest exposure group (0.058 to 0.161 mg/m^3); however, the confidence intervals around each of the estimates indicated some imprecision in these estimates (see Figure 3-9).

Epidemiological studies in occupational settings examining the incidence of asthma in a cohort of individuals after they initially enter a workplace have not been conducted. The available studies generally did not attempt to examine the timing of symptoms in relation to when the subjects are present in the workplace (i.e., over the course of a workday or comparison between workdays and weekend days) and so would not have the level of detail that would be included in a clinical workup of occupational asthma; rather, these studies can be thought of as studies of the prevalence of current asthma among workers exposed to formaldehyde. The occupational exposure literature included three *medium* confidence studies of plywood and other layered wood manufacturing workers in Canada (Herbert et al., 1994), New Zealand (Fransman et al., 2003), and Indonesia (Malaka and Kodama, 1990); each of these studies included between 93 and 112 exposed

workers (see Table 3-16). Exposure levels varied by work area, but generally ranged from 0.10 to >0.50 mg/m^3. A greater than three-fold increased risk of asthma was seen in each of these studies. One of the wood worker studies addressed potential confounding by dust exposure by the inclusion of this variable in the analysis (Malaka and Kodama, 1990), and another study specifically noted that the measured dust levels were not related to high formaldehyde exposure and that the asthma symptoms were not strongly related to other exposures including endotoxin measures (Fransman et al., 2003); these factors provide support for the idea that the associations seen with formaldehyde are not due to confounding by other work-site exposures The results from these studies may represent underestimates of risk; two factors contribute to this concern. All of the studies were prevalence surveys of workers who have remained in a workplace for some time (e.g., 2 or more years), which could be biased by the loss of affected individuals from the workforce (e.g., because of the "healthy worker effect" inherent in this type of study design). In addition, in two of the studies, the comparison group included workers who may have also been exposed to formaldehyde or other respiratory irritants (Herbert et al., 1994; Fransman et al., 2003). Inclusion of this type of exposure in the comparison group reduces the possibility that the observed associations were influenced by differential reporting of asthma among the exposed but raises the possibility that the relative risk estimated against this comparison group underestimates the risk that would be represented by a comparison with a population that does not have these other exposures. Another limitation to note is that the sensitivity and specificity of the symptom-based questionnaire measures may be lower in occupational settings than in general population studies; EPA did not find validation data specific to these types of wood manufacturing settings. However, given the strength of the relative risks, the consistency of the associations seen in the three different workplaces and populations, and the likelihood that the observed associations were underestimates of the true associations, these studies collectively support a strong association between formaldehyde concentrations above approximately 0.100 mg/m^3 in occupational settings and increased prevalence of current asthma (see Figure 3-9C).

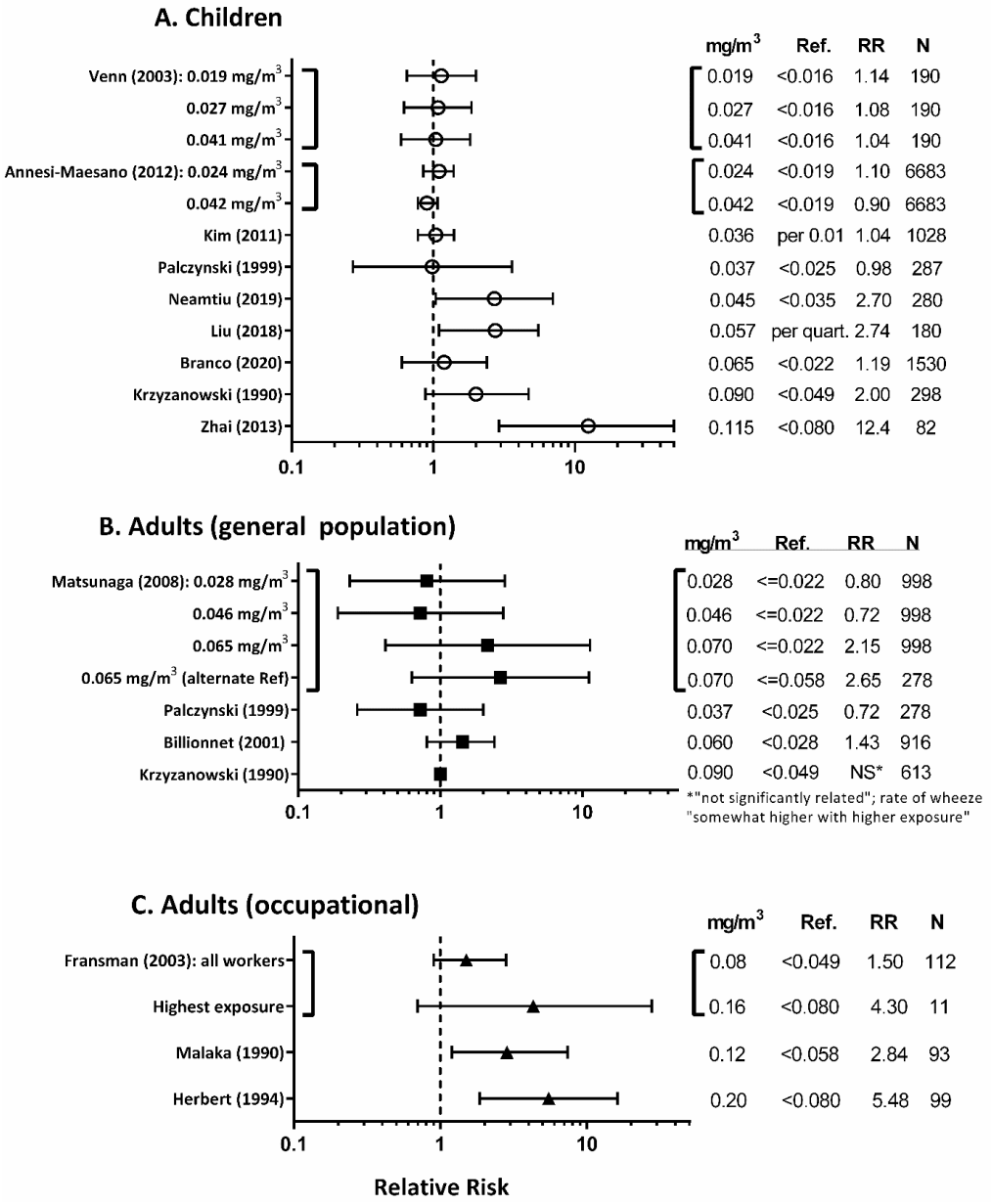


Figure 3-9. Relative risk estimates for prevalence of asthma in children and adults in relation to formaldehyde by exposure level in general population and occupational studies.

Study details are described in Tables 3-14 (Panel A), 3-15 (Panel B), and 3-16 (Panel C). Data in children = unfilled symbols; data in adults = filled symbols. Panels represent lower level exposure (circles) and higher level exposure (squares) in general population settings (Panels A and B, respectively); as well as exposure in occupational settings (diamonds, Panel C). *High* and *medium* confidence studies are included in the figures. Levels for most of the participants in the study groups in Panel A, low exposure, were < 0.05 mg/m3. Exposure levels in Billionnet et al. (2011) ranged to a maximum of 0.09 mg/m^3, which resulted in classifying the study as high exposure. Effect estimates are RR or OR. Regarding "mg/m^3": for studies which used categorical analysis, mg/m^3 is midpoint, calculated for the group being compared to the referent group; the mean + 1 SD is used for the continuous analysis conducted by Kim et al. 2011; the 75th percentile was used for the 4-quartile analysis in Liu et al (2018).

Table 3-14. Prevalence of asthma in children in relation to residential or school formaldehyde exposure in studies

Study and design[a]	Results
***High* Confidence Studies**	
Annesi-Maesano et al. (2012) (France) **Design:** Prevalence study; *n* = 6,683, ages 9–10 years, participation rate 69%. Sampling from 108 schools, all classes of specified grade level per school. **Exposure:** 5-day samples in classrooms. Median (75th percentile) 0.027 (0.034) mg/m^3; maximum 0.055 mg/m^3 (estimated from Figure 1 in paper). **Outcome:** Asthma based on ISAAC questionnaire; wheezing or whistling in chest at nighttime; taken asthma treatment in past year. **Evaluation[a]:** *High* confidence	Prevalence 6.9%, OR (95% CI) ≤0.0191 mg/m^3 1.0 (referent) >0.0191–0.0284 1.10 (0.85, 1.39) >0.0284–~0.055 0.90 (0.78, 1.07) (Confidence intervals estimated from Figure 4 in paper.) Adjusted for age, gender, passive smoking, and paternal or maternal history of asthma or allergic disease. Additional analyses examined effect modification by atopy status, see Figure 3-11 in this report.
Kim et al. (2011) (Korea) **Design:** Prevalence study; *n* = 1,028, mean age 10 years, participation rate 96%. Sampling from 12 schools, 2–3 classes per school. **Exposure:** 7-day samples in classrooms (*n* = 34) and one outdoor area per school (*n* = 12) (all samples collected in same season). Mean (±SD), (minimum, maximum) 0.028 (±0.0083) (0.016, 0.047) mg/m^3. **Outcome:** Asthma based on current use of asthma medication or asthma attack in past 12 months. **Evaluation[a]:** *High* confidence	Prevalence of asthma: 6.9% OR (95% CI), per 0.010 mg/m^3: Asthma, current 1.04 (0.78, 1.40). Adjusted for age, sex, self-reported pet or pollen allergy, environmental tobacco smoke at home, other home environment (indoor dampness, remodeling, changing floor, age of home).
***Medium* Confidence Studies**	
Branco et al. (2020) (Portugal) **Design:** Prevalence study: School children, n=648 preschoolers (3-5 years) and n=882 primary school children (6-10 years) randomly recruited from urban and rural nursery (n=17) and primary schools (n=8), participation rate 39%. **Exposure**: Daily exposure based on time-averaged air concentration and reported time in specific school locations. Continuous monitoring in each room (24 h to 9 days). Mean formaldehyde concentration (SD): 0.035 (0.043) mg/m^3; median, 75th percentile: 0.0225, 0.0646 mg/m^3 [data provided in email from author to Dr. Glinda Cooper (Branco et al., 2020)]. **Outcome**: Asthma diagnosis by study physicians based on either reported symptoms using ISAAC questionnaire or a report of ever having 1 or more symptoms plus spirometry before and after bronchodilator (ERS/ATS and Global Initiative for Asthma guidelines). **Evaluation[a]:** **Dichotomized analysis:**	Asthma prevalence: 5.5% [*Medium* confidence] OR (95% CI) above compared to below the median: 1.19 (0.60, 2.39) [*Low* confidence] OR (95% CI) per IQR increase in exposure: 0.666 (0.37, 1.21). Logistic regression models adjusted for site (urban, rural), study phase, sex, age group, BMI and parental history of asthma. Also controlled for surrogates of home indoor exposure including mother's education, living with smoker. Other covariates for contact with farm animals during 1st year of life, pets at home in previous year &/or 1st year of life.

Study and design[a]	Results
Medium confidence Low participation rate, but potential for differential participation (by formaldehyde exposure and disease status) uncertain. **Continuous variable analysis:** *Low* confidence Uncertainty regarding interpretation of linear regression given the bimodal distribution of formaldehyde. Uncertainty regarding interpretation of analysis as a continuous variable because of bimodal distribution.	
Neamtiu et al. (2019) (Romania) **Design:** Prevalence study; n = 280 children, 89.7% participation rate Sampling from five primary schools in one county, 3 classrooms per school. **Exposure:** 5-day samples in each classroom. Median (75th percentile) 0.035 (0.045) mg/m^3, maximum = 0.066 mg/m^3. **Outcome:** Asthma-like symptoms based on ISAAC questionnaire, asthma-like symptoms defined as difficult breathing, dry cough and wheezing in the past week (any symptom). **Evaluation[a]** *Medium* confidence Outcome definition (asthma-like symptoms) is limited to past week.	**Asthma-like symptoms** (prevalence not reported) OR (95% CI), above compared to below median (0.035 mg/m^3): 2.7 (1.04, 6.97) Logistic regression model adjusted for age, gender, NO_2, CO, CO_2, temperature, relative humidity, ventilation rate, and tobacco smoke exposure for the past week.
Liu et al. (2018) (China) Hospital based case-control study. *n* = 180 cases, 180 controls, mean age 10 years, sex, and age comparable. Participation rate not reported. **Exposure:** Two-month samples in living room and bedroom. NO_2 and PM also measured. Household: median (range), 75th percentile Cases 0.0384 (0.012–0.142), 0.057 mg/m^3 Control 0.0251 (0.012–0.094), 0.046 mg/m^3 **Outcome:** Asthma diagnosis via ISAAC questionnaire (2 or more incidents of cough, wheezing, and dyspnea for 3 or more consecutive days). Plus, FEV_1 increased by >15% after β-agonist inhalation and persistent asthma was stable for 3 or more months prior to study. **Evaluation[a]:** *Medium* confidence Uncertainty regarding interpretation of formaldehyde as a single variable representing 4 quartiles.	**Current asthma** OR (95% CI), formaldehyde by quartile 2.736 (1.098, 5.516) Regression models adjusted for history of allergy, breastfeeding, ETS and $PM_{2.5}$ Association of lower magnitude (0R = 2.029) also was reported for $PM_{2.5}$ Note: the units for the odds ratio were not provided, but authors stated that quartiles of concentration were included in the model.
Zhai et al. (2013) (China) **Design:** Prevalence study**;** 186 homes from a household survey, with random selection of participants within households; 82 children. **Exposure:** Samples in three rooms per house (bedroom, living room, kitchen); sampling time not specified.	Prevalence by exposure category: *n* (%) <0.08 mg/m^3 62 3.22 0.08–0.15 mg/m^3 20 40.0 RR 12.4 (2.9, 53.7) [calculated by EPA]

Study and design[a]	Results
64% of the 186 houses, and 24% of the 82 houses with children were >0.08 mg/m^3 ("polluted"). Mean formaldehyde levels in the 3 locations 0.09-0.13 mg/m^3 in the ""polluted" homes and 0.04-0.047 in the "unpolluted" homes **Outcome:** (American Thoracic Society questionnaire (physician diagnosed) Ferris (1978). **Evaluation[a]:** *Medium* confidence Uncertainty regarding exposure measurement period and validation of case ascertainment in this population. Although potential confounders were not considered in asthma-only analysis, given the magnitude of the results, the formaldehyde association is unlikely to be explained only by confounders.	
Venn et al. (2003) (United Kingdom) **Design:** Nested case-control study; *n* = 193 persistent wheeze cases, 214 controls, ages 9–11 years. Participation rate: 54% response to 1998 follow-up of 1995-1996 study; of identified cases and controls, participation was 79% among cases, 59% among controls. **Exposure:** 3-day samples in bedroom; median ~0.022 mg/m^3; 75th percentile 0.032 mg/m^3; median in top quartile 0.041 mg/m^3. **Outcome:** Parent report, wheeze in past year (reported for both of two periods, 1995–1996 and 1998), validated by medical records for 115 cases and 164 controls. **Evaluation[a]:** *Medium* confidence Uncertainty regarding impact of loss of subjects between 1995 and 1998.	(*n* cases), OR (95% CI): <0.016 mg/m^3 (49) 1.0 (referent) 0.0161–0.022 (46) 1.14 (0.65, 2.00) 0.0221–0.032 (51) 1.08 (0.62, 1.86) 0.0321–0.123 (44) 1.04 (0.59, 1.82) (trend *p* = 0.93) Adjusted for age, sex, socioeconomic status. Venn et al. (2003) did not find that evidence of an adverse effect of NO_2 or VOCs other than formaldehyde on children's respiratory health. Similar results in group with validation of case status from prescription asthma medication records. (Median in top quartile provided in email from Dr. Venn, March 29, 2012.)
Palczynski et al. (1999) (Poland) **Design:** Prevalence study; *n* = 187, ages 5–15 years from 120 households with children (random selection, 10-year old apartments). Participation rate not reported. **Exposure:** 24-hour household sample (area not specified). Mean (±SD) (minimum, maximum) 0.026 (±0.011) (0.002, 0.067) mg/m^3 2% >0.050 mg/m^3 **Outcome:** Bronchial asthma diagnosed using American Thoracic Society criteria. **Evaluation[a]:** *Medium* confidence Uncertainty regarding asthma definition. *Not informative* above 0.050 mg/m^3 because of sample size (≤5). [Data from this study on the sample of adults presented in table above]	**Children results:** Asthma prevalence 4.8% Exposure category (*n*) prevalence All children <0.025 mg/m (101) 5.0% 0.025–0.050 (82) 4.9% 0.0501–0.067 (4) 0.0%
Krzyzanowski et al. (1990) (United States, Arizona) **Design:** Prevalence study. *n* = 298 ages 5–15 years, mean 9.3, from 202 households (stratified sample	Prevalence: asthma, current (physician diagnosed) 15.8% (*n*), asthma prevalence by exposure category,

Study and design[a]	Results
from municipal employees). Participation rate not reported. 67% white. **Exposure:** Two 1-week samples (opposite seasons) in kitchen, living area, and bedroom (converted from ppb) Household: mean 0.032 mg/m^3 <0.049 mg/m^3 83.7% 0.049–0.074 10.0% >0.074–0.172 6.3% Only a few values above 0.111 mg/m^3 **Outcome:** American Thoracic Society questionnaire (physician diagnosed) Ferris (1978). **Evaluation[a]:** *Medium* confidence For children, relatively small *n* in higher exposure categories; for adults, incomplete reporting **Related references:** Quackenboss et al. (1989a); Quackenboss et al. (1989b). [Data from this study on the sample of adults presented in table above]	<0.049 mg/m^3 (248) 11.7% 0.049–0.074 (24) 4.2% >0.074–0.172 (21) 23.8% (trend $p < 0.03$) Log-linear models, stratified by environmental tobacco smoke, adjusted for socioeconomic status, ethnicity. Highest vs. lowest group: RR (95% CI) 2.0 (0.88, 4.8) (EPA calculation, unadjusted) Additional analyses demonstrated effect modification by environmental tobacco smoke, see Table 121 in this report.
***Low* Confidence Studies**	
Yon et al. (2019) (Seongnam City, Korea) **Design**: Prevalence study, n = 427 school children recruited from 22 randomly selected classrooms at 11 elementary schools; 68.9% participation rate, ages 10–12 years. **Exposure**: Formaldehyde sampling in each classroom using monitors with pumps during the 1st and 2nd half of the school year. Mean 0.027 ± 0.077 mg/m^3; as high as 0.06 mg/m^3 in some classrooms. Duration and sampling methods were not described. **Outcome**: current asthma definition: presence of characteristic symptoms and /or signs during the previous 12 months using ISAAC questionnaire, Self report. **Evaluation[a]:** *Low* confidence Uncertainty regarding validation of ISAAC questionnaire in this population; uncertainty regarding exposure measurement period and other protocol details; few (n=10) children with asthma contributed to analyses.	Current asthma prevalence n = 10 OR (95% CI) per 1 µg/m^3 1.023 (0.96, 1.089) adjusted for age, sex, environmental tobacco smoke exposure, keeping a pet at home, and physician-diagnosed asthma and allergic dermatitis in parents.
Huang et al. (2017) (Shanghai, China) **Design**: Case-control study, n = 409 children, aged 5–10 years, who were participants in a previous cross-sectional study (2011–2012) selected from 88 kindergartens located in 6 Shanghai districts. Eligible children lived in homes not renovated in prior two years and agreed to home inspection during March 2013-December 2014. **Exposure**: Formaldehyde sampling in child's bedroom, 24 hours, in breathing zone (detection	**Current wheezing 27.8**% OR (95% CI) per IQR (15.2 µg/m^3) 0.93 (0.59, 1.47) Logistic regression adjusted for age, sex, family history of atopy, family annual income, household (ETS), early and current household dampness-related exposures, early antibiotics exposure, early home decoration, and the inspection season.

Study and design[a]	Results
range: 0.012-0.08 mg/m^3). Mean (± SD) concentration (mg/m^3), 24-hr 0.0215 (± 0.0130); 75th percentile 0.0275 mg/m^3 Range 0.006–0.060 mg/m^3, 3 homes above. **Outcome:** Wheezing in past 12 months using selected questions from translated ISAAC questionnaire. **Evaluation[a]**: *Low* confidence Participation rate unclear, and potentially differential with respect to exposure and disease status; uncertainty regarding validation of truncated version of ISAAC questionnaire in this population	
Madureira et al. (2016) (Porto, Portugal) **Design:** Case-control study, October 2012–April 2013, random recruitment of 38 residences among asthmatic children and 30 residences among nonasthmatic children previously identified in a cross-sectional study. Mean age 8.5 years. Excluded respondents with a recent renovation or who had moved since responding. **Exposure:** Continuous passive sampling in bedroom over 7 days. Formaldehyde concentrations all above the detection limit; see distribution in results column. **Outcome:** For asthma cases, parents responded yes to both of 2 questions in ISAAC questionnaire: 1) Has your child ever had asthma diagnosed by a doctor? and 2) In the past 12 months, has your child had wheezing or whistling in the chest? Parents of controls responded no to both questions. **Evaluation[a]:** *Low* confidence Potential for selection bias, with greater environmental controls among asthmatic families. Differences in temperature and relative humidity not addressed in analysis.	Formaldehyde concentration in bedroom, mg/m^3 Cases / Controls N: 38 / 30 Mean (SD): 0.015 (0.010) / 0.017 (0.095) Median: 0.011 / 0.015 IQR: 0.007-0.018 / 0.009-0.022 Min; Max: 0.004; 0.051 / 0.005; 0.043 *p* value = 0.199
Hsu et al. (2012) (Taiwan) **Design:** Case-control study; *n* = 9 cases, 42 controls, recruited through kindergartens and day care centers, ages 3−9 years at enrollment (mean age 7.0 years). Participation rate (clinic exam and home measures) approximately 5% of potential cases and controls). **Exposure:** 2-hour household sample (probably bedroom; converted from ppb) Median (25th, 75th percentile): Controls 0.017 (0.005, 0.030) mg/m^3. **Outcome:** Initial screening through parent report of history (ages 2−6 years) with confirmation by clinical examination. **Evaluation[a]:** *Low* confidence Low and differential (at various steps) participation rate. Short exposure sampling period and no	Formaldehyde concentrations lower in cases than in controls: (*n*) Median (25th, 75th percentile) mg/m^3 Controls (42) 0.017 (0.005, 0.030) Asthma cases (9) 0.005 (0.004, 0.012) (*p* = 0.03) Nonparametric (Mann-Whitney) comparison of formaldehyde by group.

<table>
<tr><th>Study and design[a]</th><th>Results</th></tr>
<tr><td>information on protocol. In addition, small sample size (n = 9) for asthma.</td><td></td></tr>
<tr><td>Hwang et al. (2011) (Korea)
Design: Case-control study drawn from 1,005 elementary students (one school, all grades; 84% participation rate). 33 cases (out of 129) and 40 controls (out of unspecified number) agreed to participate in environmental measurement study. Controls selected from respondents with no asthma symptoms or diagnosis, age- and sex-matched to cases.
Exposure: 3-day household sample (2 rooms) and personal sample
Geometric mean (±geometric SD) mg/m^3 in controls: 0.036 (±0.002) household; 0.029 (±0.002) personal
Outcome: Parent report of asthma based on ISAAC questionnaire.
Evaluation[a]:
Low confidence
Asthma definition includes current asthma and ever asthma. Uncertainty regarding selection processes (high prevalence of family history of asthma in cases [86%] and controls [96%]); uncertainty about analysis and distribution of formaldehyde levels</td><td>Formaldehyde level, geometric mean (SD) mg/m^3, by group:
<table><tr><th></th><th>Household sample</th><th>Personal sample</th></tr><tr><td>Cases</td><td>0.031 (0.002)</td><td>0.027 (0.002)</td></tr><tr><td>Controls</td><td>0.036 (0.002)</td><td>0.029 (0.002)</td></tr></table>OR (95% CI), per unit increase in formaldehyde: 1.0 (1.0, 1.1)

Comparison of distributions of exposure (ttests); logistic regression adjusted for gender, age, income, education level of parents, passive smoking.</td></tr>
<tr><td>Hulin et al. (2010) (France)
Design: Case-control study; (n = 32 urban cases, 31 urban controls; n = 24 rural cases, 24 rural controls), mean age 12.5 years. Drawn from previous schoolbased surveys. Participation rates 22 and 13% in urban cases and controls, 52 and 75% in rural cases and controls, respectively.
Exposure: 7-day sample in living room; median (minimum, maximum)
Total (n = 112) 0.019 (0.004, 0.075) mg/m^3

Outcome: Parent report of child’s history of asthma, use of asthma medications, or wheezing in past 12 months.
Evaluation[a]:
Low confidence
Small sample size and uncertain interpretation of the stratified analyses (and unspecified n in analysis of current asthma).</td><td>OR (95% CI) for above vs. below median)
Total sample: 1.7 (0.7, 4.4)
urban OR = 0.24 (0.04, 1.5)
rural OR = 9.0 (1.0, 98)
(interaction $p \leq 0.05$)
(Confidence intervals estimated from figure in the paper.)
Adjusted for age, sex, family history of allergy, passive smoke exposure during childhood, and allergic rhinitis.
Levels of other pollutants that are risk factors for asthma were higher in urban areas.</td></tr>
<tr><td>Choi et al. (2009) (Korea)
Design: Case-control study. n = 36 allergic asthma cases, 28 controls, recruited through university outpatient clinic; recruitment procedures not described. Mean age cases 15.4 years (SD = 3.4; controls 16.2 years (SD = 4.1). Housing age and type: cases 58% <3 years old and 72% apartments; controls 29% <3 years old and 50% apartments. Location: 44 and 21% near road for cases and controls, respectively.
Exposure: Household sample (sampling period and area not reported, but closed windows and use of duplicates).</td><td>Formaldehyde levels (mg/m^3):
<table><tr><th></th><th>Geometric mean</th><th>75th percentile</th></tr><tr><td>Cases</td><td>0.054</td><td>0.108</td></tr><tr><td>Controls</td><td>0.043</td><td>0.115</td></tr><tr><td colspan="3">p-value not reported (>0.05)</td></tr></table></td></tr>
</table>

Study and design[a]	Results
Geometric mean, 25th, and 75th percentiles in controls: 0.043 (0.024, 0.115) mg/m^3 **Outcome:** "Allergic asthma" based on medical history, skin prick test, and IgE (criteria not provided). **Evaluation[a]:** *Low* confidence Selection and recruitment process not reported; sampling period not reported and specific criteria for case definition not reported; potential confounders (age and type of housing and location differed between cases and controls, as measure of socioeconomic status) not addressed. Limited analysis.	
Mi et al. (2006) (Shanghai, China) **Design:** Prevalence study; *n* = 1,414, ages 12−17 (mean 13) years, percentage with environmental tobacco smoke not reported, participation rate 99%. Sampling from 10 schools, 3 7th-grade classes per school. **Exposure:** 4-hour samples in 30 classrooms. Mean (±SD), (minimum, maximum) 0.009 (±0.0089) (0.003, 0.020) mg/m^3. No information on LOD or percentage <LOD. Weak correlation (Spearman r ranged from−0.15 to 0.08) with other exposures (NO_2 and ozone, indoor and outdoor measurements). Moderate correlation (Spearman r ~0.40) with room temperature and relative humidity. **Outcome:** Current asthma (medication use or asthma attack in past 12 months), symptoms in past 12 months (wheeze or whistling in the chest, daytime breathlessness attack at rest or after exercise, nighttime breathlessness attack). **Evaluation[a]:** *Low* confidence Short exposure measurement period and uncertainty about exposure distribution and analysis (e.g., percentage <LOD and treatment in analysis as continuous variable).	Prevalence of: Asthma, current 3.1% Wheeze, whistling 3.1% Daytime attack 23.0% Nighttime attack 2.6% OR (95% CI), per 0.010 mg/m^3: Asthma, current 1.30 (0.72, 2.32) Symptoms in past 12 months Wheeze, whistling 1.01 (0.56, 1.81) Daytime attack 1.09 (0.86, 1.38) Nighttime attack 1.26 (0.63, 2.53) Adjusted for age, gender, smoking, observed water leakage and indoor molds.
Tavernier et al. (2006) (United Kingdom) **Design:** Case-control study. *n* = 105 cases, 95 controls (from two primary care practices, age- and sex-matched), ages 4−16 years, lower socioeconomic status. Participation rate 50%. **Exposure:** 5-day sample in living room and bedroom. **Outcome:** Asthma based on validated screening questionnaire (84% positive predictive value; but included questions on respiratory infection). *Low* confidence Uncertainty regarding selection process and loss of almost half of the cases. Outcome classification includes questions that are not specific to asthma. Uncertainty as to exposure range, particularly upper tertile (no response from email to corresponding author).	OR (95% CI), by exposure tertile (exposure levels not reported; median in Gee et al. (2005) reported as 0.037 and 0.049 mg/m^3 in living room and bedroom, respectively) Living room Bedroom Lowest 1.0 (referent) 1.0 (referent) Middle 0.82 (0.33, 2.05) 1.26 (0.47, 3.40) Highest 1.22 (0.49, 3.07) 0.99 (0.39, 2.52) Odds ratio, conditional logistic regression, adjusted for measured exposures (e.g., endotoxin, Der p 1, particulate matter) and other risk factors.

Study and design[a]	Results
Related Reference: Gee et al. (2005)	
Smedje and Norback (2001) (Sweden). **Design:** Prospective (incidence) nested case-control study. 1,258 without asthma at baseline, 56 incident cases of asthma in 4-year follow-up (incidence rate 1.1% per year); 78% participation in follow-up, mean age 10.3 years at baseline. School-based sample; 1st, 4th, and 7th grades. **Exposure:** Two 4-hour samples in 2−5 classrooms per school; measured in 1993 (*n* = 98) and 1995 (*n* = 101). Mean 0.008 mg/m^3, geometric mean 0.004 mg/m^3, (min, max) (<0.005, 0.072) mg/m^3, 54% of 1993 samples and 24% of 1997 samples below detection limit (0.005 mg/m^3); median among those above detection limit = 0.010 mg/m^3. Individual student values based on average of 1993 and 1997 classrooms (<0.005 to 0.042 mg/m^3).[c] **Outcome:** Parent report of physician diagnosis of asthma and six lower respiratory symptom questions; previous validation study (73% sensitivity, 99% specificity). **Analysis:** Odds ratio, adjusted for sex, age, history of atopy, smoking. **Evaluation[a]:** *Low* confidence Exposure measures in only 2 of the 4 years and 2/3 of students left the school more than a year before follow-up; uncertainty about distribution; relatively high percentage <LOD. Confounding by other exposures not fully addressed but pattern of results differed among the exposures examined. **Related Study:** Smedje et al. (1997).	OR (95% CI) per 0.010 mg/m^3: total sample: 1.2 (0.8, 1.7) with history of atopy: 0.6 (0.3, 1.3) no history of atopy: 1.7 (1.1, 2.6) (Atopy defined at baseline based on positive response to questions on childhood eczema, allergy to pollen, or allergy to pet dander.) Additional analyses examined effect modification by atopy status, see Figure 3-11 in this report.
Garrett et al. (1999) (Australia) Case-control study. 53 cases (physician diagnosis), 95 controls (no asthma diagnosis) from 80 households (some cases and controls from same household), ages 7−14 (mean 10.2) years. **Exposure:** 4-day (1 per season) measures in home (bedroom, living room, kitchen), and outdoors. Median (maximum) Indoor 0.0158 (0.139) mg/m^3 **Outcome:** Parent report, doctor-diagnosed asthma, and respiratory symptom questionnaire. **Evaluation[a]:** *Low* confidence Uncertainty about asthma definition (current asthma or ever asthma?). Uncertainty about effect of recruitment process and ability to fully address household correlation of cases and controls; could result in attenuated effect estimate. Incomplete reporting of results (adjusted results reported as "not statistically significant").	Incomplete reporting of results (*n*), proportion with asthma (overall proportion 53/148 = 0.36): <0.020 mg/m^3 (31) 0.16 0.020−0.050 (76) 0.39 >0.050−0.139 (41) 0.44 (trend = 0.02) Adjusted for parental asthma history, sex. **Adjusted results reported as "not statistically significant" (numeric results not reported).**

Organized by study confidence, then descending publication year. Results for *low* confidence studies are shaded gray.

[a]Evaluation of sources of bias or study limitations (see Appendix B.3.4). Direction of anticipated bias is indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact is likely to be away from the null (i.e., spurious or inflated effect estimate).

Table 3-15. Prevalence of asthma in adults in relation to residential formaldehyde exposure

Study and design[a]	Results
***Medium* Confidence Studies**	
Billionnet et al. (2011) (France) **Design:** Prevalence study, *n* = 905 adults from 490 dwellings (drawn from nationally representative sample; 13.6% participation rate), median age 44 (15–89) years; 48% men. **Exposure:** One-week sample in bedroom Median, 75th percentile (minimum, maximum) 0.0194, 0.028 (0.0013, 0.0863) mg/m^3 **Outcome:** Asthma based on self-report, asthma attack, woken by shortness of breath, or using asthma medication in past 12 months **Evaluation[a]:** *Medium* confidence Low participation rate but potential for differential participation (by formaldehyde exposure and disease status) uncertain.	Prevalence of asthma: 8.6% OR (95% CI), adjusted for multiple risk factors, above vs. below 75th percentile (0.028–0.0863 vs. <0.028 mg/m^3): 1.43 (0.8, 2.4) *(Confidence intervals estimated from graph)* Adjusted for age, gender, smoking status, relative humidity, mold, pets, outdoor sources of pollution within 500-meter radius, highest education level in household, time of data collection.
Matsunaga et al. (2008) (Japan) **Design:** Prevalence study. Adults, *n* = 998 women, mean 17th week of pregnancy, median age ~30 years. Recruited through obstetric clinics and public health nurses. Osaka prefecture, Japan. Participation rate 17% of pregnant women in the area. **Exposure:** 24-hour personal sample (converted from ppb) Median 0.030, maximum 0.161 mg/m^3 Cutpoints based on 30th, 60th, and 90th percentiles (<0.022, 0.022–0.033, 0.034–0.57, and ≥0.058 mg/m^3) **Outcome:** Self-report, treatment for asthma in past 12 months **Evaluation[a]:** *Medium* confidence Low participation rate but potential for differential participation (by formaldehyde exposure and disease status) uncertain. Some uncertainty pertaining to sensitivity and specificity of outcome assessment, but considered adequate	Asthma (2.1% prevalence) mg/m^3 | *n* | OR | (95% CI) <0.022 | 298 | 1.0 | (referent) 0.022–0.033 | 299 | 0.80 | (0.23, 2.84) 0.034–0.057 | 301 | 0.72 | (0.19, 2.77) 0.058–0.161 | 100 | 2.15 | (0.41, 11.3) (trend *p*-value = 0.47) 0.058 to 0.161 vs. <0.058 | 2.65 | (0.63, 11.1) Adjusted for age, gestation, parity, family history (asthma, atopic eczema, allergic rhinitis), smoking, passive smoking, mold in kitchen, indoor domestic pets, dust mite antigen level, family income, education, season of data collection.
Palczynski et al. (1999) (Poland) **Design:** Prevalence study; *n* = 278, ages 16–65 years from 120 households with children (random selection, 10-year old apartments). Participation rate not reported. **Exposure:** 24-hour household sample (area not specified). Mean (±SD) (minimum, maximum) 0.026 (±0.011) (0.002, 0.067) mg/m^3 2% >0.050 mg/m^3 **Outcome:** Bronchial asthma diagnosed using American Thoracic Society criteria. **Evaluation[a]:** *Medium* confidence	Asthma prevalence: 5.8% Exposure category (*n*) prevalence All adults <0.025 mg/m^3 (142): 6.3% 0.025–0.050 (131): 4.6% 0.0501–0.067 (5): 20.0%

Study and design[a]	Results
Uncertainty regarding asthma definition. *Not informative* above 0.050 mg/m^3 because of sample size (≤5). [Data from this study on the sample of children presented in table above]	
Krzyzanowski et al. (1990) (United States, Arizona) **Design:** Prevalence study. *n* = 613 ages >15 years, mean 37) from 202 households (stratified sample from municipal employees). Participation rate not reported. 67% white. **Exposure:** Two 1-week samples (opposite seasons) in kitchen, living area, and bedroom (converted from ppb) Household: mean 0.032 mg/m^3 <0.049 mg/m^3 83.7% 0.049–0.074 10.0% >0.074–0.172 6.3% Only a few values above 0.111 mg/m^3 **Outcome:** American Thoracic Society questionnaire (physician diagnosed) Ferris (1978). **Evaluation[a]:** *Medium* confidence For children, relatively small *n* in higher exposure categories; for adults, incomplete reporting **Related references:** Quackenboss et al. (1989a); Quackenboss et al. (1989b). [Data from this study on the sample of children presented in table above]	Prevalence of asthma: 12.9% wheeze without a cold: 21.5% shortness of breath with wheezing: 14.0% Reported as "not significantly related" but rate of wheeze was "somewhat higher" with higher exposure.
***Low* Confidence Studies**	
Zhai et al. (2013) (China) **Design:** Prevalence study, with random selection of participants within households; 186 homes 186 adults. **Exposure:** Samples in three rooms per house (bedroom, living room, kitchen); sampling time not specified. 64% of the 186 houses, and 24% of the 82 houses with children were >0.08 mg/m^3 ("polluted"). Mean formaldehyde levels in the 3 locations 0.09-0.13 mg/m^3 in the ""polluted" homes and 0.04-0.047 in the "unpolluted" homes **Outcome:** (American Thoracic Society questionnaire (physician diagnosed) Ferris (1978). **Evaluation[a]:** *Low* confidence Uncertainty regarding exposure measurement period and validation of case ascertainment in this population. Although potential confounders were not considered in asthma-only analysis, given the magnitude of the results, the formaldehyde association is unlikely to be explained only by confounders. For adults, small number (n=2) of positive responses. Data from this study on the sample of children presented in table above]	Prevalence by exposure category **Adults** *n* (%) <0.08 mg/m^3 66 (0.0) 0.08–0.15 mg/m^3 120 (1.6) RR not calculated
Norback et al. (1995) (Sweden) **Design:** Nested case-control within random population sample; *n* = 47 cases, *n* = 41 controls, ages 20–44 (mean	Mean (minimum, maximum) formaldehyde levels for nocturnal breathlessness: With symptom 0.029 (<0.005, 0.110) mg/m^3

<table>
<tr><th>Study and design[a]</th><th>Results</th></tr>
<tr><td>32) years. Participation rate 64 and 57%, respectively, among selected cases and controls.
Exposure: 2-hour sample measured in bedroom. Mean (Min, Max) 0.029 (<0.005, 0.110) mg/m^3. Strongly correlated with total volatile organic compounds (correlation coefficient not shown). Mean duration in home = 6 years (minimum 0.5, maximum 31).
Outcome: Cases defined by positive response to: asthma attack in past 2 months, nocturnal breathlessness in past 12 months, or current use of asthma medication. Controls responded “no” to all three questions.
Evaluation[a]:
Low confidence (↑)
Uncertainty about exposure (most values <LOQ). Similar results for volatile organic compounds, and not possible to distinguish effects of formaldehyde and these other compounds; could result in inflated effect estimate.</td><td>Controls 0.017 (<0.005, 0.060) mg/m^3
(p < 0.01)
OR 12.5 (2.0, 77.9) per 10-fold increase in formaldehyde (log-transformed), similar results for volatile organic compounds.
Odds ratio, adjusted for age, sex, current smoking, wall-to-wall carpets, and house dust mites.</td></tr>
<tr><th colspan="2">***Low* Confidence Studies: Combined analysis of adults and children**</th></tr>
<tr><td>Yeatts et al. (2012) (United Arab Emirates)
Design: Prevalence studyurvey; n = 1,590 (1,007 ages 19−50 years, 583 ages 6−18 years from 628 nationally representative sample of household (75% household participation).
Outcome: Asthma, wheeze symptoms based on several standardized questionnaires.
Analysis: Odds ratio, adjusted for sex, urban/rural area, age group, household tobacco smoke; children and adults combined in analysis.
Exposure: 7-day sample (living room)
71% <limit of quantification (0.0074 mg/m^3); 95th percentile 0.059 mg/m^3; 99th percentile 0.114 mg/m^3 (converted from ppm)
Correlation with sulfur dioxide relatively high (r = 0.63); also higher in homes using incense >1 per week
Evaluation[a]:
Low confidence (↑)
Difficult to disentangle possible effects of sulfur dioxide from those of formaldehyde (similar effect sizes; moderate–strong correlation; could result in inflated effect estimate. Does not separate analysis of children and adults; only 29% above LOD—analyzed as above vs. below LOD</td><td>
<table>
<tr><th></th><th>Prevalence %</th><th>OR (95% CI)</th></tr>
<tr><td>Wheezing in past 12 months</td><td>9.2</td><td>0.64 (0.71, 2.42)</td></tr>
<tr><td>Wheezing in past 4 weeks</td><td>6.1</td><td>3.5 (0.81, 14.9)</td></tr>
<tr><td>Difficulty breathing or chest tightness in past 12 months</td><td>12.0</td><td>1.43 (0.83, 2.46)</td></tr>
<tr><td>Difficulty breathing or chest tightness once or more times a month</td><td>7.0</td><td>6.5 (1.9, 22.3)</td></tr>
<tr><td colspan="3">Similar results seen with sulfur dioxide.</td></tr>
</table>
Odds ratio, adjusted for sex, urban/rural area, age group, household tobacco smoke; children and adults combined in analysis.</td></tr>
</table>

Organized by study confidence, then descending publication year. Results for *low* confidence studies are shaded gray.

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.4). Direction of anticipated bias indicated by arrows: “↓” for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); “↑” for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Table 3-16. Prevalence of asthma in relation to occupational formaldehyde exposure

Study and design[a]	Results
***Medium* Confidence Studies**	
Fransman et al. (2003) (New Zealand) **Design:** Prevalence study. Plywood mill workers, *n* = 112. Participation rate 66%. Mean age 34.5 years, 71% men, mean duration 4.7 years. Internal comparison by exposure level and external comparison group (*n* = 415) from general population (random sample) surveys in the study area. **Exposure:** Personal samples (15-minute samples) in jobs held by 49 workers: (*n*), geometric mean (±geometric standard deviation) (mg/m^3); none exceeded 1.25 mg/m^3 all (22) 0.080 (3.0) dryers (14) 0.070 (3.2) (one outlier) pressing (5) 0.160 (2.7) other areas 0.030–0.040 mg/m^3 (at or near detection limit) Total inhalable dust (full-shift personal samples): geometric mean 0.7 mg/m^3. Dust levels highest among composers; formaldehyde levels in this group were <detection limit (0.030 mg/m^3) **Outcome:** Current use of asthma medications or history in past 12 months of an asthma attack or being woken by shortness of breath **Evaluation[a]:** *Medium* confidence (↓) Selection out of the exposed work force of "affecteds" possible in this type of prevalence study. "Low" exposure group exposed to levels of formaldehyde up to 0.080 mg/m^3. Either limitation could result in reduced (attenuated) effect estimate.	Prevalence of asthma in exposed workers, external comparison group 20.5%, 12.5% (*n*) OR (95% CI): All workers (112) 1.5 (0.9, 2.8) By duration: <2 years (34) 0.5 (0.2, 1.7) 2–6.5 years (39) 1.0 (0.3, 2.7) >6.5 years (39) 3.1 (1.3, 7.2) By category: Low (<0.080 mg/m^3) (38) 1.0 (referent) High (>0.080 mg/m^3) (11) 4.3 (0.7, 27.7) Weaker association with terpenes (OR 2.0 for high vs. low exposure); no association with other exposures (e.g., dust, endotoxin) examined in this study. Adjusted for age, sex, ethnicity, smoking. Internal comparison by exposure category based on job title (limited to workers with same job titles as those with the 22 air sample measurements).
Herbert et al. (1994) (Canada) **Design:** Prevalence study. Oriented strand board manufacturing (*n* = 99). Comparison group (*n* = 165) oil field workers, not exposed to gas or vapors. Participation rate 98% in workers, 82% in comparison group. Mean age ~35 years. **Exposure:** 21 hours continuous area sampling, two consecutive days Saw line, debarking: 0.090–0.160 mg/m^3 Postheat, press conveyor, packaging, storage 0.200–0.290 mg/m^3 Preheat conveyor 0.330 mg/m^3 Total dust: mean 0.27 mg/m^3, median aerodynamic equivalent diameter = 2.5 µm **Outcome:** International Union Against Tuberculosis and Lung Disease (1986) questionnaire (symptoms past 12 months). **Evaluation[a]:** *Medium* confidence (↓) Selection out of the exposed work force of "affecteds" possible in this type of prevalence study. Uncertainty about exposures in referent group. Either limitation could result in reduced (attenuated) effect estimate.	Prevalence in exposed workers, comparison group Asthma 13.3%, 3.0% Wheeze attacks 25.3%, 9.7% Woken by shortness of breath 8.1%, 1.2% OR (95% CI) Asthma 5.48 (1.85, 16.2) Wheeze attacks 3.34 (1.66, 6.73) Woken by shortness of breath 6.78 (1.40, 32.7) Adjusted for age, smoking. Dust exposure considered low, not included in analysis.
Malaka and Kodama (1990) (Indonesia) **Design:** Prevalence study. Plywood workers, *n* = 93 exposed (93% participation rate), 93 unexposed from same plant, matched by age, ethnicity, smoking history (all men). Mean age ~27 years, mean duration 6 years.	Prevalence in exposed workers, comparison group: Occupational asthma 14%, 8% Asthma 30%, 8%

Study and design[a]	Results
Exposure: Personal and area samples (duration not reported) Mean by area (converted from ppm) Exposed—Plywood: 0.78 mg/m^3; Particle board: 2.9 mg/m^3; Block board: 0.62 mg/m^3 Other ("unexposed"): ≤0.086 mg/m^3 **Outcome:** Ferris (1978) questionnaire. Asthma based on "ever had attack of wheezing that made you feel short of breath?" or ever diagnosed with asthma and experienced currently; occupational asthma not defined. **Evaluation[a]:** *Medium* confidence Selection out of the exposed work force of "affecteds" possible in this type of prevalence study. "Unexposed" exposure group exposed to levels of formaldehyde up to 0.086 mg/m^3. Either limitation could result in reduced (attenuated) effect estimate. Unclear definition of asthma used in the analysis: "Occupational asthma" not defined, and lack of clarity in asthma definition pertaining to current prevalence.	OR (95% CI): Occupational asthma 2.84 (not reported) (p = 0.02) Asthma 6.31 (not reported) (p < 0.01) Adjusted for age, smoking, dust
***Low* Confidence Studies**	
Neghab et al. (2011) (Iran) **Design**: Prevalence study, melamine-formaldehyde resin plant, n = 70 exposed, 24 unexposed (office workers from same plant, no present or past exposure to formaldehyde or other respiratory irritant chemicals; all men). Similar demographics, smoking history. Participation rate 100%. Duration ≥2 years. **Exposure**: Area samples (40 minutes) in seven workshops and one area sample in office area (converted from ppm) Exposed (mean ±SD) 0.96 (±0.49) mg/m3; unexposed nondetectable Outcome: Ferris (1978) questionnaire, wheezing symptoms (period not specified). **Evaluation[a]**: Low confidence Selection out of the exposed work force of "affecteds" possible in this type of prevalence study; could result in reduced (attenuated) effect estimate. Potential low specificity and low sensitivity of outcome measure; no covariates.	Prevalence in exposed workers, comparison group: Wheezing symptoms 48.6%, 8.3%; OR (95% CI not reported) OR 10.4 (p = 0.001)
Holness and Nethercott (1989) (Canada) **Design:** Prevalence study, funeral home workers, n = 84 exposed (funeral directors and apprentices); 38 unexposed (from community service organization and students). Participation rate 87% of invited funeral home workers. Average exposure (embalming) duration 10 years. **Exposure:** 2 area samples during embalming, 30 to 180 minutes. Range in exposed 0.10–1.0 mg/m^3, referent mean 0.025 mg/m^3 **Outcome:** Ferris (1978) questionnaire: wheeze (no details of questions). **Evaluation[a]:** *Low* confidence Uncertainty regarding asthma definition. Differences in source populations for exposed and referent groups lead to uncertainty in comparability. No consideration of potential confounding.	Prevalence in exposed workers, comparison group: Wheeze 19%, 11% p = 0.32

Organized by study confidence, then descending publication year. Results for *low* confidence studies are shaded gray.

[a]Evaluation of sources of bias or study limitations (see Appendix B.3.4). Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious, or inflated effect estimate).

Asthma control studies

The previous discussion focused on the association between formaldehyde and prevalence of current asthma (i.e., symptoms or use of medications in the past 12 months). A different question concerns the association between formaldehyde and asthma control among people with asthma. This population could represent a group with greater susceptibility or vulnerability than the general population. EPA identified two observational studies that examined symptom frequency and medication use in the past 4 weeks and an intervention study that examined symptoms and medical care utilization in 12 months before and after an air quality control measures were taken to reduce residential formaldehyde levels (see Table 3-17). These studies provide additional support for the effects of formaldehyde exposure among children with asthma at levels at or below those seen in the studies of formaldehyde in relation to the prevalence of asthma.

In the United Kingdom, Venn et al. (2003) examined symptoms recorded in daily diaries over the course of 1 month in relation to formaldehyde levels measured in the child's home (3-day samples from bedrooms). No association was seen with the prevalence of wheezing during the past year in the case-control analysis (as discussed in the previous section), but among the 193 cases, a two- to three-fold increased risk of frequent symptoms (defined as symptoms recorded on ≥10 consecutive days) was seen in the highest quartile of exposure (>0.032 mg/m^3) compared with exposures <0.016 mg/m^3, with some evidence of an increased risk at even lower exposures (see Figure 3-10; *p*-value for trend = 0.05). For nighttime symptoms, which may be most relevant with respect to measurements taken in the bedroom, the relative risk estimate was 3.33 (95% CI 1.23, 9.02; *p*-value for trend = 0.02). The case definition of wheezing during the past year is interpreted as relevant to the definition of current asthma as used in this assessment, since 88% of the cases also reported using a reliever inhaler in the past year. These results were not impacted by inclusion of measures of room dampness in the models and were stronger when limited to patients with atopy (based on positive skin prick test results). Venn et al. (2003) did not find evidence of an adverse effect of NO_2 or VOCs other than formaldehyde on children's respiratory health. In a smaller study of 37 low-income children in Boston, Dannemiller et al. (2013) observed higher formaldehyde levels in homes of children with poor asthma control compared to those with better asthma control (geometric mean 0.066 and 0.042 mg/m^3, $p = 0.078$).

Intervention studies

A randomized controlled trial measured the impact of an intervention on indoor air contaminants (including formaldehyde) on symptom exacerbation among asthmatic children (Lajoie et al., 2014). A 50% reduction in formaldehyde concentrations in the bedroom was associated with a 14 to 20% decrease in the annual change in some symptoms or medical care (one or more episodes of wheezing, night cough, or one or more emergency room visit; *p*-values between 0.01 and 0.037) in the intervention group (Lajoie et al., 2014). Smaller reductions (7–11% decreases) were seen for more severe outcomes (severe wheezing, ≥ 4 episodes wheezing, ≥ 1 hospitalization, p-values between 0.17 and 0.25). Pre-intervention, formaldehyde levels in 30% of

the intervention home were > 0.050 mg/m^3; post-intervention all formaldehyde levels were < 0.050 mg/m^3. Other coexposures were reduced by the intervention resulting in uncertainty in the independent effect of formaldehyde, although the reductions were smaller in magnitude and separate effects of the other factors were not analyzed.

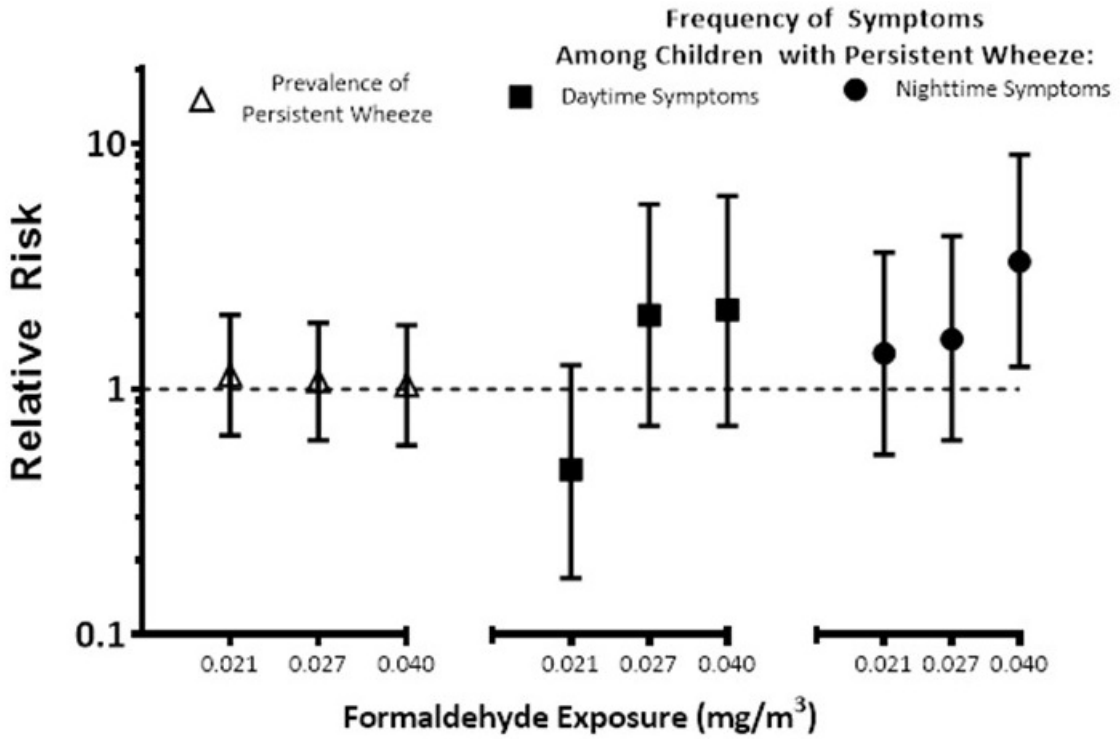


Figure 3-10. Relative risk of persistent wheeze and of increased frequency of symptoms among children with wheeze in relation to residential formaldehyde exposure.

Effect modification by disease status: comparison of formaldehyde associations with prevalence of current asthma (persistent wheeze) and with increased frequency of symptoms only among cases. Data from Venn et al. (2003); study details in Table 3-17.

Table 3-17. Exacerbation of asthma symptoms in relation to residential formaldehyde exposure

Study and design [a]	Results
Observational Studies	
Venn et al. (2003) (United Kingdom) **Design:** Nested case-control study; Symptom control among persistent wheeze cases (symptoms during past year) (*n* = 193), ages 9–11 years. Participation rate 79%. **Exposure:** 3-day samples in bedroom during home visit.	(*n* cases, percentage with frequent symptoms), OR (95% CI): Frequent nighttime symptoms <0.016 mg/m^3 (39, 41%) 1.0 (referent) 0.0161–0.022 (35, 49%) 1.40 (0.54, 3.62) 0.0221–0.032 (36, 53%) 1.61 (0.62, 4.19) 0.0321–0.083 (33, 67%) 3.33 (1.23, 9.01) (trend *p* = 0.02)

<table>
<tr><th>Study and design [a]</th><th>Results</th></tr>
<tr><td>Median ~0.022 mg/m^3; 75th percentile 0.032 mg/m$^{3;}$
Median in top quartile 0.039 mg/m^3
[Maximum and median in top quartile provided in email from Dr. Venn to Glinda Cooper, March 29, 2012; (Venn, 2012)]
Outcome: 1-month daily diaries recording symptoms: daytime and nighttime wheezing, chest tightness, breathlessness, and cough, each measured on 0-to-5 scale. “Frequent” symptoms defined as recorded on ≥10 days.
Evaluation:
High confidence</td><td>OR per quartile increase:
full sample 1.45 (1.06, 1.98)
limited to atopic cases 2.06 (1.37, 3.09)
Frequent daytime symptoms
<0.016 mg/m^3 (37, 62%) 1.0 (referent)
0.020–0.022 (34, 47%) 0.47 (0.17, 1.25)
0.022–0.032 (37, 73%) 2.00 (0.71, 5.65)
0.032–0.083 (32, 73%) 2.08 (0.71, 6.11)
(trend p = 0.05)
OR per quartile increase:
full sample 1.40 (1.00, 1.94)
limited to atopic cases 1.68 (1.10, 2.57)
Odds ratio, adjusted for age, sex, and Carstairs deprivation index
Additional adjustment for dampness or other exposures including visible mold, total VOCs, or NO_2, did not affect formaldehyde results.
No evidence of an adverse effect of NO_2 or VOCs other than formaldehyde on children’s respiratory health.
Similar results in group with validation of case status from prescription asthma medication records.</td></tr>
<tr><td>Dannemiller et al. (2013) (United States)
Design: Symptom control among 37 asthma cases, mean age 10.5 years. Participation rate 79% (37 out of 47)
Exposure: 30-minute pumped sample in kitchen (converted from ppb)
Median 0.044 mg/m^3
Range 0.006–0.162 mg/m^3
31% >0.060 mg/m^3
Outcome: Five-question survey about symptom control in past 4 weeks at same time as environmental sampling.
Evaluation[a]:
Medium confidence
Recruitment is not from a well-defined population.
Limited exposure measurement period (but quality control details provided, and none were < LOD).
Related reference: Sandel et al. (2014)</td><td>Asthma Control Question
Geometric mean formaldehyde (mg/m^3)
<table><tr><th>Frequency during past 4 weeks</th><th>N (%) with most severe rating</th><th>Most severe group</th><th>All other groups</th><th>p-value</th></tr><tr><td>Asthma interfered with activities</td><td>5 (14%)</td><td>0.070</td><td>0.042</td><td>0.066</td></tr><tr><td>Shortness of breath</td><td>3 (8%)</td><td>0.079</td><td>0.043</td><td>0.086</td></tr><tr><td>Nighttime symptoms</td><td>4 (11%)</td><td>0.065</td><td>0.043</td><td>0.184</td></tr><tr><td>Used rescue inhaler or nebulizer medication</td><td>4 (11%)</td><td>0.055</td><td>0.044</td><td>0.409</td></tr><tr><td>Asthma control rating</td><td>3 (8%)</td><td>0.074</td><td>0.043</td><td>0.128</td></tr><tr><td>Score <12 (very poor control)</td><td>6 (16%)</td><td>0.066</td><td>0.042</td><td>0.078</td></tr></table>Similar results adjusted for season.
Examined season, temperature, and relative humidity in the analysis</td></tr>
<tr><td colspan="2">Intervention Studies</td></tr>
</table>

Study and design [a]	Results
Lajoie et al. (2014) (Quebec, Canada) **Design:** Intervention study October 2008–June 2011, n = 43 intervention group, n = 40 control group; Asthmatic children with exacerbation requiring medical care in the past year referred by physicians at tertiary care center, 3–12 years old, (n=83, 71.5% of those meeting inclusion criteria) in homes with low ventilation rates [<0.30 air exchange per hour (ACH)). Randomly assigned to intervention to increase ventilation rates by 0.15 ACH. **Exposure:** Passive air sampling for formaldehyde in bedroom, 6–8 days, during winter and summer seasons; **Outcome:** Symptom prevalence (rhinitis and asthma) over last 12 months based on ISAAC questionnaire administered to parents pre- and post-intervention. Also include questions on asthma control and a daily symptom diary completed for two weeks per month in November through March for both the pre- and the post-intervention years. **Evaluation:** *Medium* confidence Other coexposures that have been associated in literature with asthma symptoms also declined in intervention group (toluene, ethylbenzene, styrene, limonene, alpha-pinene, airborne mold spores), although formaldehyde reduction was greatest.	**Asthma symptoms** Change from year 1 to year 2 in prevalence of asthma symptoms and medical care in the past year associated with a 50% reduction in formaldehyde concentration. Analyses in intervention group, n = 43: **Outcome** **% Change (95% CI)** **p value** **≥ 1 episode** Wheezing -14.8 (-28.6, -0.9) 0.037 Night cough -20.4 (-35.7, -5.0) 0.010 ≥ 1 emergency Room visit -16.0 (-30.5, -1.5) 0.031 Analyses used mixed linear models with repeated measures. adjusted for age and eczema. Other outcomes analyzed with smaller reductions were disturbed sleep (-15.7%, change, p = 0.130), ≥ 4 episodes wheezing -7.2% change, p = 0.255), effort wheezing (-9.1% change, p = 0.173) and 1 or more hospitalization (-7.9% change, p = 0.218). There was no change or non-significant increases in severe wheezing (1.5% change, p = 0.888) and rhinitis (11.0% change, p = 0.105). Change in exposure levels: Intervention group pre- and post-intervention, Fall/winter measurements: Pre-geometric mean 0.037 (0.032–0.043) mg/m^3; 30.1% homes ≥ 0.050 mg/m^3; post- geometric mean 0.024 (0.021–0.028) mg/m^3; 0% homes ≥ 0.050 mg/m^3; Control group, pre- geometric mean 0.037 (0.031–0.043) mg/m^3; 25.5% homes ≥ 0.050 mg/m^3; post- geometric 0.035 (0.030–0.041) mg/m^3; 22.9% homes ≥ 0.050 mg/m^3.

Organized by study confidence, then descending publication year.
[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.4).

Acute exposure—controlled chamber studies—people with asthma

Most of the acute formaldehyde exposure studies among adults with asthma provide little or no evidence of an immediate effect on pulmonary function in response to formaldehyde inhalation (see Table 3-18); however, no controlled exposure studies have been conducted in children with asthma. The exposure duration in these studies ranges from 10 minutes to 3 hours, and so does not represent a chronic exposure scenario. The studies are fairly small (ranging from 7 to 19 participants) and use various measures of pulmonary function (e.g., FEV_1, FVC) and airway reactivity. Only two of these studies included an assessment of the response to an allergen challenge: dust mite in Casset et al. (2006) and grass pollen in Ezratty et al. (2007). One of these studies demonstrated a reduction in the average dose of mite allergen required for a 20% decrease in FEV_1 from baseline (PD_{20} FEV_1) after a 30-minute exposure via mouth breathing only to 0.092 m/m^3 of formaldehyde compared to ambient air controls (0.032 mg/m^3 formaldehyde) [54.7 ng versus 73.2 ng, respectively; (Casset et al., 2006)]. Formaldehyde exposure also increased the late-phase response, expressed as the maximum fall in FEV_1 from baseline observed during the 6-hour

follow-up, by 15% in FEV_1 in the exposed individuals compared to an 11% reduction among controls. However, these effects were not observed in the study by Ezratty et al. (2007). One difference in these studies is that the Casset et al. (2006) protocol used a nose clip, thus resulting in inhalation solely by mouth. In addition, for all of these studies, the severity of asthma among the volunteers in these experiments is not known; thus, the results may not be generalizable to all people with asthma.

Table 3-18. Controlled acute exposure chamber studies of pulmonary function with formaldehyde exposure among people with asthma

Study and design	Exposure measures	Results	
		Pulmonary function	Bronchial challenge—airway reactivity
Studies with allergen challenge			
Ezratty et al. (2007) *n* = 12, ages 18–44, nonsmoking, positive history of pollen allergy. **Design:** Random assignment to order of exposure (2 weeks apart); double blinded. Testing pre-exposure and every hour up to 8 hours postexposure. Grass pollen (5 allergens) challenge (protocol described). **Evaluation[a]:** *High* confidence	60 minutes, 0 and 0.500 mg/m^3	No difference in FVC or FEV_1 before or immediately after (data not shown)	Early phase response—PD_{15} FEV_1 grass allergen: compared with placebo, higher in five subjects and unchanged in seven after exposure. Median (range) index of reactivity: Placebo 0.25 (0.10–2.0) Exposed 0.80 (0.15–2.0) (p = 0.06) Late-phase response (8 hours postexposure and allergen challenge) PD_{15} FEV_1 Placebo 0.17 (0.03–4.0) Exposed 0.23 (0.01–3.6) (p = 0.42)
Casset et al. (2006) *n* = 19, ages 19–35 years, nonsmoking, positive IgE to dust mites. **Design:** Random assignment to order of exposure (3 weeks apart); double blinded. Mean formaldehyde exposure at home 0.037 ± 0.004 mg/m^3 (24-hour sample). Testing pre-exposure and every hour up to 6 hours postexposure. House dust mite challenge (Der p 1 11.08 µg/mL, 11.12 µm) (protocol described). **Evaluation[a]:** *High* confidence Note: applies to mouth breathing.	30 minutes, 0.032 (background) and 0.092 mg/m^3 Nose clip (breathing by mouth)	No difference in at-pretreatment or early-posttreatment assessment; Late-phase response— Mean ± SE reduction FEV_1: Placebo 11 ± 1.6 Exposed 15 ± 1.6 (p = 0.046)	Early phase response—PD_{20} FEV_1 Der p1 Mean ± SE; median (ng): Placebo 73.2 ± 17.3; 39.7 Exposed 54.7 ± 12.6; 28.1 (p = 0.05)

Study and design	Exposure measures	Results	
		Pulmonary function	Bronchial challenge—airway reactivity
Studies without allergen challenge			
Witek et al. (1986); Witek et al. (1987)[b] *n* = 15, ages 18–35 years, nonsmoking **Design:** Two protocols (at rest and during exercise). Random assignment to order of exposure; double blinded. Testing during and at 10 and 30 minutes postexposure; PEFR assessed from 1 to 24 hours postexposure. **Evaluation[a]:** *High* confidence Note: nonparametric analysis could be preferred but individual data provided	40 minutes, 0 and 2,000 ppb [0, 2.46 mg/m^3]	Few differences in FVC, FEV_1, R_{aw}, or other lung function measures At 30 min postexposure, resting protocol FVC: Control 0.82; 2 ppm −2.78 FEV_1: Control −0.31; 2 ppm 0.60 R_{aw}: Control −6.64; 2 ppm −3.05 Similar patterns in exercise protocol. No decline in PEFR over 24 hours in either group.	PD_{20} FEV_1 mean ± SD; median Pre-exposure: 24.0 ± 15.7; 27.4 Postexposure: 13.6 ± 20.5; 3.1 (p = 0.12)
Harving et al. (1990) *n* = 15, ages 15–36, nonsmoking. **Design:** Random assignment to exposure order (one per week); double blinded. Testing pre-exposure and near end of exposure period. **Evaluation[a]:** *High* confidence **Related Reference**: Harving et al. (1986)	90 minutes, filtered air (8), 0.120 and 0.850 mg/m^3	No difference in: FEV_1, R_{aw}, SG_{aw} 0.008 mg/m^3: 100.9; 2.21; 10.67 0.12 mg/m^3: 99.4; 2.23; 10.63 0.85 mg/m^3: 105.0; 2.29; 11.17	No difference in challenge test: PC_{20} PEF 0.008 mg/m^3: 0.29 0.12 mg/m^3: 0.36 0.85 mg/m^3: 0.26
Green et al. (1987) *n* = 16, ages 19–35 years, nonsmoking. **Design:** Two 15-minute exercise segments in 60-minute exposure period. Random assignment to order of exposure; single blinded. Testing pre- and during exposure period, ~15 minute intervals. **Evaluation[a]:** *Medium* confidence Randomized, single blinded	60 minute, clean air and 3,000 ppb [0, 3.69 mg/m^3]	No difference in FVC, FEV_1, SG_{aw}, or other lung function measures At 55 minutes: FVC; FEV_1; SG_{aw} Control: 4.62; 3.54; 0.114 3 ppm: 4.56; 3.46; 0.111	No difference in challenge test: PD_{35} SG_{aw} Control: 3.69 3 ppm: 3.86
Sauder et al. (1987) *n* = 9, ages 26–40, nonsmoking. **Design:** Clean air followed by formaldehyde (1 week apart); blinding of participant not specified. Testing during and at end of exposure. **Evaluation[a]:** *Low* confidence Not randomized, blinding not specified	3 hours, clean air and 3,000 ppb [0, 3.69 mg/m^3]	No difference in FVC, FEV_1, SG_{aw}, or other lung function measures. At 180 minutes: FVC; FEV_1; SG_{aw} Control: 4.11; 3.02; 0.101 3 ppm: 4.16; 3.07; 0.106	No difference in challenge test: PD_{35} SGaw Control: 0.93 3 ppm: 0.96

Study and design	Exposure measures	Results	
		Pulmonary function	Bronchial challenge—airway reactivity
Krakowiak et al. (1998) *n* = 10, ages 23–52 years, some smokers, with occupational formaldehyde exposure **Design:** Single blinded. Testing 2 hours pre-exposure and up to 24 hours after exposure. **Evaluation[a]:** *Low* confidence Not randomized, single blinding, SE or SD not reported	2 hours, 0.500 mg/m^3	No difference in FEV_1 or PEF (mean values shown on graph; no indication of variability in measures)	No difference in challenge test (PD_{20} FEV_1) (mean values shown on graph; no indication of variability in measures)
Sheppard et al. (1984) *n* = 7, ages 18–37, nonsmoking **Design:** Two protocols (at rest and during exercise). ≥1 day apart; blinding of participant not specified. Testing before and 2 minutes after exposure. **Evaluation[a]:** *Low* confidence Not randomized, blinding not specified	10 minutes, 0, 1,000, and 3,000 ppb [0, 1.23, 3.69 mg/m^3]	No difference between pre- and post SG_{aw}[c] in either protocol: Resting Exercise Control −1.0 1.8 1 ppm 0.2 2.2 3 ppm NC 2.9 NC= not conducted	Not assessed

Within each category, organized by study confidence, then descending publication year. Results for *low* confidence studies are shaded gray.

Abbreviations: Double blinded = investigator and participants unaware of which exposure; single blinded = participants were unaware of exposure. Late phase: between 4 and 6 hours after end of house dust mite bronchial challenge. PD_x = dose required to induce an x% reduction in the specified pulmonary function measure (i.e., PD_{15} FEV_1 = dose required to induce a 15% reduction in FEV_1); R_{aw} = airway resistance; SG_{aw} = specific airway conductance (corrected for lung volume); PEFR = peak expiratory flow rate.

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.4).

[b]Witek et al. (1987) includes the same subjects as the Witek et al. (1986) paper, but with additional results presented in 1987.

[c]Postminus preexposure SG_{aw} (liters × cm H_2O/liter); negative value indicates lower SG_{aw} postexposure.

Lower respiratory tract symptoms in infants and young children

Five studies (all *medium* confidence) examined other respiratory conditions in infants (followed up to age 18 months) and young children (age 6 months to 3 years); these studies focused on wheeze-relating symptoms, with or without accompanying lower respiratory tract infection (see Table 3-19). Li et al. (2019) is essentially a replication of Yu et al. (2017) in that it is conducted in the same area with the same study design but using a later birth cohort. These two studies are presented as a single entry in Table 3-19. Rumchev et al. (2002) is a study of emergency room visits for what was characterized as asthma (based on discharge diagnosis); information on the recruitment and selection process was not presented. The relatively young age of the children (mean 24 months, range 6 to 36 months) does not reflect the phenotypic expression of asthma, and thus this study likely represents wheezing episodes and various respiratory tract infections. Two 8-

hour measures, in different seasons, of formaldehyde were taken in case and control homes; the length of time between the hospital visit and the study was not specified. Roda et al. (2011) was a follow-up of 2,940 infants in a birth cohort, with questionnaires regarding respiratory symptoms including lower respiratory infections and wheeze, completed by parents at 1, 3, 6, 9 and 12 months. Formaldehyde exposure was modeled based on housing characteristic data and the mean of four 1-week samples taken in homes at 1, 6, 9, and 12 months in a randomly selected subset of 196 homes. The sensitivity and specificity of the modeling was estimated as 72.4 and 73.6% respectively for categorization based on the median and 57.4 and 82.1% for categorization based on tertiles. EPA noted in its evaluation, however, that the modeling was not tested on a separate sample, and thus these model characteristic estimates may be high. Both of these studies reported associations between the examined outcome and residential formaldehyde levels, with effects seen above 0.020 mg/m^3 in Roda et al. (2011) and above 0.060 mg/m^3 (possibly above 0.050 mg/m^3) in Rumchev et al. (2002). Another cohort study of infants used daily symptom diaries to assess wheezing episodes and did not see an association with formaldehyde at relatively low levels (OR 0.67, 95% CI: 0.29, 1.54, for exposures at 0.026 to 0.035 mg/m^3 compared to 0.012 mg/m^3) Raaschou-Nielsen et al. (2010). The two studies in Hong Kong were prospective studies of new-onset wheeze in infants. Both of these found increased risk of development of a first wheeze episode in relation to formaldehyde levels measured in the home. Li et al. (2019) Yu et al. (2017). The hazard ratio for time to first episode was 1.002 and 1.004 per 0.010 mg/m^3 increase in formaldehyde at a mean level of 0.051 mg/m^3. Although the conditions included in these studies do not fit within the usual classification of asthma, the observation of wheezing episodes at these early ages may have implications for subsequent disease risk, and in the case of Rumchev et al. (2002) (emergency room visits), also reflects an outcome with accompanying health care costs. The association of formaldehyde exposure with symptoms consistent with increased lower respiratory infections also may be indicative of immune suppression in the children, although this was not directly tested in the available studies, and mechanistic findings that may support these observations were similarly indirect and inconclusive (see *Evidence on Mode-of-Action* Section below). Although the congruence between the outcomes examined within these studies is not clear, the results of these studies indicate that the relationship between indoor formaldehyde exposure and respiratory conditions in infants and young children is an area requiring additional research.

Table 3-19. Lower respiratory tract conditions in infants and young children in relation to residential formaldehyde exposure

Study and design[a]	Results
[Note: these two related studies were considered together; see below] Li et al. (2019) (Hong Kong)	**New onset wheeze** Li et al. (2019) Prevalence 12.5% at mean age of 13.4 months. HR (95% CI) per 10 µg/m^3

Study and design[a]	Results
Design: Prospective study of birth cohort (2013-2014), Infants aged <4 months (≥2.5 kg, gestation ≥36 weeks) followed to 18 months; *n* = 963 (67% of recruited) with outcome and exposure data. Yu et al. (2017) (Hong Kong) **Design:** Prospective study of birth cohort (2009-2011), Infants aged <4 months, followed to 18 months; *n* = 535 (76% of recruited) with outcome and exposure data. **Exposure:** Air sampling (NO_2, formaldehyde), 72 hour samples at 6 months of age (concentrations not reported), ISAAC questionnaire included questions on environmental conditions in residence. Exposure levels provided in Yu et al. (2017) Mean (SD) concentrations formaldehyde 0.051 (0.075) mg/m^3 **Outcome:** Parent questionnaire (ISAAC) prior to 4 months, weekly respiratory health diary and monthly telephone survey to 18 months. New onset wheeze (time to event) measured from 6 to 18 months of age. **Evaluation:** *Medium* confidence Low participation rate but potential for differential participation (by formaldehyde exposure and disease status) uncertain. Authors did not respond to queries; EPA assumed exposure measurement details and exposure levels were similar in these two studies.	1.002 (1.001,1.003) Cox proportional hazard models adjusted for NO_2, sex, neo-natal respiratory illness, sibling, keeping pets, cooking fuel, and family history of non-asthma allergy or asthma. Yu et al. (2017) Prevalence 11% at mean age of 11.4 months. Hazard Ratio (95% CI) per 10 µg/m^3 1.004 (1.001,1.007) Also adjusted for living area (ft^2)
Roda et al. (2011) (France) **Design:** Prospective study of birth cohort, infants (singleton, >2,500 g) followed through age 1 year; *n* = 2,940 with 12-month questionnaire and formaldehyde measures (70% of 4,177 initial enrollees; 76% of those completing at least one questionnaire). **Exposure:** Questionnaire on home characteristics at baseline and updated at 3, 6, 9 and 12 months. *N* = 196 randomly selected for predictive modeling analysis; 4 1-week measures at 1, 6, 9 and 12 months. Predictive model used to assign subjects to categorical levels. LOD 0.008 mg/m^3. Median (25th, 75th percentile) 0.020 (0.014, 0.027) mg/m^3. Exposure prediction model for high vs. low (based on median): Exposure prediction model for high vs. low (based on median): Sensitivity 72.4%; Specificity 73.6%	OR (95% CI) Lower respiratory tract infection (Prevalence through age 1 year 45.8%) Per interquartile range increase: 1.32 (1.11, 1.55) Above vs. below median (0.02 mg/m^3): 1.20 (1.03, 1.41) Top tertile vs. lowest tertile: 1.31 (1.10, 1.57) Lower respiratory tract infection with wheeze (Prevalence through age 1 year 22.3%) Per interquartile range increase: 1.41 (1.14, 1.74) Above vs. below median (0.02 mg/m^3) 1.31 (1.07, 1.59) Top tertile vs. lowest tertile: 1.43 (1.14, 1.79) Adjusted for sex, prenatal and postnatal environmental tobacco smoke exposure, breastfeeding history, number of older siblings, day

Study and design[a]	Results
Exposure prediction model by tertile: Sensitivity 57.4%; Specificity 82.1%. **Outcome:** Parent questionnaire at 1, 3, 6, 9, and 12 months used to define lower respiratory infections with and without wheeze **Evaluation[a]:** *Medium* confidence Did not test predictive model on separate sample (may overestimate sensitivity and specificity)	care attendance, furry pets in the home, humidity, parental history of asthma, and socioeconomic status.
Raaschou-Nielsen et al. (2010) (Denmark) **Design:** Prospective study of birth cohort, *n* = 343, infants of mothers with asthma (83% of 411 enrollees, 90% of 378 who participated through 18 months). **Exposure:** 10-week samples in bedrooms, 1 to 3 sampling periods (at 6, 12, and 18 months of age). Analysis of variance: 31% between and 69% within person. mean 0.020 mg/m^3 median 0.018 mg/m^3 95th percentile 0.037 mg/m^3 **Outcome:** Daily symptom diaries kept from birth to 18 months (reviewed at clinic visit every 6 months), recording of wheezing symptoms affecting activity or sleep.[b] **Evaluation[a]:** *Medium* confidence Analysis does not take into account important features of the data (e.g., temporal variations in symptoms and large within individual variability in formaldehyde levels).	(*n*), OR (95% CI) by exposure quintiles. Outcome = any wheezing symptom day: <0.012 mg/m^3 (67) 1.0 (referent) 0.012–0.016 (69) 1.11 (0.47, 2.63) 0.016–0.020 (68) 1.21 (0.51. 2.92) 0.020–0.026 (71) 1.40 (0.57, 3.47) >0.026 (68) 0.67 (0.29, 1.54) (trend *p* = 0.49) Adjusted for sex, area of residence, education of mother and log transformed baseline lung function
Rumchev et al. (2002) (Australia) **Design:** Case-control study, *n* = 88 cases, *n* = 104 controls (health department); ages 6 months to 3 years (mean 25 months for cases, 20 months for controls). Participation rates not reported. **Exposure:** Two 8-hour measures (winter, summer) in home (living room, bedroom) mean (max) (mg/m^3) living room: 0.028 ((0.189); bedroom: 0.030 0.244) **Outcome:** Emergency room discharge diagnosis of asthma **Evaluation[a]:** *Medium* confidence Recruitment process not described; uncertainty as to what is included within this case definition and length of time between emergency room visit and subsequent exposure measure. **Related References:** Rumchev et al. (2004)	OR (95% CI) by exposure category[b]: Emergency room discharge diagnosis of asthma 0.010–0.029 mg/m^3 0.95 (0.8, 1.1) 0.030–0.049 0.95 (0.8, 1.2) 0.050–0.059 1.2 (0.9, 1.6) ≥0.060 1.39 (1.1, 1.7) Per 0.010 mg/m^3: 1.003 (1.002, 1.004) *(OR and 95% CI for all categories except ≥0.060 mg/m^3 estimated from figure in the paper; numbers in each exposure were not reported)* Adjusted for age, sex, allergic sensitization to common allergens, family history of asthma, relative humidity, indoor temperature, socioeconomic status, pets, air conditioning, gas appliances, smoking inside, house dust mite levels

Organized by study confidence, then descending publication year.
[a]Evaluation of sources of bias or study limitations (see Appendix B.3.4).

Susceptibility: modifying factors affecting prevalence of asthma or allergic sensitization

Asthma and atopic sensitization are hypothesized to be affected by a combination of genetic and environmental factors. Several sensitization and asthma studies included analyses pertaining to effect modification by factors that may help elucidate pathogenesis and susceptibility, such as atopy. In the study of adult women by Matsunaga et al. (2008), the association between use of medication for atopic eczema and formaldehyde exposure was stronger among women with no family history of allergy (OR 2.96, 95% CI 0.87, 10.12) than among women with a family history of allergy (OR 1.63, 95% CI 0.58, 4.57) at exposures of 0.058 to 0.161 mg/m^3 compared with <0.058 mg/m^3. The pattern across exposure levels also revealed an increase in risk of atopic eczema at lower exposures in the negative family history group (OR 1.37, 1.88, and 4.21) compared with the positive family history group (OR 0.80, 0.92, and 1.45) (see Figure 3-11A). The pattern is difficult to interpret in the study by Annesi-Maesano et al. (2012) (see Figure 3-11 B), as an indication of effect modification at lower exposures was not seen at higher exposures. Note that the direction of effect modification seen in Matsunaga et al. (2008) differs from that described in the preceding section (i.e., the stronger association between formaldehyde and asthma control among children with atopy compared to nonatopics in Venn et al. (2003). Examination of the presence of interactions and the factors contributing to them requires large studies designed to test specific hypotheses defined a priori; thus, additional research is needed to address the question of potential effect modification of atopic eczema or asthma symptom prevalence by atopy status.

Tobacco smoke represents an environmental factor that may increase the incidence of hypersensitivity responses in formaldehyde-exposed individuals. Two studies included IgE or asthma analyses stratified by environmental tobacco smoke exposure among children and adults (nonsmokers) (Palczynski et al., 1999; Krzyzanowski et al., 1990). There was some evidence of effect modification by environmental tobacco smoke (i.e., stronger associations, or associations seen at lower formaldehyde exposures, seen with this coexposure). In the Palczynski et al. (1999) study, there was no association between formaldehyde and either IgE levels or asthma prevalence in the full sample of children or of adults. Analyses stratified by the presence of environmental tobacco smoke exposure in the home, however, indicated associations between formaldehyde (at levels of 0.025–0.050 mg/m^3) and (1) elevated IgE in children (but not adults), and (2) asthma in adults (but not in children). In the study by Krzyzanowski et al. (1990), an association between formaldehyde and asthma was seen in children exposed to environmental tobacco smoke, but evidence of this type of effect modification was not seen in adults (see Table 3-20). Additional studies are needed to establish if this interaction is seen only in children, only in adults, in adults and children, or in neither group.

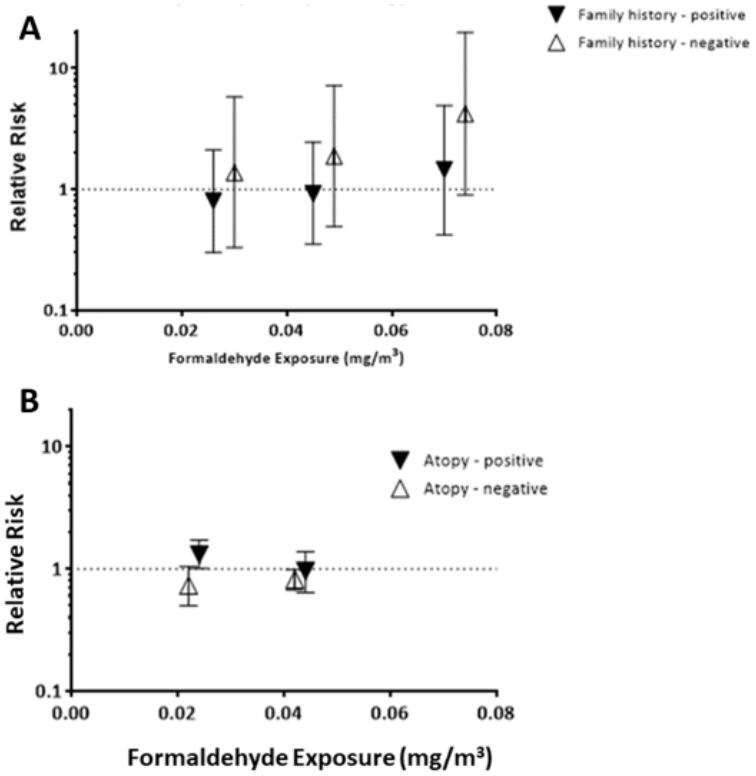


Figure 3-11. Examination of effect modification by family or personal history of atopy.

(A) Relative risk of prevalence of atopic eczema in adults (Matsunaga et al., 2008). Family history defined as parent or sibling with doctor-diagnosed asthma, atopic eczema, or allergic rhinitis. (B) Relative risk of prevalence of asthma in children (Annesi-Maesano et al., 2012). Atopy based on positive skin prick test (10 allergens).

Table 3-20. Effect modification by environmental tobacco smoke: results from studies in children and adults

Study and design[a]	Results		
Palczynski et al. (1999) (Poland) **Design:** Prevalence study, *n* = 278, ages 16−65 and *n* = 187, ages 5−15 years from 120 households with children (random selection, 10-year old apartments). Participation rate not reported. **Exposure:** 24-hour household sample (area not specified) Mean (±SD) (minimum, maximum) 0.026 (±0.011) (0.002, 0.067) mg/m^3 2% >0.050 mg/m^3 **Outcome:** Bronchial asthma diagnosed using American Thoracic Society criteria.		*N* per group (Percentage with Current Asthma)	
		Environmental Tobacco Smoke	
	Exposure (mg/m^3)	Positive	Negative
	Children, IgE >100 kU/L		
	<0.025	39 (38.5)	55 (29.1)
	0.025−0.050	44 (52.3)	46 (23.9)
	0.051−0.067	2 (0.0)	1 (100.0)
	(Fisher's exact test *p*-value, children)	**(0.005)**	
	Adults, IgE >100 kU/L		
	<0.025	34 (23.5)	67 (29.9)
	0.025−0.050	36 (22.2)	57 (26.3)
	0.051−0.067	2 (0.0)	2 (0.0)

<table>
<tr><th>Study and design[a]</th><th>Results</th></tr>
<tr><td>Evaluation[a]:
Medium confidence
Uncertainty regarding asthma definition. Not informative above 0.050 mg/m^3 because of sample size (*n* = 4).</td><td>
<table>
<tr><td>Children, Asthma</td><td></td><td></td></tr>
<tr><td><0.025</td><td>39 (6.9)</td><td>55 (5.4)</td></tr>
<tr><td>0.025–0.050</td><td>44 (2.3)</td><td>46 (6.5)</td></tr>
<tr><td>0.051–0.067</td><td>2 (0.0)</td><td>1 (0.0)</td></tr>
<tr><td>Adults, Asthma</td><td></td><td></td></tr>
<tr><td><0.025</td><td>34 (5.9)</td><td>67 (4.4)</td></tr>
<tr><td>0.025–0.050</td><td>36 (13.9)</td><td>57 (1.8)</td></tr>
<tr><td>0.051–0.067</td><td>2 (0.0)</td><td>2 (0.0)</td></tr>
<tr><td>(Fisher's exact test *p*-value, adults)</td><td>(0.03)</td><td></td></tr>
</table>
</td></tr>
<tr><td>Krzyzanowski et al. (1990) (United States, Arizona)
Design: Prevalence study, adults (n = 613 ages >15, mean 37) and children (n = 298 ages 5–15, mean 9.3) from 202 households (stratified sample from municipal employees). Participation rate not reported. 67% whites
Exposure: Two one-week samples (opposite seasons) in kitchen, living area, and bedroom (converted from ppb). Household: mean 0.032 mg/m^3
<0.049 mg/m^3 83.7%
0.049–0.074 10.0%
>0.074–0.172 6.3%
Only a few values above 0.111 mg/m^3.
Outcome: Current asthma (doctor diagnosed) and asthma symptoms based on American Thoracic Society questionnaire (physician diagnosed) Ferris (1978).
Evaluation[a]:
Medium confidence
or children, relatively small n in higher exposure categories; for adults, incomplete reporting.
Related references: Quackenboss et al. (1989a); Quackenboss et al. (1989c)</td><td>
N per group (Percentage with Current Asthma)
<table>
<tr><td>Children</td><td colspan="2">Environmental Tobacco Smoke</td></tr>
<tr><td>Exposure (mg/m^3)</td><td>Positive</td><td>Negative</td></tr>
<tr><td><0.049</td><td>106 (15.1)</td><td>142 (8.5)</td></tr>
<tr><td>0.049–0.074</td><td>12 (0.0)</td><td>12 (8.3)</td></tr>
<tr><td>>0.074–0.172</td><td>11 (45.5)</td><td>10 (0.0)</td></tr>
<tr><td>(trend p-value)</td><td>(<0.05)</td><td>(>0.50)</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>
Log-linear models, stratified by environmental tobacco smoke, adjusted for socioeconomic status, ethnicity.
Adults: Results reported as "not significantly related" but rate of wheeze was "somewhat higher" with higher exposure; analyses stratified by environmental tobacco smoke exposure not reported.
</td></tr>
</table>

Organized by study confidence, then descending publication year.
[a]Evaluation of sources of bias or study limitations (see Appendix B.3.4).

Summary of Human Evidence Synthesis Judgments on Immune-Mediated Conditions

Allergic Conditions

The following factors, in particular the consistency, strength, and precision were influential to the synthesis judgment that the human studies of allergic conditions provide *moderate* evidence of formaldehyde exposure-induced effects.

- *Consistency and Study Confidence* Among the seven *high* or *medium* confidence studies in residential and school settings, elevated risks for at least one of the allergy-related conditions examined (symptoms relating to nose, eyes, or skin) at exposures around 0.04 mg/m^3 and above were seen. These studies were conducted in 6 different countries in Europe and Asia, using a variety of study designs that were considered appropriate by the expert panel consulted by EPA.

- *Biological Gradient*: An exposure-response gradient was seen across categories of disease severity, and in the studies of rhinoconjunctivitis in children and eczema in adults *t*hat examined multiple exposure categories.

- *Strength and Precision*: The effect size was relatively small for rhinitis and rhinoconjunctivitis (RR around 1.2); stronger effects were seen in the only study of eczema in adults, and in a study examining the combination of symptoms involving eyes, nose, and skin.

Asthma

The consistent and strong magnitude of effects at formaldehyde levels > 0.05 mg/m^3 were most influential to the synthesis judgment that the human studies of the prevalence of current asthma provide *moderate* evidence of formaldehyde exposure-induced effects.

- *Consistency and Biological Gradient:* The five *medium* or *high* confidence studies at exposures of ≤0.050 mg/m^3 do not indicate risk at these lower exposure levels. In contrast, seven residential or school studies with higher exposure levels reported an elevated risk for asthma, beginning around exposure levels of 0.05 mg/m^3 formaldehyde, with most of these risk ratios around 2.0 for children. Two studies with relatively high exposures included both children and adults (Zhai et al., 2013; Krzyzanowski et al., 1990), and each provides evidence of a greater susceptibility in children. The set of *high* or *medium* confidence studies in residential and school settings were conducted in the United States, Europe, and Asia, and used a variety of study designs that were considered appropriate by the expert panel consulted by EPA. In addition, the three *medium* confidence occupational studies at higher formaldehyde levels similarly observed increased risk, with relative risk estimates between 1.5 and 5.5 for exposures ranging from 0.1 mg/m^3 to > 0.5 mg/m^3 formaldehyde.

- *Strength and Precision*: Large elevations in risk were observed in three *medium* confidence occupational studies; the summary RR for the high-exposure (> 0.1 mg/m^3) occupational studies was 3.79 (95% CI 1.98, 7.28). These findings were supported by smaller (around 2-fold) elevations across residential- and school-based exposure studies above 0.05 mg/m^3.

- *Coherence:* The two *medium* or *high* confidence studies of control of asthma symptoms provide additional support for the effects of formaldehyde exposure among children with asthma at levels at or below those seen in the studies of formaldehyde in relation to the prevalence of asthma. This effect on symptom control is further supported by indirect evidence from a randomized controlled trial designed to improve ventilation rates and thus reduce exposure to formaldehyde and other indoor air pollutants; although levels of formaldehyde showed the largest decline in this study, it is not possible to solely attribute the improvements seen in symptoms control to formaldehyde.

  The studies of wheezing episodes in infants, particularly the birth cohort studies, are not classified as studies of asthma *per se,* but could be indicative of respiratory effects with implications for subsequent disease risk. Thus, the associations seen between residential formaldehyde exposure above 0.50 mg/m^3 and frequency or onset of first wheezing event in these studies provides further support for the relevance of the body of evidence relating to asthma.

Animal Studies

The animal studies most relevant to evaluating potential effects on allergy-related conditions and asthma, as well as a single study suggesting a potential increased vulnerability to respiratory infections, are discussed in the sections below.

Allergy-related conditions and asthma

There are currently no universally accepted animal models applicable to humans for determining dose-response relationships or the potency of low molecular weight chemicals to induce allergic symptoms via the inhalation route (IPCS, 2012). The majority of the experimental animal formaldehyde studies that are most relevant to interpreting these respiratory immune-mediated conditions used the ovalbumin (OVA) murine model, the best studied animal model of asthma. However, the OVA mouse model has several limitations relative to human data for hazard characterization. They include the following:

- Key features of human asthma are absent or minimal in the OVA model, including a lack of airway remodeling (Shin et al., 2009) and minimal airway hyperreactivity and eosinophilic inflammation (Mullane and Williams, 2014)
- OVA challenge models a small subset of endpoints and genes compared with those in humans (Mullane and Williams, 2014)
- The OVA model elicits an acute disease in contrast to the chronic condition in humans (Shin et al., 2009), and the antigen ovalbumin has questionable relevance and poor translatability for human asthma (Mullane and Williams, 2014; Bates et al., 2009)
- A standardized method for OVA administration is lacking; this precludes comparing results between laboratories and evaluating study protocols (Bates et al., 2009)
- There is uncertainty regarding the biological significance of airway hyperreactivity in mice (Bates et al., 2009)

In light of these limitations, EPA concluded for this assessment that the OVA model was more appropriate for examining mechanistic questions in support of hazard identification, based in part on the reasonably large number of well-conducted human studies on these endpoints. As such, the experimental animal studies were considered to be less informative than human studies for drawing interpretations regarding the potential for formaldehyde inhalation exposure to induce or exacerbate allergy-related conditions or asthma, and these studies are discussed below as mechanistic information that may add insight to the apical effects observed in exposed humans.

Other respiratory conditions

One experimental animal study of *medium* or *high* confidence evaluated endpoints related to the potential for formaldehyde exposure to cause other immune-mediated respiratory conditions and reported a decrease in pulmonary antibacterial activity in mice exposed to 1.23 mg/m^3

formaldehyde for less than 1 day (Jakab, 1992). While such a finding could indirectly suggest that formaldehyde exposure might predispose animals to developing lower respiratory infections, this hypothesis was not specifically tested and other notable uncertainties with the study design exist (see Appendix B.3.6). Animal studies of long-term duration that are specifically designed to examine the functional capacity of the respiratory immune response would be informative.

Summary of Animal Evidence Synthesis Judgments

As described above, the available animal studies most relevant to evaluating potential effects on allergy-related conditions and asthma were ultimately considered as mechanistic information rather than as an independent line of evidence. Taken together with the other available mechanistic information (see below), the available data are interpreted to provide *slight* animal evidence for an effect of formaldehyde inhalation on both allergic conditions and the prevalence of current asthma.

Evidence on Mode of Action

An integrated evaluation of the abundant mechanistic information that might be relevant to the potential development of immune-mediated conditions following formaldehyde inhalation exposure is described in Appendix C.7, including evaluations of the individual mechanistic studies (Appendix B.3.6). The evaluation includes the somewhat heterogeneous data related (either directly or indirectly) to possible increases in respiratory infections after exposure, although those data are not discussed in detail in this section. Thus, this discussion focuses on mechanistic information that may inform the potential for formaldehyde to affect allergic conditions or asthma. This includes animal models using the allergen, OVA, which, although they do not fully capture the phenotype of human asthma or allergy-related conditions, can provide insight into some of the mechanistic changes that are relevant to these human conditions.

As shown in Figure 3-12, the integrated analysis identified three pathways describing potential associations between the most relevant mechanistic data available, with several of the initial or early events in these hypothesized pathways (e.g., oxidative stress and molecular or cellular inflammatory changes) generally observed to occur at lower formaldehyde levels than other downstream changes (see Table 3-21). Overall, the mechanistic support for airway inflammation-induced hyperresponsiveness was stronger than for the other potential pathways (i.e., based primarily on moderate evidence of mechanistic events and their relationships). Although a definitive MOA(s) could not be defined, and it is unclear whether some important events would occur with chronic low-level formaldehyde exposure, the data were interpreted to identify an incomplete mechanism(s) by which formaldehyde exposure could cause this effect (see Figure 3-12), providing biological plausibility for inflammatory airway changes that could contribute to respiratory immune-mediated conditions. The mechanistic support for allergic sensitization was less clear (i.e., based on some potentially relevant events interpreted with moderate evidence and, in general, slight evidence for the relationships between events), because

reliable data identifying mechanistic changes typically thought to be essential for sensitization, including changes in IgE, were lacking. However, moderate evidence for several mechanistic changes relevant to these responses was identified, providing some biological support. Importantly, while many individual mechanistic events observed in animals are considered to be relevant to interpreting changes that may occur in the human airways, including potentially amplified responses to inhaled materials, it is unclear how translatable these pathways are to interpreting complex human diseases like asthma, and notable key events have not been observed. Some of the data most informative to drawing conclusions for these health endpoints are described in greater detail below (see Tables 3-21 and 3-22).

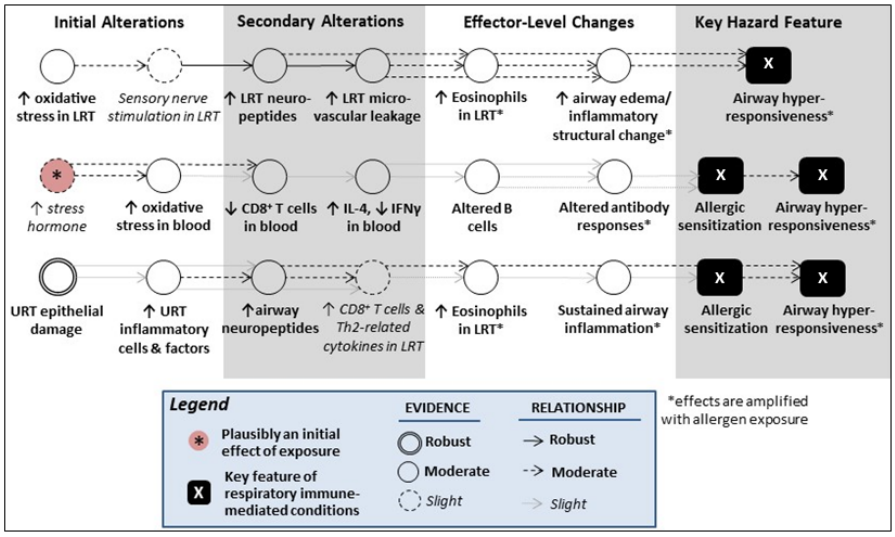


Figure 3-12. Possible mechanistic associations between formaldehyde exposure and immune-mediated conditions, including allergies and asthma.

An evaluation of the formaldehyde exposure-specific mechanistic evidence informing the potential for formaldehyde exposure to cause respiratory health effects (see Tables 3-21 and 3-22, and Appendix C.7) identified these mechanistic pathways as most relevant to interpreting effects on respiratory immune-related conditions such as asthma and allergic responses. Similar to effects on pulmonary function, events related to indirect stimulation of lower respiratory tract (LRT) sensory nerve endings (top pathway) were considered as likely to represent an incomplete mechanism by which formaldehyde inhalation could cause airway hyperresponsiveness, although whether certain events occur with chronic, low-level exposure remains unclear. While the observed alterations to circulating antibodies (i.e., primarily related to IgG and not IgE) following formaldehyde exposure might contribute to the development of both allergic sensitization and airway hyperresponsiveness (middle pathway), in the absence of additional clarifying data, this could not be identified as a likely mechanism for these effects. Likewise, the slight evidence of altered T cell-related airway responses and, secondarily, inflammatory eosinophil responses might be useful for explaining allergic sensitization (bottom pathway) if additional data were available to better explain the pattern and strength of these associations. Conversely, sustained airway inflammation, at least in animals previously sensitized to an allergen, was interpreted as likely to be an incomplete explanatory mechanism for airway hyperresponsiveness, although the sequence of events leading to inflammation remain unclear. Interdependencies between the top and bottom pathways are likely to exist for airway hyperresponsiveness.

It is informative to consider the formaldehyde-specific mechanistic information in the context of the known pathogenesis of human asthma and related conditions. Asthmatic airways are characterized by an infiltration of eosinophils, plasma B cells, activated mast cells, and T cells that contribute to thickening of the airway wall, mucous secretion, airway remodeling, and airway hyperresponsiveness. Initiation and perpetuation of asthma are believed to be the result of T_H2 activity (Cohn et al., 2004). Specifically, T_H2 cells accumulate in the airway and secrete cytokines IL-4 and IL-13, which stimulate B cells to produce IgE (Barnes, 2008) (see Figure 3-13). Mast cells bind IgE and display this immunoglobulin as an allergen-specific receptor on their surfaces. When an allergen binds to this IgE, the mast cell is activated, triggering its release of several bronchoconstrictors (e.g., histamine, leukotrienes), which drive the disease state. T_H2 cells also release IL-5 that activates eosinophils following their migration into the airways. The precise role of eosinophils in asthma is unknown, but they are thought to contribute to inflammation (Barnes, 2008). Immune function and inflammatory responses do not fully explain the pathogenesis of asthma, particularly with respect to the varying phenotypes seen at a clinical level (Anderson, 2008). The interaction between nerve cells and the immune system also includes evidence that neuropeptide release may contribute to neurogenic inflammation and heightened airway responsiveness (Veres et al., 2009).

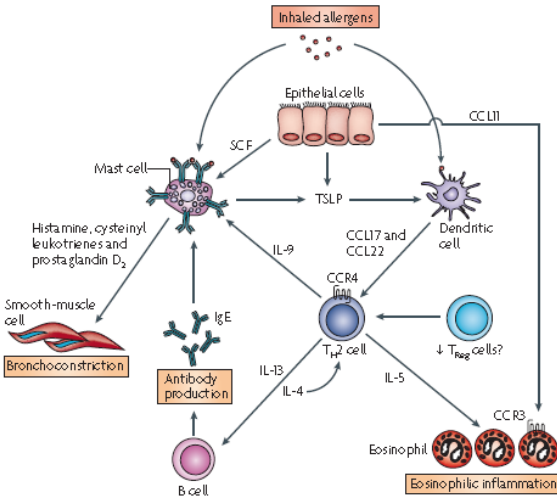


Figure 3-13. Inflammatory and immune cells involved in asthma

Inhaled allergens activate sensitized mast cells by crosslinking surface-bound IgE molecules to release prostaglandin D2. Epithelial cells release stem-cell factor (SCF), which is important for dendritic cells, which are conditioned by thymic stromal lymphopoietin (TSLP) secreted by epithelial cells and mast cells to release the chemokines CC-chemokine ligand 17 (CCL17) and CCL22, which act on CC-chemokine receptor 4 (CCR4) to attract T-helper 2 (T_H2) cells. T_H2 cells have a central role in orchestrating the inflammatory response in allergy through the release of interleukin-4 (IL-4) and IL-13 (which stimulate B cells to synthesize IgE), IL-5 (which is necessary for eosinophilic inflammation), and Il-9 (which stimulates mast-cell proliferation). Epithelial cells release CCL11, which recruits eosinophils via CCR3. Patients with asthma may have a defect in regulatory T (T_{reg}) cells, which may favor further T_H2-cell proliferation. Reprinted from Barnes (2008) with permission from Nature Publishing Group.

The mechanistic evidence that provides the most direct information regarding the potential role of formaldehyde in respiratory hypersensitivity responses consists of five *high or medium* confidence studies, some of which appeared to study the same animals (Swiecichowski et al., 1993; Riedel et al., 1996; Larsen et al., 2013; Ito et al., 1996; Fujimaki et al., 2004b).[20] These studies all differed in the conditions under which formaldehyde affected asthma-relevant endpoints, specifically increased bronchoconstriction and airway hyperresponsiveness, using short-term and acute exposures in sensitized and nonsensitized animals. Formaldehyde exposure of 0.369 to 36.9 mg/m^3 increased bronchoconstriction in guinea pigs exposed for 2 to 8 hours (Swiecichowski et al., 1993). Both the in vivo and ex vivo data from this study indicate that smooth muscle airways are a (presumably indirect) target for formaldehyde. A 5-day formaldehyde exposure of 0.31 mg/m^3 prior to OVA sensitization increased OVA-induced bronchoconstriction in guinea pigs, indicating that formaldehyde exposure enhances reactivity to OVA sensitization (Riedel et al., 1996). Finally, a single 60-minute formaldehyde exposure of 7.0 mg/m^3 induced bronchoconstriction in OVA-sensitized mice housed only in humid, but not dry, environments, indicating that the bronchoconstrictive effects of formaldehyde may be impacted by humidity (Larsen et al., 2013). Taken together with supportive findings from a number of *low* confidence human and animal studies (see Appendix C.7, with study evaluation documentation in Appendix B.3.6), results across multiple species indicate that formaldehyde exposure is sufficient to trigger bronchoconstriction in both sensitized and nonsensitized animals, and that exposure appears to result in the development of hyperresponsive airways,[21] particularly in sensitized animals. This finding is consistent with the evidence supporting increases in microvascular leakage, edema, and other inflammatory airway changes with formaldehyde exposure after allergen sensitization (see Section 3.2.2 and Appendix C.7). Overall, the data do not indicate that formaldehyde is itself immunogenic, but instead suggest formaldehyde may augment immune responses to other allergens.

Other findings that may be relevant to asthma or allergic conditions with at least a moderate level of evidence include increases in airway eosinophils, increases in protein mediators of bronchoconstriction such as tachykinins, and changes in antibody titers (see Section 3.2.2 and Table 3-21). Although a precise role for eosinophils in asthma is unknown (i.e., eosinophilia is not necessary for the development of asthma), eosinophilic airway inflammation (presumably mediated by T_H2 lymphocytes) is a hallmark of asthma (George and Brightling, 2016); the formaldehyde-specific evidence supports that eosinophils are increased in both the upper and

[20]Note: Swiecichowski et al. (1993) and Leikauf (1992) are interpreted to use the same cohort of animals.
[21]As the challenge stimuli used in the formaldehyde studies included allergens as well as nonimmunological stimuli, and because most experiments did not attempt to delineate the specifics of the functional changes, "airway hyperresponsiveness" or "hyperresponsive airways" encompasses any of a range of possible airway features: hyperreactivity (exaggerated response), hypersensitivity (lower dose to elicit response), altered ventilatory parameters (e.g., maximal response, resistance), recovery (longevity of response), or others.

lower airways following formaldehyde exposure, particularly with allergen sensitization (see Section 3.2.2). As activation of eosinophils can induce airway hyperresponsiveness and perpetuate further recruitment of inflammatory mediators into the airway (Cohn et al., 2004), these changes provide coherent biological support for the more apical immune-mediated conditions. In addition, as previously discussed (see Section 3.2.2), it appears that formaldehyde exposure mediates (at least in part) lung inflammation via tachykinins in rats and mice. For example, *high* or *medium* confidence studies show that substance P, a tachykinin and NK1 ligand, is dose-dependently increased in mice exposed for 12 weeks to 0.1 to 2.5 mg/m^3 formaldehyde (Fujimaki et al., 2004b), and that an antagonist of the NK1 receptor can completely abrogate formaldehyde-induced airway inflammation, at least following a 10-minute formaldehyde exposure at 18 mg/m^3 (Ito et al., 1996). Somewhat surprisingly, however, the formaldehyde-induced increases in substance P observed by Fujimaki et al. (2004b) were not observed in animals sensitized to OVA, despite the observation that airway eosinophils were increased at 2.5 mg/m^3 formaldehyde only in animals that were sensitized. Thus, some uncertainties remain. The results related to antibody production, although providing moderate evidence of an effect, were difficult to interpret in the context of their relevance to asthma. Specifically, while evidence from human and animal studies suggests that formaldehyde exposure modifies antibody responses, the most consistently observed responses were associated with changes in IgG, not IgE (see Table 3-21). The relevance of IgG-related responses to asthma or allergies is unclear.

Several other airway changes relevant to asthma or allergic conditions were not supported by moderate or robust evidence in the available studies. For example, slight evidence supports changes in CD8$^+$ T cells or asthma-relevant T_H2 cytokines, including IL-4 [and, to a lesser extent, IL-5 and RANTES (regulated on activation, normal T cell expressed and secreted)], in the lungs after exposure to 0.5–12 mg/m^3 formaldehyde in both sensitized and nonsensitized rodents; however, no changes in IL-13 or histamine have been reported. At the cellular level, while slight evidence supports that CD8$^+$ T cells might be increased in naïve rodents exposed to >7 mg/m^3 formaldehyde, mast cells or other T cell populations did not appear to be changed in the few studies that examined them, and none of the identified studies investigated other cells of interest (e.g., dendritic cells, smooth muscle cells).

Immune-related changes in the blood may also be relevant to interpreting the development of allergic conditions, and possibly asthma, albeit indirectly. A number of studies, across different human and animal populations, spanning an array of formaldehyde exposure scenarios, have reported changes in blood cell counts and secreted factors (see Table 3-22). Although some of the specific changes vary across studies, taken together, the data provide robust evidence of an association between formaldehyde exposure and hematological effects. Interestingly, some changes noted in the blood of individuals exposed to formaldehyde are contrary to the cellular changes noted in the respiratory tract (e.g., CD8$^+$ T cells appear to be increased in the respiratory tract and decreased in the blood) (see additional discussion in Appendix C.7). Potential explanations could

include recruitment of subsets of immunoresponsive cells from the circulation to the irritated and inflamed respiratory tract (e.g., due to a gradient of chemoattractants or other factors across tissue compartments, potentially resulting from sustained airway inflammation), or species differences in responses (i.e., LRT data are mostly from animal studies, while the data in blood are primarily from humans); however, none of the identified human studies report data across tissue compartments, and the animal data do not address such hypotheses. Overall, similar to the cellular changes in the LRT, no explanation exists for how formaldehyde exposure could affect blood immune cell counts.

One of the most consistent blood cell changes observed across studies was a decrease in the total number of white blood cells (WBCs), including moderate evidence of $CD8^+$ T cell decreases following formaldehyde exposure and a corresponding increase in the ratio of $CD4^+/CD8^+$ T cells (see Table 3-22). Depending on the specific stimuli, stimulated $CD8^+$ T cells can produce interferon-γ (IFN-γ) and inhibit production of IL-4 and immunoglobulin (i.e., IgE) responses (Holmes et al., 1997), or their phenotype can be driven toward production of excess IL-4, a situation hypothesized to be associated with atopic asthma (Lourenço et al., 2016). IL-4 can stimulate T cell receptors on $CD4^+$ and $CD8^+$ T cells (Serre et al., 2010), and can both drive $CD4^+$ T cells toward a T_H2 response (Kopf et al., 1993) and influence the activation and development of antigen-specific $CD8^+$ T cell immunity by shifting the phenotype of these cells from IFN-γ production to IL-4 production (Erb and Le Gros, 1996). Moderate evidence provides support for increases in blood IL-4 (slight evidence supports similar increases in the LRT) and decreases in IFN-γ after formaldehyde exposure. Interestingly, several lines of evidence suggest a pattern of immune cell effects related to formaldehyde concentration, with potential stimulation at lower formaldehyde exposure levels and decreases at higher levels. This included slight evidence of changes in total T cells, NK cells, and IL-10. A complex relationship exists between IL-10, NK cells, and subsets of $CD4^+$ T cells (e.g., T_H1 and T_H2 cells), which can affect antibody responses (Moore et al., 2001). However, the potential effects of formaldehyde exposure on the specific phenotype of CD4+ or CD8+ T cells, or on the relationship between changes in lymphocyte populations or secreted factors and respiratory hypersensitivity, have not been well studied and remain to be elucidated.

Several other changes in the blood are of interest to the development of immune-mediated conditions (see Appendix C.7 for additional discussion). Moderate evidence supports that formaldehyde exposure alters the percentage of B cells in the circulation. These cells produce antibodies upon stimulation with antigen (e.g., allergens) and can contribute to airway hyperresponsiveness (Hamelmann et al., 1997). While this finding, along with slight evidence of increased antigenic markers, suggests the potential for alteration of the adaptive immune response after formaldehyde exposure, this observation alone is insufficient to indicate functional changes such as exposure-induced differences in clonal expansion and differentiation to antibody-producing cells, evidence of which would support a more convincing biological relationship. In addition, red blood cell counts were decreased in both human and animal studies (moderate evidence), generally at formaldehyde concentrations above 0.5 mg/m^3, although the relevance of these changes to

respiratory system health effects is unknown. It is plausible that sustained increases in oxidative stress (markers for which are consistently elevated in blood and respiratory tissues after formaldehyde exposure), or other soluble factors that could result from airway inflammation, might affect the viability of circulating erythrocytes and immune cells, or the circulating precursors for these cells; however, no evidence exists to substantiate this hypothesis. An increased level of the circulating stress hormone, corticosterone (the major animal glucocorticoid; in humans, it is cortisol), with short-term, but not acute, formaldehyde exposure is also suggested. Persistent increases in circulating glucocorticoids can also negatively impact the function and health of circulating immune cells, causing immunosuppression of most cell types (O'Connor et al., 2000). However, these potential linkages have also not been examined.

Overall, although additional studies clarifying inconsistencies across the studies would be informative, the available data support a conclusion that formaldehyde exposure can modify immune system function in the blood across a range of concentrations and exposure durations. Many of these observations would benefit from more specific studies on WBCs focused on understanding the phenotype of the modified cells, and the profile of secreted factors in the blood, particularly after formaldehyde exposures of varying duration and concentration. Taken together, the available mechanistic studies provide consistent evidence that formaldehyde may stimulate a number of immunological and neurological processes related to allergic or asthmatic responses; however, a molecular understanding of how formaldehyde exposure might favor asthmatic T_H2 responses has not been established and additional experimental support is necessary to interpret the translatability of these pathways to complex human airway diseases such as asthma. Importantly, the evidence supports that formaldehyde exposure induces bronchoconstriction with and without allergen sensitization, providing strong biological support for the development of hyperresponsive airways that could contribute to at least some of the observed respiratory immune-related symptoms. This heightened bronchoconstriction response may be due to a combination of neurogenic mechanisms through reduction of anti-inflammatory molecules or increased tachykinins, increased T_H2 cytokines and antibodies, and eosinophil recruitment and activation in the lung. Immune- and inflammatory-related changes in the blood provide additional support for exposure-induced alterations relevant to the development of these immune-mediated conditions. Additional studies are necessary to clarify the incomplete understanding of mechanisms that describe the association between formaldehyde exposure and these effects, as well as the exposure concentration and duration dependence of some of the more influential findings from the current studies. Collectively, the available studies provide mechanistic support for the biological plausibility of the formaldehyde exposure-induced changes observed in humans.

Table 3-21. Mechanistic evidence most informative to the development of immune-mediated conditions after formaldehyde inhalation[a]

Endpoint		Endpoint-specific findings and confidence	Summary of evidence	Conclusion
Modifications in the upper or lower respiratory tract (URT or LRT)				
Some of these mechanistic changes have been discussed in previous sections. *See Section 3.2.2, Evidence on Mode of Action, for presentation of the evidence for:* **↑ LRT oxidative stress** (moderate); **LRT sensory nerve activation** (slight); **↑ LRT neuropeptides** (moderate); **↑ LRT microvascular leakage** (moderate); **↑ LRT eosinophils** (moderate); **↑ airway edema or other inflammatory structural change**; and **URT epithelial damage** (robust)				
Upper airway indicators of altered immune function (inferred from URT infections)	*High or Medium*	*Human*: Increased frequency and duration of URT infections in symptomatic workers; increased chronic URT inflammation (and decreased function of blood neutrophils, but N/C in leukocyte counts) in exposed workers (Lyapina et al., 2004): chronic (years) exposure at 0.87 mg/m^3 (Note: recent URT infection was often an exclusion criterion in observational studies focusing on pulmonary function)	Indirect evidence of decreased immune capacity in a human study of long-term exposure at 0.87 mg/m^3 (note: mRNA changes were not necessarily indicative of a decreased immune response)	Slight (indirect evidence of ↑URT infection)
		Animal: mRNA changes suggestive of altered immune response (Andersen et al., 2010): short-term (≥1 week) exposure at ≥12.3 mg/m^3		
	Low	*Human*: None	No evidence to evaluate	
		Animal: None		
Lower airway indicators of altered immune function (inferred from LRT infections)	*High or Medium*	*Human*: Increased LRT infections in infants (Roda et al., 2011): 32–41% increase in incidence per 0.0124 mg/m^3 increase in formaldehyde (LOD: 0.008 mg/m^3); ~1-year exposure at 0.020 mg/m^3 (median)	Indirect evidence in a single study of infants exposed to a median of 0.020 mg/m^3 observing an association between exposure and increased infections. One acute mouse study also provided indirect support for an increased likelihood of respiratory infections.	Moderate (indirect support for an increased propensity for LRT infections, particularly during development)
		Animal: Decreased antibacterial activity in mice (Jakab, 1992): acute exposure at 1.23 mg/m^3, noting that this finding appeared to be particularly sensitive to the pattern of formaldehyde exposure		
	Low	*Human*: Increased emergency room visits for episodes including LRT infections (Rumchev et al., 2002): children aged 6–36 months at mean levels 0.028–0.030 mg/m^3 (maximum 0.12–0.22)	Direct and indirect evidence of impaired LRT immune function in children and in a short-term rat study, respectively	
		Animal: Decreased expression of immune-related genes in rat lung (Sul et al., 2007), specifically HSP701a (involved in antigen presentation), complement four binding protein (binds necrotic or apoptotic cells for cleanup), and Fc portion of IgGiii (involved in leukocyte activation): 2 week exposure at ≥6.15 mg/m^3		
Changes in pulmonary function with	*High or Medium*	*Human*: None	Acute and short-term studies in two animal species demonstrate that formaldehyde increases	Robust (↑ Hyper-responsive airways[b])
		Animal: [allergen challenge]: With ovalbumin [OVA] sensitization, increased airway obstruction in guinea pigs (Riedel et al., 1996): short-term exposure at 0.31 mg/m^3 and		

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
challenge (e.g., with broncho-constrictor allergen) (Note: un-provoked responses are not included)		increased reactivity in mice (Larsen et al., 2013): acute exposure at ~5–7 mg/m^3 in humid or dry environments; [acetylcholine challenge]: Increased airway resistance and reactivity in guinea pigs (Swiecichowski et al., 1993; Leikauf, 1992): acute exposure at 1.23 mg/m^3	responsiveness to allergens and bronchoconstrictors, particularly with prior sensitization, at levels as low as 0.31 mg/m^3	
	Low	*Human*: [histamine challenge]: Hyperreactive airways with prolonged exposure (Górski and Krakowiak, 1991): ≥1 year exposure at ≤0.5 mg/m^3, but N/C after acute exposure (Krakowiak et al., 1998): at 0.5 mg/m^3; [allergen challenge]: hypersensitivity with acute exposure when exposure was restricted to mouth breathing in allergic asthmatics with a large allergen (mite) (Casset et al., 2006): acute exposure at 0.1 mg/m^3; N/C after oronasal exposure in allergic asthmatics using a different allergen (pollen), including a methacholine (MCh) responsiveness test after allergen exposure (Ezratty et al., 2007): acute exposure at 0.5 mg/m^3	Suggestive evidence of increases with prolonged exposure, and possibly acute mouth-breathing exposure when challenged with specific allergens, but not acute exposure alone, to ≤0.5 mg/m^3 in human adults; also, increased at ≥3 mg/m^3 in short-term or acute studies across three species, particularly with prior sensitization	
		Animal: [MCh challenge]: Hyperresponsive airways (increased reactivity and sensitivity) with exposure in mice and rats (Wu et al., 2013; Qiao et al., 2009; Liu et al., 2011a): short-term exposure at ≥3 mg/m^3, and in monkeys (Biagini et al., 1989): acute exposure at 3.1 mg/m^3; in mice and rats, this response was amplified with OVA sensitization; TRP antagonists reduced the hyperresponsiveness in mice (Wu et al., 2013)		
Sustained Inflam-mation	*High or Medium*	*Human*: Increased exhaled nitric oxide, a noninvasive and indirect marker of lower airway inflammation and oxidative stress, in healthy or asthmatic children (Franklin et al., 2000; Flamant-Hulin et al., 2010): unknown exposure duration (likely months to years; in classrooms or homes) at 0.04–0.06 mg/m^3	Immune cell counts are continually elevated in a subchronic mouse study with allergen stimulation at 2.46 mg/m^3; increased biomarkers (indirect evidence) of lower airway inflammation are observed in children with prolonged exposure.	Moderate (may require allergen sensitization)
		Animal: Eosinophils and monocyte counts remain elevated with continued exposure for subchronic duration with allergen (OVA) sensitization (Fujimaki et al., 2004b): 12-week exposure at 2.46 mg/m^3		
	Low	*Human*: None	BAL cell counts and histologic evidence suggest that inflammation persists for several weeks with short-term exposure, and these effects are amplified by allergen	
		Animal: Immune cell counts were increased with short-term exposure in several studies at ≥0.5 mg/m^3 (see Table 1-23; histological evidence of inflammation without epithelial damage was noted in short-term exposure studies, typically at higher concentrations, which were amplified by allergen (e.g., ≥3 mg/m^3; (Wu et al., 2013; Kimura et al., 2010)		
↑ CD8+ T cells in LRT	*High or Medium*	*Human:* none	No evidence to evaluate	Slight (at >7 mg/m^3, but allergen
		Animal: none		
	Low	*Human:* none		

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
		Animal: Increased in short-term exposure studies in rats [at 7.4 mg/m^3; (Sandikci et al., 2007b)] and mice [at 12.3 mg/m^3; (Jung et al., 2007)]; no change with short-term exposure in a mouse study at ≥6.2-12.3 mg/m^3 (Kim et al., 2013a)	A study in rats and another in mice suggest that CD8+ T cells in the BAL might be increased after short-term exposure to high (>7 mg/m3) levels, although a second mouse study reported no changes	stimulus unstudied) (note: mixed, indeterminate evidence for B cells, and CD4+ cells; Appendix A.5.6)
↑ Th2-related (primarily) cytokines in LRT	*High or Medium*	*Human:* none *Animal*: none	No evidence to evaluate	Slight (↑ IL-4 at ≥0.5 mg/m^3 and IL-5 at >6 mg/m^3) (note: mixed, indeterminate evidence for IL-10, IL-6, IL-13, and for Th1 cytokines; see Appendix A.5.6)
	Low	*Human:* No change in IL-4 or IL-5 at 0.5 mg/m^3 after acute exposure and pollen coexposure (Ezratty et al., 2007) *Animal*: ↑ IL-4 in 4 studies in mice and one study in rats (all short-term exposure) testing exposures of 0.5-12.3 mg/m^3 and observing larger increases with antigen (OVA) administration (Wu et al., 2013; Qiao et al., 2009; Lu et al., 2005; Liu et al., 2011a; Jung et al., 2007) ↑ IL-5 in 2 short-term exposure studies in mice at ≥6.2 mg/m^3 (Sadakane et al., 2002; Jung et al., 2007) No change in IL-4 in a short-term exposure study in mice at >12.3 mg/m^3 with co-administered house dust mite antigen (Sadakane et al., 2002) [c]	IL-4 was increased in short-term studies of rats and mice at levels as low as 0.5 mg/m^3, with amplified increases with antigen; IL-5 was increased in 2 of 3 studies in mice only testing higher (>6mg/m^3) levels	
Modifications in the blood				
[[See Table 3-22 for cellular and cytokine responses in the blood]]				
Total IgE	*High or Medium*	*Human*: None *Animal*: No evidence suggesting changes (Fujimaki et al., 2004b): subchronic exposure at ≤2.46 mg/m^3	Slight (at ≥ 3 mg/m^3) Based on no changes in a *high or medium* confidence subchronic mouse study at ≤2.46 mg/m^3 and evidence of increased IgE in two short-term *low* confidence formalin studies in mice at ≥3 mg/m^3, but no evidence for changes in *low* confidence studies in mice or humans at <2 mg/m^3	Moderate for IgG Slight for IgE (only with specific exposure scenarios) Indeterminate for IgM or IgA (i.e., very little evidence; data not shown: see Appendix A.5.6)
	Low	*Human*: No evidence suggesting changes (Wantke et al., 1996b; Wantke et al., 2000; Palczynski et al., 1999; Ohmichi et al., 2006; Erdei et al., 2003): short-term exposure at ≤1.8 mg/m^3 (duration in Erdei et al. unknown) *Animal*: Evidence of increases in mice, which were increased further by OVA sensitization (Wu et al., 2013; Jung et al., 2007): short-term exposure at ≥3 mg/m^3; evidence of no changes in mice by FA alone (Kim et al., 2013b; Gu et al., 2008), although FA exacerbated house dust mite-induced IgE (Kim et al., 2013b): short-term exposure at 0.12−1.2 mg/m^3		
Formal-dehyde (FA)-Specific IgE	*High or Medium*	*Human*: Elevated in one study of children (Wantke et al., 1996a): years of exposure (assumed) at ~0.06 compared to ~0.03 mg/m^3 (note: elevations were unrelated to symptoms); N/C in adults (Kim et al., 1999): 4 years at 3.74 mg/m^3 *Animal*: None	Slight (in children) Based on increases in a *high or medium* confidence long-term study of children at <0.1 mg/m^3; although, no	

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
	Low	*Human*: No evidence of changes across multiple studies in adults (Zhou et al., 2005; Wantke et al., 1996b; Thrasher et al., 1987; Ohmichi et al., 2006; Górski and Krakowiak, 1991): short-term (weeks) or long-term (years) exposure at ~0.1–1.81 mg/m^3; however, findings were unclear in two adult studies of long-term exposure in which a small proportion of subjects did have FA-IgE (Thrasher et al., 1990; Dykewicz et al., 1991), and one study noted slight increases with longer exposure (Wantke et al., 2000): 10 week, not 5 week, at 0.265 mg/m^3	changes were observed in a *high or medium* confidence long-term study of adults at 3.74 mg/m^3 and there was no clear evidence of changes across multiple *low* confidence short-term and long-term studies in adults at ≤1.81 mg/m^3	
		Animal: No change in guinea pigs with acute challenge (Lee et al., 1984) at 2.5 or 4.9 mg/m^3 after short-term exposure to 7.4 or 12.3 mg/m^3 (note: no measures without formaldehyde and isotype was unspecified)		
Antigen-Specific IgE (does not include FA-specific Ig)	*High or Medium*	*Human*: None	Slight Based on no changes in a *high or medium* confidence subchronic study with i.p. antigen sensitization and evidence in *low* confidence short-term studies in mice exposed to ≥1 mg/m^3 that appears to be highly situational (e.g., dependent on duration and periodicity of formaldehyde exposure, and antigen type and administration route)	
		Animal: N/C in OVA-IgE (Fujimaki et al., 2004b): 12 week exposure at 0.1–2.46 mg/m^3 (OVA i.p.)		
	Low	*Human*: None		
		Animal: Increased OVA-specific IgE in mice in two short-term exposure studies (Tarkowski and Gorski, 1995; Gu et al., 2008): 10 d at 2 mg/m^3 (but not 1 d/week for 7 week, or when OVA sensitization i.p.) and 5 week at 0.98 mg/m^3 with i.p. OVA (but not ≤4 week), respectively; however, N/C in mice in three short-term (all 4-week) exposure studies: (Wu et al., 2013) at 3 mg/m^3 with s.c. OVA sensitization, (Kim et al., 2013b) at 0.2–1.23 mg/m^3 with dermal house dust mite (HDM) sensitization, and (Sadakane et al., 2002) at >12.3 mg/m^3 with i.p. HDM sensitization [b]		
Total IgG	*High or Medium*	*Human*: Decreased in a single study of exposed workers (Aydın et al., 2013): 7 year exposure at 0.264 mg/m^3	Moderate Based on decreased total IgG in a *high or medium* confidence long-term study in adult workers exposed to 0.264 mg/m^3, and a *high or medium* confidence short-term study in rats exposed to ≥6.15 mg/m^3. IgG isoforms were affected in 2 of 3 *low* confidence short-term mouse studies, but not a *low* confidence study of children at low levels	
		Animal: Decreased total IgG in rats (Sapmaz et al., 2015): short-term exposure at ≥6.15 mg/m^3		
	Low	*Human*: N/C in children at ~0.007–0.07 mg/m^3 (Erdei et al., 2003): unknown exposure duration (likely months-years)		
		Animal: IgG1 (N/C in IgG2a) increased by FA alone, whereas FA exacerbated IgG2a increases (N/C in IgG1) in atopic-prone mice (Kim et al., 2013b): short-term exposure at 0.25, but not 1.2, mg/m^3; increased IgG1 and IgG3, but decreased IgG2a and 2b, in C57 mice (Jung et al., 2007): short-term exposure at ≥6.15 mg/m^3; N/C in IgG Balb/c mice (Gu et al., 2008): short-term exposure at <1 mg/m^3		
FA-Specific IgG	*High or Medium*	*Human*: Slight (i.e., <10%) increase in a single study of adults (Kim et al., 1999): years of exposure at 3.74 mg/m^3	Moderate Based on slight increases in a *high or medium*	
		Animal: None		

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
	Low	*Human*: Increased in two studies (Thrasher et al., 1987; Thrasher et al., 1990) and unclear in one study in which 5/55 subjects did have FA-IgG (Dykewicz et al., 1991): all three studies examined years of exposure at <0.1–<1.0 mg/m^3; N/C in one study (Wantke et al., 2000): short-term exposure at 0.265 mg/m^3	confidence long-term study of adults at 3.74 mg/m^3 and increases in *low* confidence studies of adults with long-term exposure at <1 mg/m^3, but not with short-term exposure at higher levels; studies in children were not identified	
		Animal: No change in guinea pigs with acute challenge (Lee et al., 1984) at 2.5 or 4.9 mg/m^3 after short-term exposure to 7.4 or 12.3 mg/m^3 (note: the study did not present measures without formaldehyde exposure, and isotype was unspecified)		
Antigen-Specific IgG (does not include FA-specific Ig)	*High or Medium*	*Human*: None	Moderate (with inhaled antigen) Based on increased OVA-IgG1 in a *high or medium* confidence short-term study in guinea pigs at 0.31 mg/m^3 with inhaled allergen, but not a longer *high or medium* confidence mouse study at similar levels using injected allergen. Similarly, a long-term *low* confidence study observed increased IgG sensitization to airway antigens in children, whereas several *low* confidence studies in mice and rats suggest that IgG sensitization does not occur when antigen is injected.	
		Animal: Increased OVA-specific IgG1 in guinea pigs (Riedel et al., 1996): 5 d at 0.31 mg/m^3 with inhaled OVA; questionable decrease (i.e., effects were observed at 0.49, but not 2.46, mg/m^3) in OVA-IgG1 and OVA-IgG3 in mice (Fujimaki et al., 2004b): 12 weeks exposure with i.p. OVA sensitization (N/C in OVA-IgG2)		
	Low	*Human*: Increased IgG against 2 bacterial pathogens in 3rd grade children with respiratory complaints (Erdei et al., 2003): <0.1 mg/m^3, unknown exposure duration (likely years, home measures)		
		Animal: N/C in OVA-IgG or Der f-IgG1 in mice (Wu et al., 2013; Sadakane et al., 2002; Gu et al., 2008): up to 5 week exposures at 0.123–3 mg/m^3 or >12.3 mg/m^3 [b]; N/C in IgG specific to vaccine antigens in rats (Holmstrom et al., 1989a): 22 months exposure at 15.5 mg/m^3. In all cases, s.c. or i.p. exposure was used for sensitization		
↑ **Circulating Stress Hormones**	*High or Medium*	*Human*: None	Increased at 3 mg/m^3 formaldehyde in a study in rats with short-term, but not acute, exposure	Slight
		Animal: Increased corticosterone in rats with short-term, but not acute, exposure (Sorg et al., 2001a): at ~3 mg/m^3		
	Low	*Human*: None	No evidence to evaluate	
		Animal: None		
Modifications in other non-Respiratory Tissues				
↑ **Oxidative stress in nonrespira-tory tissues**	*High or Medium*	*Human*: Increased marker of lipid peroxidation in adult serum lymphocytes (Bono et al., 2010): likely months-to-years exposure (assumed) at ≥0.066 mg/m^3; Increased F2-Isoprostanes (suggested as the best in vivo biomarker of lipid peroxidation) in urine (Romanazzi et al., 2013): 0.21 mg/m^3 chronic occupational exposure (indirect for effects in blood), although smoking and formaldehyde were not additive, both were independently associated with ROS—Note: serum and urine IsoP measures are often correlated [e.g., (Rodrigo et al.,	Two studies in adults indicate elevated oxidative stress markers at ≥0.066–0.21 mg/m^3 with long-term exposure. Given the uncertainty regarding use of urine to reflect associations in blood, one study	Moderate

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
		2007)], suggesting that urine levels may reflect similar serum changes	contributes as indirect evidence	
		Animal: None		
	Low	*Human*: Increased oxidative stress biomarkers (F2-Isoprostanes; malondialdehyde) in urine (Bellisario et al., 2016): work-shift exposure at ~0.034 mg/m^3 (indirect for effects in blood; responses likely reflect short-term exposure)	Several studies in three species suggest increases in markers of oxidative stress with acute or short-term exposure, even at formaldehyde levels ≤1 mg/m^3; it is not clear whether and to what extent this persists with long-term exposure	
		Animal: Increased oxidative stress markers in mice (Ye et al., 2013b; Matsuoka et al., 2010): acute or short-term exposures at as low as 0.12 mg/m^3; increased oxidative stress markers and protein indicators in rats (Im et al., 2006; Aydin et al., 2014): short-term exposure at 6.48–12.3 mg/m^3, although one study with a longer exposure (10 week) observed a decrease in MDA in rats (Katsnelson et al., 2013): at 12.8 mg/m^3; other indicators in rodents included decreased GSH (Ye et al., 2013b; Katsnelson et al., 2013) and increased NO and SOD (Matsuoka et al., 2010): short-term exposure at ≥1 mg/m^3		
Cell counts in immune tissues (not including bone marrow)	*High or Medium*	*Human*: None	Suppression of CD8+ T cells in immune tissues (e.g., spleen) is indicated in one 8-week mouse study, with indirect support from a second short-term mouse study, at around 2 mg/m^3 ; effects on CD4$^+$/CD8$^+$ ratio were mixed across 2 subchronic mouse studies	Moderate (for ↓ CD8+ T cell response in spleen and thymus) Slight NK cells (↑ at low level; ↓ at high level) Indeterminate for other cell counts
		Animal: Decreased CD8+ T cells and increased CD4$^+$/CD8$^+$ ratio in both thymus (immature immune cells) and spleen (mature immune cells) in male mice (Ma et al., 2020): Eight weeks of exposure at 2 mg/m^3; No change in splenic CD4$^+$/CD8$^+$ ratio in female mice (Fujimaki et al., 2004b): 12 week at up to 2.46 mg/m^3; Increased splenic regulatory T cells (subset of CD4+) and indirect markers for suppression of effector T cell (CD8+) activity in female mice (Park et al., 2020): short-term exposure at ≥1.38 mg/m^3		
	Low	*Human*: None	Multiple short-term mouse studies suggest that overall splenic cell T and B cells are unchanged; however, 2 studies suggest that NK cells may be affected (1 study showed NK cells were stimulated at low formaldehyde levels, and another that high levels are inhibitory/toxic)	
		Animal: N/C in tissue weight, total cellularity or T or B cell counts in mice (Kim et al., 2013a; Gu et al., 2008; Dean et al., 1984); altered NK cell number and function was noted in mice, with one study showing decreases (Kim et al., 2013a): 2–3 week at 12.3 mg/m^3, and another showing increases (Gu et al., 2008): 5 week at up to 0.12 mg/m^3, and a third showing N/C in lymphocyte proliferation, functional parameters, IgM production, or NK cytotoxicity (Dean et al., 1984): 3 week at 18.5 mg/m^3		
Systemic indicators of altered immune function	*High or Medium*	*Human*: None	No evidence to evaluate	Indeterminate
		Animal: None		
	Low	*Human*: Increased autoantibodies in adults (Thrasher et al., 1990): long-term exposure at 0.06–0.95 mg/m^3	1 study in adults suggests that autoantibodies are	

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
		Animal: Improved cell-mediated immune response to bacteria challenge, but N/C against tumor challenge or delayed-type hypersensitivity response in mice (Dean et al., 1984): 3 week exposure at 18.5 mg/m^3 (Note: N/C in vitro measures of immune cell function in the same study)	elevated with low-level, long-term exposure; somewhat in contrast, one mouse study suggests short-term high-level exposure improves host response to bacteria	

[a]Several studies examining the lineage and maturity of immune and non-immune cells in the bone marrow and other systemic tissues (e.g., blood; spleen) are not discussed in this section. Although it is possible that differences in the maturation phenotype of cells could indirectly contribute to the immune changes of interest to this section, such alterations would be expected to cause functional or other detectable changes in more apical mechanistic events relevant to immune responses in the respiratory system. Thus, this discussion focuses on those mechanistic events considered more directly relevant to these POE outcomes. Please see Section 3.3.3 for a discussion of these cell lineage and maturation markers in the context of lymphohematopoietic cancer MOA.

[b]As the challenge stimuli used in the formaldehyde studies included allergens as well as nonimmunological stimuli, and because most experiments did not attempt to delineate the specifics of the functional changes, "airway hyperresponsiveness" or "hyperresponsive airways" encompasses any of a range of possible airway features: hyperreactivity (exaggerated response), hypersensitivity (lower dose to elicit response), altered ventilatory parameters (e.g., maximal response, resistance), recovery (longevity of response), or others.

[c]Reported as 0.5% formaldehyde solution; concentration assumed to be >12.3 mg/m^3 (Sadakane et al., 2002).

Table 3-22. Summary of changes in cell counts and soluble immunological factors in the blood following formaldehyde exposure

Endpoint		No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
		mg/m^3	Length[b]	References (details)	mg/m^3	Length[b]	References (details)	
White blood cells (WBCs)	Total WBCs	**0.87** **0.25** 0.018	**Years** **Years** Years[c]	**(**Lyapina et al., 2004**)*** **(**Aydın et al., 2013**)*** (Erdei et al., 2003) (asthmatic children)	**↓ 1.6** ↓ N/A[e] (≤1) ↓≤0.29	**Years (same cohort)** Year vs. Mo Years	**(**Hosgood et al., 2013**)*;** **(**Zhang et al., 2010**)*[d]** **(**Bassig et al., 2016**)*** (Thrasher et al., 1990) (Kuo et al., 1997)	Moderate ↓ in WBCs [g]
		≥9.23	**8 week**	**(**Morgan et al., 2017**) (mice)***	**≥2.46**[f] (indirect) ↓ 0.5–3	**Short** Short	**(**Rager et al., 2014**)* (rats)** (Zhang et al., 2013b) (mice)	

Endpoint			No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
			mg/m^3	Length[b]	References (details)	mg/m^3	Length[b]	References (details)	
Granulocytes	All					**↓ 1.6**	**Years (same cohort)**	**(Hosgood et al., 2013)*; (Zhang et al., 2010)*[d] (Bassig et al., 2016)***	Slight ↓ in granulocytes (appears to reflect potential changes in neutrophils at higher concentrations with short-term or longer exposure)
			18.5	Short	(Dean et al., 1984) (mice) [h]				
	Neutrophils		**0.25** ≤0.29 0.018	**Years** Years Years [c]	**(Aydın et al., 2013)*** (Kuo et al., 1997) (Erdei et al., 2003) (asthmatic children)	**↓ 0.87**	**Years**	**(Lyapina et al., 2004)* (i.e., function, in workers with URT dysfunction)**	
			≥9.23 0.5–3	**8 week** Short	**(Morgan et al., 2017) (mice) (mice)** (Zhang et al., 2013b) (mice)	↓ 13	Short	(Katsnelson et al., 2013) (rats)	

Endpoint			No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
			mg/m^3	Length[b]	References (details)	mg/m^3	Length[b]	References (details)	
		Eosinophils	≤0.29 0.018	Years Years [c]	(Kuo et al., 1997) (Erdei et al., 2003) (asthmatic children)				
			≥9.23	**8 week**	**(Morgan et al., 2017)** **(mice) (mice)**				
		Basophils	≤0.29	Years	(Kuo et al., 1997)				
			No animal studies identified						
	Lymphocytes	All	**0.2 & 0.8** N/A[e] (≤1) 0.51 ≤0.29 0.018	**Months** Year vs. Mo Weeks Years Years [c]	**(Jia et al., 2014)*** (Thrasher et al., 1990) (Ying et al., 1999) (Kuo et al., 1997) (Erdei et al., 2003) (asthmatic children)	**↓ 1.6** **↑ 0.25**	**Years (same cohort)** **Years**	**(Hosgood et al., 2013)*;** **(Zhang et al., 2010)* [d]** **(Bassig et al., 2016)*** **(Aydın et al., 2013)***	Indeterminate (multiple changes noted, but pattern is indiscernible)

Endpoint	No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
	mg/m^3	Length[b]	References (details)	mg/m^3	Length[b]	References (details)	
	18.5 **≥9.23**	Short **8 week**	(Dean et al., 1984) (mice) [h] **(Morgan et al., 2017)* (mice)**	↑ 13 ↓ 0.5–3	Short Short	(Katsnelson et al., 2013) (rats) (Zhang et al., 2013b) (mice)	
B Cells	**1.6** **0.25** 0.09–0.7	**Years (same cohort)** **Years** Years	**(Hosgood et al., 2013)*;** **(Zhang et al., 2010)*** **(Bassig et al., 2016)*** **(Aydın et al., 2013)*** (Thrasher et al., 1987)	**↑ 0.99** **↑ 0.2 & 0.8** ↑ N/A[e] (≤1) ↑ 0.51 **↓ 0.47** **↓ 0.36**	**Months** **Months** Year vs. Mo Weeks **Years** **Years**	**(Ye et al., 2005)* (peak levels up to 1.69 mg/m^3)** **(Jia et al., 2014)*** (Thrasher et al., 1990) (Ying et al., 1999) **(Costa et al., 2019)* (peak levels to 3.94 mg/m^3)** **(Costa et al., 2013)* (peak levels to 0.69 mg/m^3)**	Moderate for altered number of B cells (direction of change may differ by exposure levels or duration)
	No animal studies identified						
T Cells (Total)	**0.2–0.8** N/A[e] (≤1)	**Months** Year vs. Mo	**(Jia et al., 2014)*** (Thrasher et al., 1990)	**↓ 1.6** **↓ 0.99** **↑ 0.36** **↑ 0.25** ↓ 0.9 ↓ 0.51 ↓ ≥0.09	**Years (same cohort)** **Months** **Years** **Years** Years Weeks Years	**(Hosgood et al., 2013)*;** **(Zhang et al., 2010)* [d]** **(Bassig et al., 2016)*** **(Ye et al., 2005)* (peak levels to 1.69 mg/m^3)** **(Costa et al., 2013)* (peak levels to 0.69 mg/m^3)** **(Aydın et al., 2013)*** (Jakab et al., 2010) (Ying et al., 1999) (Thrasher et al., 1987) (levels up to 0.68 mg/m^3)	Slight for altered total T cells (mixed results suggest dose-dependence, with ↓ at higher levels; possible ↑ at low levels, with longer duration)

Endpoint	No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
	mg/m^3	Length[b]	References (details)	mg/m^3	Length[b]	References (details)	
				↑ 7.4	Short	(Sandikci et al., 2007a, b) (rats)	
T Cells (CD4$^+$)	**1.6** **0.99** **0.47** **0.25** **0.2–0.8**	**Years (same cohort)** **Months** **Years** **Years** **Months**	**(Hosgood et al., 2013)*** **(note: ↓ T_{reg} cells)** **(Zhang et al., 2010)*** **(Bassig et al., 2016)*** **(Ye et al., 2005)* (peak levels up to 1.69 mg/m^3)** **(Costa et al., 2019)* (peak levels to 3.94 mg/m^3)** **(Aydın et al., 2013)*** **(Jia et al., 2014)***	**↑ 0.36** ↓ 0.51	**Years** Weeks	**(Costa et al., 2013)* (peak levels to 0.69 mg/m^3)** (Ying et al., 1999)	Indeterminate (mostly N/C, but variable and, considering also studies of spleen (above), suggests effects might exist for certain subsets of CD4 cells)
	No animal studies identified						
T Cells (CD8$^+$)	**0.36** **0.25** **0.2–0.8**	**Years** **Years** **Months**	**(Costa et al., 2013)* (peak levels to 0.69 mg/m^3)** **(Aydın et al., 2013)*** **(Jia et al., 2014)***	**↓ 1.6** **↓ 0.99** ↓ 0.51 **↑ 0.47**	**Years (same cohort) Months** Weeks **Years**	**(Hosgood et al., 2013)*;** **(Zhang et al., 2010)* [d]** **(Bassig et al., 2016)*** **(particularly memory cells)** **(Ye et al., 2005)*** **(peak levels to 1.69 mg/m^3)** (Ying et al., 1999) **(Costa et al., 2019)* (peak levels to 3.94 mg/m^3)**	Moderate ↓ CD8 and ↑ CD4/CD8 ratio (likely dose-dependence, as consistent observations are at higher levels)

Endpoint	No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
	mg/m^3	Length[b]	References (details)	mg/m^3	Length[b]	References (details)	
	N/C CD4/CD8 ratio in these 3 studies (or in (Thrasher et al., 1990) comparing durations)			**↑ CD4/CD8 ratio in all but one of these studies**			
	No animal studies identified						
NK Cells				**↓ 1.6** **↓ 0.36** **↑ 0.25** **↑ 0.2 N/C at 0.8**	**Years (same cohort)** **Years** **Years** **Months**	**(Hosgood et al., 2013)*; (Zhang et al., 2010)* [d]; (Bassig et al., 2016)*** **(Costa et al., 2013)* (peak levels to 0.69 mg/m^3)** **(Aydın et al., 2013)*** **(Jia et al., 2014)***	Slight for altered number of NK cells (mixed results suggest dose-dependence like total T cells)
	No animal studies identified						
Mono cytes	**1.6** **0.25**	**Years (same cohort)** **Years**	**(Hosgood et al., 2013)*; (Zhang et al., 2010)* [d] (Bassig et al., 2016)*** **(Aydın et al., 2013)***	↑ 0.018	Years [c]	(Erdei et al., 2003) (asthmatic children)	Indeterminate (data suggest N/C, at least in human adults)

Endpoint	No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
	mg/m^3	Length[b]	References (details)	mg/m^3	Length[b]	References (details)	
	≥9.23	**8 week**	**(Morgan et al., 2017) (mice)**	↓ 18.5 ↓ 0.5, not 3	Short Short	(Dean et al., 1984) (mice) (Zhang et al., 2013b) (mice)	
Red Blood Cells	**0.25** ≤0.29 0.018	**Years** Years Years [c]	**(Aydın et al., 2013)*** (Kuo et al., 1997) (Erdei et al., 2003) (asthmatic children)	**↓ 1.6** **↓ 0.87**	**Years** **Years**	**(Hosgood et al., 2013)*;** **(Zhang et al., 2010)* [d]** **(Lyapina et al., 2004)* (association with duration)**	Moderate ↓in RBCs[i] (suggests dose- and duration-dependence)
	≥9.23	**8 week**	**(Morgan et al., 2017) (mice)**	↓ 0.5–3	**Short**	(Zhang et al., 2013b) (mice)	
Platelets	**0.87** ≤0.29 0.018	**Years** Years Years [c]	**(Lyapina et al., 2004)*** (Kuo et al., 1997) (Erdei et al., 2003) (asthmatic children)	**↓ 1.6**	**Years (same cohort)**	**(Hosgood et al., 2013)*;** **(Zhang et al., 2010)* [d]** **(Bassig et al., 2016)***	Slight ↓ in platelets [j] (possible dose-dependence as noted above)
	≥9.23	**8 week**	**(Morgan et al., 2017) (mice)**	↑ 0.5–3	Short	(Zhang et al., 2013b) (mice)	
Secreted factors and immune — Primarily Th1-related — TNF-α	**1.8** **0.2–0.8**	**Years** **Months**	**(Seow et al., 2015)* (peak levels to 6.9 mg/m^3)** **(Jia et al., 2014)***	**↑ 0.25**	**Years**	**(Aydın et al., 2013)***	Slight ↑ TNF-α and C3
	No animal studies identified						
Secreted factors and immune — Primarily Th1-related — Complement	**0.25**	**Years**	**(Aydın et al., 2013)* (i.e., C3, C4)**				

Endpoint		No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
		mg/m^3	Length[b]	References (details)	mg/m^3	Length[b]	References (details)	
					↑ 6.15	**Short**	**(Sapmaz et al., 2015)* (rats; i.e., C3)**	
	IFN-γ				**↓ 0.8**	**Months**	**(Jia et al., 2014)***	Moderate ↓ IFN-γ
					↓ 6.2–12.3	Short	(Im et al., 2006) (rats)	
Primarily Th2-related	**IL-4**				**↑ 0.8**	**Months**	**(Jia et al., 2014)***	Moderate ↑ IL-4
					↑ 6.2–12.3	Short	(Im et al., 2006) (rats)	
	IL-10				**↓ 1.8** **↑ 0.2–0.8**	**Years** **Months**	**(Seow et al., 2015)* [d] (i.e., using less strict 20% FDR)** **(Jia et al., 2014)***	Slight IL-10 (suggests dose-dependence like total T cells)
		No animal studies identified						
	IL-6	**No human studies identified**						Indeterminate IL-6
		0.12	Acute	(Matsuoka et al., 2010) (mice)				
Chemoattractants	**CXCL11 and CCL17**				**↓ 1.8**	**Years**	**(Seow et al., 2015)* (i.e., using stringent 10% FDR)**	Slight ↓ (chemo-attractants for neutrophils: IL-8, and lymphocytes: Cxcl11, Ccl17)
		No animal studies identified						

Endpoint		No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
		mg/m^3	Length[b]	References (details)	mg/m^3	Length[b]	References (details)	
	IL-8				**↓ 0.2–0.8**	**Months**	**(Jia et al., 2014)***	
		No animal studies identified						
Other	Ta1 and IL-2R				↑ N/A[e] (≤1)	Year vs. Mo	(Thrasher et al., 1990) (antigen reactivity markers)	Indeterminate (data suggest N/C in B cell activation markers)
		No animal studies identified						
	CD27 and CD30	**1.6**	**Years**	**(Bassig et al., 2016)* (B cell activation markers)**				
		No animal studies identified						

Abbreviations and definitions: Der f = *Dermatophagoides farina* (house dust mite) and OVA = ovalbumin (major protein of chicken egg whites): both immunogenic materials used to stimulate an allergy-like response; FDR = false discovery rate; N/C = no change; T_{reg} = T regulatory cells, a subset of helper T cells; short = short-term.

Notes: Formaldehyde concentrations typically reflect average or median levels in human studies (e.g., when effects were not observed); Gray shading = no data meeting the inclusion criteria were available (see Appendix B.2.6 and B.3.6); one study observing increased substance P and related changes in the serum (Fujimaki et al., 2004b) was previously presented in the context of changes in the respiratory system (see Section 3.2.2).

[a]Primarily, this reflects reporting of a statistically significant change; in rare instances where a *p*-value was not given, changes are indicated if the authors discussed the change as a significant effect.

[b]Human study exposure durations are indicated as "years," "months," "weeks," "acute," or "Year vs. Mo" (see footnote d) and defined based on the anticipated exposure duration for the majority of the exposed population(s); these durations are interpreted to approximate animal study exposure durations of chronic (>1 year), subchronic (several months), short term ("Short" in table; <30 days), and acute (1 day or less).

[c]Erdei et al. (2003) studied 9- to 11-year-old students symptomatic with respiratory issues, so duration of exposure was presumed to be years in schools (average exposure concentration is indicated).

[d]The differences in lymphocyte subset levels between exposed and unexposed workers reported by Zhang et al. (2010) were challenged by Mundt et al. (2017) in a reanalysis who did not find evidence of an exposure-response trend within the exposed group, although the difference between unexposed and exposed subjects was reconfirmed. The critique by Mundt was responded to in a letter to the editor by the study investigators who explained that the study was not designed to provide a range of exposures wide enough to evaluate exposure-response relationships given the expected effect size and sample size in the study (Rothman et al., 2017).

[e]The exposure level is, in general, considered not applicable (N/A), as the comparison presented by Thrasher et al. (1990) reflected differences in exposure duration (i.e., years of exposure [Year], as compared to weeks or months [Mo] of exposure), but there appeared to be minimal differences in concentration from the controls.

[f]The studies by (Rager et al., 2013; Rager et al., 2014) were molecular studies (e.g., miRNA) interpreted as *high* or *medium* confidence that provide some indirect evidence of inflammatory changes.

[g]This finding (decreased total WBCs) is supported by three studies in humans based on an evaluation by NRC (2014b): [(Tong et al., 2007; Tang and Zhang, 2003; Cheng et al., 2004)], but these studies were not evaluated in this analysis (i.e., they were not indexed in any of the searched databases); additionally, this finding is supported by a study in mice (Yu et al., 2014) and a study in rats (Brondeau et al., 1990), which are not included above as they only tested excessive formaldehyde levels (i.e., ≥20 mg/m^3).

[h]The authors indicated no changes in "WBC differentials" other than decreased monocytes, but further details NR (Dean et al., 1984). This test was assumed to include basic granulocyte and lymphocyte counts.

[i]This finding (decreased erythrocytes) is supported by one study in humans based on an evaluation by the NRC (2014b): [(Yang, 2007)], but this study was not evaluated in this analysis.

[j]This finding (decreased platelets) is supported by two studies in humans based on an evaluation by NRC (2014b): (Yang, 2007; Tong et al., 2007), but these studies were not evaluated in this analysis. The finding is also supported by a mouse study testing excessive formaldehyde levels (Yu et al., 2014).

Summary of Inferences Regarding Mode of Action

Understanding of the partial MOA likely to underly the development of allergic conditions and effects on the prevalence of current asthma following formaldehyde inhalation is primarily based on experimental studies in animals. This strong mechanistic evidence alone is considered to support an animal evidence synthesis judgment of *slight* (see above).

Evidence Integration Summary

The general population studies in children and adults provide *moderate* evidence of an association between formaldehyde exposure and prevalence of rhinitis or rhinoconjunctivitis, with a relative risk of approximately 1.2 for formaldehyde exposures of around 0.04 mg/m^3 and above. Although the effect size is small, these are relatively common conditions. The observation of an increase in the magnitude of the association with increasing severity of rhinitis provides coherence and greater certainty in the evidence (Yon et al., 2019). A stronger association (2-fold risk) was seen in the only study of eczema and a 3-fold risks of experiencing allergy-like symptoms involving the eyes, nose or skin within the past week was observed for students exposed to formaldehyde concentrations in classrooms >0.035 mg/m^3 (median 0.045 mg/m^3) compared to <0.035 mg/m^3 (OR 3.23, 95% CI 1.31, 8.00).

The available general population and occupational studies also provide a *moderate* level of evidence of an association between formaldehyde exposure and prevalence of current asthma, as determined by symptoms or medication use in the past 12 months for asthma in studies with exposures above 0.05 mg/m^3. The pattern of results across studies in children indicates no association at exposures < 0.05 mg/m^3, and a moderate association (RRs around 2.0) in residential or school-exposures above 0.05 (the maximum levels seen in these studies was generally around 0.08-0.10 mg/m^3). Stronger associations were seen in studies examining prevalence of current asthma in relation to higher levels of formaldehyde exposure in occupational settings (RR 2-5 for exposures above 0.10 mg/m^3). The two studies examining asthma control or severity among

children with asthma suggest associations may be seen at lower exposures (e.g., 0.04 mg/m^3) in this potentially susceptible population.

Sensitivity may also be increased by other attributes as well disease severity. Although associations with either eczema, prevalence of asthma, or asthma control were either increased or decreased by a positive atopy status in studies of adults or children, studies in allergen-sensitized animals suggest that atopy may increase sensitivity to formaldehyde-related asthma endpoints. In addition, associations with IgE levels or prevalence of asthma symptoms were stronger among groups exposed to environmental tobacco smoke, although inconsistencies by lifestage were reported. Relatively strong associations were seen in studies examining prevalence of current asthma in relation to higher levels of formaldehyde exposure in occupational settings (exposures above 0.10 mg/m^3). Mechanistic studies in animals indicate that formaldehyde exposure can induce bronchoconstriction with and without allergen sensitization. This heightened bronchoconstriction response may be due to a combination of increased tachykinins, increased T_H2 cytokines and antibodies, and eosinophil recruitment and activation in the lung. Mechanistic studies of respiratory tissues and the blood provide consistent evidence that formaldehyde exposure can stimulate a number of immunological and neurological processes that may drive asthmatic responses; however, a molecular understanding of how formaldehyde exposure favors asthmatic T_H2 responses has not been experimentally established. Separately, the possibility that formaldehyde exposure might increase the risk or severity of respiratory infections, particularly in young children, has not been well studied.

Overall, based primarily on a *moderate* level of human evidence supporting an association from the available epidemiology studies, with corresponding *slight* evidence for an effect in animals based on mechanistic studies in animals supporting biological plausibility, the **evidence indicates** that inhalation of formaldehyde likely causes an increased risk of prevalent allergic conditions and prevalent asthma symptoms, as well as decreased control of asthma symptoms, given sufficient exposure conditions (see Table 3-23). The primary basis for this conclusion involves studies of occupational settings (>0.1 mg/m^3) and population studies where formaldehyde concentrations measured in schools and homes were > 0.05 mg/m^3, although lower exposures (above 0.03 mg/m^3 may be relevant with respect to control of asthma symptoms.

Table 3-23. Evidence integration summary for effects of formaldehyde inhalation on allergic conditions

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Allergic Conditions					
Human	*Consistency and Study Confidence*	• Elevated risks for at least one allergic symptom were consistently observed in the seven *high* and *medium* confidence studies among adults and children in residential and school settings with exposures around 0.04 mg/m^3 formaldehyde and above. • The minority of studies (two) that did not observe an association did not reduce certainty, as they were conducted in lower exposure settings (0.004-< 0.025 mg/m3)		*Moderate* (for allergic conditions) Consistent and dose-dependent, but small, elevations in risk for allergy-related conditions in residential and school settings around 0.04 mg/m^3 and above across varied study designs and populations.	The **evidence indicates** that inhalation of formaldehyde likely increases the prevalence of allergic conditions in humans, given sufficient exposure conditions[a] This judgment is primarily based on studies of residential and school settings where mean formaldehyde concentrations were around 0.05 mg/m^3 and above. *Potential Susceptibilities*: Variation in sensitivity is anticipated depending on respiratory health, physiologic changes during pregnancy, age, and exposure to tobacco smoke.
	Strength and Precision		• Effect sizes for rhinitis and rhinoconjunctivitis were small (RR around 1.2); however, because these are relatively common conditions, even small risks can be meaningful on a population level		
	Dose-Response	• Increasing risk was seen across levels of rhinitis severity and in the studies examining more than two exposure groups			
	Coherence	• Findings included increases in the prevalence of several potentially			

		related conditions, including rhinitis, rhinoconjunctivitis, and eczema			
	Biological Plausibility	Studies in humans do not provide robust or moderate evidence for mechanistic events that clearly support the development of allergic conditions, although observed effects in the blood, such as cytokine, cell, and antibody changes, might contribute.			
Animal	Experimental animal models are generally considered to be unable to reproduce the overt manifestations of allergic conditions and are not interpreted to provide direct support.			*Slight* (for immune-mediated respiratory effects) The available animal studies most relevant to evaluating potential effects on allergic conditions and other mechanistic information were interpreted to provide *slight* animal evidence for an effect.	
	Biological Plausibility	• Understanding of the partial MOA likely to underly the development of allergic conditions following formaldehyde inhalation is primarily based on experimental studies in animals. This strong mechanistic evidence alone is considered to support an animal evidence synthesis judgment stronger than *indeterminate*.			
Other inferences	• *Relevance to humans*: The primary effect of interest was observed in humans (*moderate* evidence). • *MOA*: Not established, but several incomplete MOAs involving airway inflammatory changes are considered likely to be involved, contributing to augmented or hyperactive airway responses. Specifically, robust evidence for mechanistic events exists in relation to formaldehyde-induced augmentation of responses to allergens and airway bronchoconstrictor effects in animal models. Although several events typically associated with asthma were not corroborated (i.e., slight or indeterminate evidence exists for these events), moderate evidence for mechanistic events exists for stimulation by formaldehyde of important immunological and neurological processes. These include airway eosinophil increases and other inflammatory changes in the airways and systemic circulation that can be reasonably associated with effects on airway hyperreactivity or other responses relevant to the development of allergic conditions and, potentially, asthma. The most relevant mechanistic findings in animals involve neurological and immunological constituents present in both human and rodent airways, so these findings are considered relevant to humans.			

[a]The "sufficient exposure conditions" are more fully evaluated and defined through dose-response analysis in Section 5.1.

Table 3-24. Evidence integration summary for effects of formaldehyde inhalation on asthma

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Prevalence of Current Asthma					
Human	*Consistency and Study Confidence*	• Elevated risks were consistently observed in nine *medium* confidence studies of prevalence of current asthma in residences or schools at exposures above 0.05 mg/m^3 and in three *medium* confidence studies in occupational settings with exposures from 0.100 to >0.500 mg/m^3; greater susceptibility was observed among children. • The minority of studies (five studies in residences or schools) that did not observe an association with formaldehyde exposure did not reduce certainty, as they were conducted in lower exposure settings (< 0.05 mg/m^3).		*Moderate* (for asthma) Consistently elevated risks for increased prevalence of asthma or decreased control of asthma symptoms around 0.050 mg/m^3 and above across *medium* confidence studies in residential and school settings, with higher risks at higher exposures in occupational settings supporting dose-dependence.	The **evidence indicates** that inhalation of formaldehyde likely increases the prevalence of asthma symptoms in humans, as well as decreased control of asthma symptoms, given sufficient exposure conditions[a] This judgment is primarily based on studies in residential settings above 0.05 mg/m^3 and occupational settings at similarly high levels *Potential Susceptibilities*: Variation in sensitivity is anticipated depending on respiratory health, physiologic changes during pregnancy, age, and exposure to tobacco smoke. Children are more sensitive than adults.
	Strength and Precision	• Strongly elevated risks in occupational settings with exposures from 0.100 to >0.500 mg/m^3.			
	Dose-Response	• Although dose-response relationships were not strong within individual studies, a gradient of risk was seen across the sets of studies (see above).			

	Coherence	• The two studies (one *medium* and one *high* confidence) of control of asthma symptoms provide additional support for the effects of formaldehyde exposure among children with asthma at levels at or below those seen in the studies of formaldehyde in relation to the prevalence of asthma. This effect on symptom control is further supported by indirect evidence from a randomized controlled trial. • The studies of wheezing episodes in infants, particularly the birth cohort studies, are not classified as studies of asthma *per se,* but could be indicative of respiratory effects with implications for subsequent disease risk. Thus, the associations seen between residential formaldehyde exposure above 0.50 mg/m^3 and frequency or onset of first wheezing event in these studies provides further indirect support for the body of evidence relating to asthma.			
	Biological Plausibility	Studies in humans do not provide robust or moderate evidence for mechanistic events that clearly support the development of asthma, although effects in the blood, such as cytokine, cell, and antibody changes, might contribute.			
Animal	Experimental animal models are generally considered to be unable to reproduce the overt manifestations of asthma and are not interpreted to provide direct support.			*Slight* The available animal studies most relevant to evaluating potential effects on asthma and other mechanistic	
	Biological Plausibility	• In the same way the available mechanistic data are interpreted to provide *slight* animal evidence			

		supporting the development of allergic conditions in humans, these same data provide *slight* animal evidence supportive of effects on asthma.		information were interpreted to provide *slight* animal evidence for an effect.	
Other inferences	• *Relevance to humans*: The primary effect of interest was observed in humans (*moderate* evidence). • *MOA*: Not established, but several incomplete MOAs involving airway inflammatory changes are considered likely to be involved. Regarding the animal mechanistic data, while several events (e.g., amplified bronchoconstriction; eosinophil increases) have an unclear direct linkage to complex human diseases like asthma, these findings inform the potential for exposure to result in changes to relevant neurological and immunological constituents present in both human and rodent airways and are therefore viewed as human relevant.				

[a]The "sufficient exposure conditions" are more fully evaluated and defined through dose-response analysis in Section 5.1.

3.2.4. Respiratory Tract Pathology

This section describes research on formaldehyde inhalation and pathology endpoints in the respiratory system. Of the human studies that met the PECO criteria, one was concluded to be *not informative* (Berke, 1987) during study evaluation. The study evaluations are included in Appendix B.3.5.

Numerous well-conducted experimental animal studies consistently demonstrate concentration- and, to a lesser extent, duration-dependent URT hyperplasia and metaplasia after formaldehyde exposure. Supporting these observations, a set of four studies in formaldehyde-exposed workers provides consistent findings of an elevated prevalence of nasal lesions such as hyperplasia and metaplasia. The workers were generally exposed to lower levels of formaldehyde than those eliciting changes in experimental animals. While the evidence for both of these nonneoplastic lesions indicates that formaldehyde exposure changes the morphology and function of the URT tissue, the evidence for metaplasia, in particular, is considered to be the best representation of a potential health hazard.

In the URT, both hyperplasia and metaplasia are adaptive tissue responses. These cellular responses help reduce the impact of stressors by changing the structure or function of the locally affected tissue (Harkema et al., 2013). Hyperplasia, generally a response to cell injury, involves an increase in the population of resident cells that results in additional cell layers noticeable by histology, whereas metaplasia, which typically occurs following prolonged or repeated insults, results in the replacement of one differentiated cell type with another more resilient cell type (Harkema et al., 2013). While hyperplasia and metaplasia may also be relevant, but not necessary, to the development of cancer (see Section 3.2.5), they are, by themselves, nonneoplastic lesions. Importantly, metaplasia results in a hardened, drier, and nonciliated skin-like layer (Tomashefski, 2008). Along with the acquisition of a protective, barrier-type phenotype, this metaplastic change causes a loss of normal tissue function, including reduced mucous secretion and ciliary clearance. Thus, this loss of normal function is judged to be an adverse outcome in and of itself (i.e., independent from its potential role in progression to cancer). As an interpretation regarding adversity is less clear for hyperplasia, this discussion emphasizes the data on squamous metaplasia.

Both hyperplasia and metaplasia are typically associated with cellular proliferation (Harkema et al., 2013). As compared to transient increases in cell number, sustained cell proliferation is required for the formation of hyperplasia. This type of change can be precipitated by damage to the nasal epithelium, which is evaluated histologically by measures of, for example, cell loss or necrosis, epithelial degeneration, and erosions. Relatedly, squamous metaplasia is an adaptive response to continued toxic insult that involves cellular substitution. Thus, it is useful to consider these cellular damage-related endpoints in the context of hyperplasia and metaplasia. While evaluations of necrosis- and cytotoxicity-related pathology are informative to this section, these endpoints were generally inconsistently measured or poorly reported across the available studies and are therefore are only summarily discussed. Although hyperplasia and metaplasia

might have been underevaluated or underreported for similar reasons (e.g., most studies focus on carcinogenic lesions), the potential development of these lesions appears to have been considered and documented in nearly all the long-term formaldehyde inhalation studies examining URT histopathology.

Studies that evaluated related outcomes, such as mucociliary flow rates, cellular proliferation counts based on DNA labeling, and mucosal swelling, are evaluated in Appendix B.3.6 and summarized in Appendix C.7.1). These types of effects were generally evaluated after acute or short-term exposure and typically represent immediate response repair mechanisms rather than tissue remodeling (e.g., hyperplasia, metaplasia), the latter of which is often a consequence of longer-term exposure or sustained injury. Accordingly, those related outcomes are interpreted to be most relevant to the mechanistic progression of the more overt URT lesions considered in this section, and they are discussed as such in the MOA analysis. Overall, mechanistic insights from the human and animal data indicate a clear role for altered mucociliary function or cellular proliferation in the occurrence of the more overt lesions. Consistent with some of the animal health effect studies, these mechanistic data also suggest that concentration is likely to be more of a driver of these effects than duration (noting that duration still contributes).

Given the large number of long-term exposure studies with information on URT pathology and the focus of the assessment on the effects of lifetime formaldehyde exposure, this section generally focuses on animal studies of subchronic or chronic exposure, and on human studies of occupational exposure where exposed employees were generally employed for longer than 5 years. Exceptions include discussion of shorter-term studies that might inform the potential for relationships between lesion types and studies specifically considering differences in the exposure paradigm (e.g., intermittent versus constant exposures) for lesion induction. Dysplastic lesions and other evidence of carcinogenicity, which are examined in many of the same studies addressed in this section, are discussed in Section 3.2.5.

Overall, the strength of the evidence for hyperplasia and squamous metaplasia includes *robust* evidence from animal studies and *moderate* human evidence from observational epidemiology studies, and strong support for a plausible MOA based largely on mechanistic evidence in animals (supported by more limited, coherent findings in human mechanistic studies). Therefore, the **evidence demonstrates** that inhalation of formaldehyde causes respiratory tract pathology in humans given sufficient exposure conditions. The primary support for this conclusion is based on rat bioassays of chronic exposure, which consistently observed squamous metaplasia at formaldehyde exposure levels ≥2.5 mg/m^3.

Human Studies

A small number of studies were available that reported the results of histological examinations of nasal tissues from formaldehyde-exposed occupational groups. These are described in Table 3-25, organized by publication year. Although the evidence was more equivocal in one study (Boysen et al., 1990), the four *medium* confidence studies examining histopathology

found that exposed participants had a higher average histopathological score than their respective comparison group (Holmstrom et al., 1989c; Edling et al., 1988; Ballarin et al., 1992). Average formaldehyde levels ranged from 0.05 to 0.6 mg/m^3. These were cross-sectional studies of current workers who may have been less sensitive to the long-term respiratory irritant effects of formaldehyde, which would cause survival bias and an attenuation of comparisons between exposed and comparison groups. Although the studies were limited by probable survival bias, and in some cases, other limitations resulting in a bias toward the null, a consistent association with histopathological endpoints was observed. Edling et al. (1988) did not adjust analyses for differences in smoking prevalence between the exposed and referent groups; smoking prevalence was higher among participants in the referent group. Therefore, the expected effect on the association with formaldehyde exposure would again be toward the null. However, the association observed by Edling et al. (1988) was consistent with those reported by the other studies that did address potential confounding by smoking status. There was no evidence of a time-dependent relationship with formaldehyde. Additionally, there was no indication that coexposure with wood dust or smoking modified the pathological effects of formaldehyde.

The preponderance of evidence shows that the increases in histopathological score levels were due to a high level of squamous metaplasia among participants exposed to formaldehyde levels ranging from 0.1 to 2.5 mg/m^3. Squamous metaplasia was seen in 32–67% of exposed participants (Edling et al., 1988; Boysen et al., 1990; Ballarin et al., 1992).

Table 3-25. Formaldehyde effects on respiratory pathology in occupational settings

Study and design and exposure	Results
Histological analyses	
Ballarin et al. (1992) Italy Prevalence study **Population:** 15 plywood factory workers (mean age 31 years, employment duration 6.8 years) compared to 15 university or hospital clerks matched for age and sex. All nonsmokers. **Exposure:** Personal sampling; 8-hr TWA Kominsky and Stroman (1977) Warehouse (N = 3), 0.39 ± 0.20 mg/m^3, range 0.21–0.6 mg/m^3 Shearing-press (N = 8), 0.1 ± 0.02 mg/m^3, range 0.08–0.14 mg/m^3 Sawmill (N = 1), 0.09 mg/m^3 Inspirable wood dust: 0.11–0.69 mg/m^3, 0.73 in sawmill **Methods:** Cytopathology analysis of nasal respiratory mucosa cells blinded by two readers, scoring and classification analogous to Torjussen et al. (1979) and Edling et al. (1988); most severe score present assigned. Mean histological scores exposed compared to referent using Mann-Whitney U test; difference by exposure group for classification of pathology, χ^2 test.	**Distribution of histological scores of nasal respiratory mucosa cells** Description / Exposed / Referent Normal: 0 / 4 (26%) Loss of ciliated cells: 15 (100%) / 10 (67%) Hyperplasia: 6 (40%) / 5 (33%) Squamous metaplasia: 10 (67%)* / 1 (6%) Mild dysplasia: 1 (6%) / 0 **Score (Mean (SD))**: 2.3 (0.5)* / 1.6 (0.5) *Mann-Whitney U test (p < 0.01) or χ^2 test (p < 0.01)

<table>
<tr><th>Study and design and exposure</th><th>Results</th></tr>
<tr><td>Evaluation:[a]
Medium confidence (↓)
Inclusion only of current workers raises possibility of healthy worker survival effect due to irritation effects.</td><td></td></tr>
<tr><td>Boysen et al. (1990)
Prevalence survey
Oslo, Norway
Population: 37/74 exposed volunteers from a chemical company producing formaldehyde (50% of exposed workforce). Mean age 51, range 27–66 years. Mean years employed 20, range 3–36 years.
37 age-matched referent subjects without overt nasal disease or occupations associated with nasal cancer. Office staff at two Oslo chemical companies, hospital laboratory personnel, and outpatients at the ear, nose, and throat department of hospital. Mean age 49, range 35–66 years.
Exposure: Systematic formaldehyde monitoring after 1980. Before 1980, exposure assessed by plant health officer with knowledge of the production process, recent measurements, and worker sensations. Range of formaldehyde 0.5 ppm to >2 ppm.
Methods: Scoring and classification of histologic samples per Tojussen, 1979 protocol but on a 0–5-point scale by two authors blinded to clinical or occupational status. Wilcoxon rank sum test used to compare histological findings in the two groups. X^2 test used to compare the rhinoscopical findings and subjective complaints.
Evaluation:[a]
Medium confidence (↓)
Inclusion only of current workers and long duration of employment raises possibility of healthy worker survival effect due to irritation effects.</td><td>Rhinoscopy: 75% of exposed workers and 89% of controls had normal mucosa. 24% of the exposed and 8% of the unexposed had hyperplastic nasal mucosa (difference not statistically significant). Degree of metaplastic alterations more pronounced among the exposed workers than in controls (difference not statistically significant).

Higher prevalence of subjective nasal complaints in formaldehyde-exposed workers (43%) compared to 5% in unexposed controls ($p < 0.01$).
Distribution of histological scores
<table>
<tr><th></th><th>Description</th><th>Exposed</th><th>Referent</th></tr>
<tr><td>0</td><td>Columnar epithelium</td><td>3</td><td>5</td></tr>
<tr><td>1</td><td>Stratified cuboidal epithelium</td><td>16</td><td>17</td></tr>
<tr><td>2</td><td>Mixed stratified cuboidal/stratified squamous epithelium</td><td>5</td><td>10</td></tr>
<tr><td>3</td><td>Stratified squamous epithelium, nonkeratinizing</td><td>9</td><td>5</td></tr>
<tr><td>4</td><td>Stratified squamous epithelium, keratinizing</td><td>1</td><td>0</td></tr>
<tr><td>5</td><td>Dysplasia</td><td>3
1.9/5</td><td>0
1.4/5</td></tr>
</table></td></tr>
<tr><td>Holmström and Wilhelmsson (1988); Holmstrom et al. (1989a)
Sweden
Prevalence study
Population: Two exposed groups 170 total; 70 formaldehyde production workers, Mean age 36.9 years, 87% male, mean duration employment 10.4 year. 100 workers exposed to wood dust and formaldehyde at five furniture factories. Mean age 40.5 years, 93% male, mean duration employment 16.6 year. Referent: 36 persons from local government in the same village as the furniture workers, with no history of occupational exposure to formaldehyde or wood</td><td>Formaldehyde-only nasal specimens had higher mean score of 2.16 (range 0–4) ($p < 0.05$, comparison to referent) while formaldehyde dust group had mean score of 2.07 (range 0–6) ($p > 0.05$, comparison to referent). Referent group score was 1.56 (range 0–4). Combining formaldehyde-only and formaldehyde-dust group mean score of 2.11 ($p < 0.05$). No correlation observed between smoking habits and biopsy score, nor was a correlation found between the duration of exposure and any histological changes.</td></tr>
</table>

Study and design and exposure	Results
dust. Mean age 39.8 years, 56% male, mean duration employment 11.4 year. "Slightly" larger number of smokers in the exposed group than control group, but difference not statistically significant (data not provided). **Exposure:** Personal sampling in breathing zone for 1–2 hours in 1985. Total dust and respirable dust also measured. Previous measurements 1979–1984 in chemical company combined with 1985 values to estimate average annual values for each participant. Only 1985 values available for wood factories. Formaldehyde concentration: Chemical Plant: 0.05–0.5 mg/m^3, mean 0.26 [SD 0.17 mg/m^3]. Furniture Factory: 0.2–0.3 mg/m^3, mean 0.25 [SD 0.05 mg/m^3]. Referent mean 0.09 mg/m^3 (based on four measurements in four seasons). **Methods:** Pretesting questionnaire, histological changes in nasal mucosa graded by a pathologist blind to exposure according to Torjussen et al. (1979) grading scale of 0–8. 2 tailed *t*-test for group comparisons. **Evaluation:**[a] *Medium* confidence (↓) Inclusion of only current workers and long duration of employment raises possibility of healthy worker survival effect due to irritation effects.	
Edling et al. (1987a, 1988) *Prevalence Study* *Sweden* **Population**: 75 of 104 exposed male factory workers from three plants (2 particle board plants and one laminae-processing). Mean duration of employment: 10.5 years. Mean age: 38 years; range 22–63 years. 35% smokers and 9% ex-smokers. Referents: 25 men with similar age and smoking habits and no known industrial exposures to formaldehyde. Mean age: 35 years, range 25–60. 48% smokers and 10% ex-smokers. **Exposure:** Past TWA formaldehyde measurements made by plant industrial hygienists sporadically between 1975 and 1983. Levels of formaldehyde in air ranged from 0.1 to 1.1 mg/m^3, with peaks up to 5 mg/m^3. No measurements available before 1975 but estimated levels higher during the 1960s and early 1970s. Particle board plants contained low concentrations of wood dust at 0.6–1.1 mg/m^3. **Methods:** Nasal mucosa histological grading by pathologist blinded to exposure using Torjussen et al. (1979) grading system with 0–8 ranking. Compared differences in nasal mucosa histological score using Wilcoxon nonparametric test. **Evaluation:**[a] *Medium* confidence (↓) Inclusion of only current workers and long duration of employment (mean 10.5 years) and high prevalence of symptoms raises possibility of healthy worker survival.	Prevalence in exposed of normal nasal mucosa, 75%; prevalence swollen or dry or both changes, 25%. Histological scores higher in exposed compared to referents, mean 2.9 vs. 1.8; ($p < 0.05$) (Wilcoxon). No association with years of exposure. **Histological scores in exposed**[a] Characteristics / Score / # / % Normal respiratory epithelium / 0 / 3 / 4 Loss of ciliated cells / 1 / 8 / 11 Mixed cuboid/squamous epithelium, metaplasia / 2 / 24 / 32 Stratified squamous epithelium / 3 / 18 / 24 Keratosis / 4 / 16 / 21 Budding of epithelium / 5 / 0 / 0 Mild or moderate dysplasia / 6 / 6 / 8 Severe dysplasia / 7 / 0 / 0 Carcinoma / 8 / 0 / 0 [a]Data for referent group were not reported

Organized by study confidence, then descending publication year.
[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.5. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Summary of Human Evidence Synthesis Judgments

The following factors, primarily the consistency across occupational studies, were influential to the synthesis judgment that the human studies on respiratory tract pathology provide *moderate* evidence of formaldehyde exposure-induced effects.

- *Consistency and Study Confidence*: Three of four of the available *medium* confidence studies, all occupational, observed a higher prevalence of abnormal nasal histopathology with higher formaldehyde exposure.
- *Biological Plausibility*: Although sparse, evidence in humans shows effects of relatively high formaldehyde exposure (≥ 0.25 mg/m^3) on nasal mucociliary function.

Animal Studies

A large database of well-designed studies has characterized formaldehyde-induced respiratory tract pathology in mice, hamsters, and monkeys, but primarily in rats. The durations of these studies range from a few hours to longer than 2 years, and several studies included recovery periods that explored the reversibility of lesions. While a few studies include the examination of tissues in other areas of the respiratory tract, most studies focus on pathology in the nasal mucosa. This synthesis focuses on the incidence of hyperplasia and metaplasia formed after inhaled formaldehyde exposure. To the extent the available data allow, the discussion separately addresses the lesion locations along the URT and specifically within the nasal mucosa, the influence of concentration and exposure duration on lesion formation and lesion persistence, and sex and species differences in pathology. Because of the abundance of studies that evaluated respiratory tract pathology, only those studies judged to be of *high* and *medium* confidence (see Appendix B.3.5) are presented in detail in the synthesis and evidence tables below. Note that unlike some other sections, this includes well-performed formalin studies. Thus, this section does not synthesize the studies that met the PECO criteria but were classified as *not informative* (Yorgancilar et al., 2012; Schreiber et al., 1979; Ohtsuka et al., 1997; Murta et al., 2016; Lima et al., 2015; Ionescu et al., 1978; Holmstrom et al., 1989b; Coon et al., 1970; Casanova et al., 1994; Bhalla et al., 1991; Bansal et al., 2011; Arican et al., 2009), nor those studies classified as *low* confidence (Monticello et al., 1996; Kamata et al., 1996; Horton et al., 1963; Chang et al., 1983; Buckley et al., 1984).

Likewise, as animal studies of effects from long-term exposure are most pertinent to lifetime human exposure, and because some of these lesions can be very slow to develop, long-term studies (preferably ≥52 weeks of exposure and follow-up) were generally considered to be more informative. Accordingly, evidence tables of the experimental animal studies are organized by study duration, with chronic and subchronic respiratory pathology studies ordered according to species,

study confidence, and descending publication year in Tables 3-26 and 1-27, respectively. Short-term studies, generally ≤1−4 weeks long, are sometimes discussed in the synthesis, but are only described in detail if they provide insights unavailable in the longer-term studies, specifically those including information on species differences or the relationship between the concentration and duration dependency of lesion formation (see Table 3-28; see Appendix C.6.1 for evidence tables of the other short-term studies). Some studies reported multiple endpoints (e.g., pathological effects and cell proliferation), which were individually considered. Studies that reported URT pathology-related mechanistic information relevant to interpreting the progression of events leading to overt respiratory tract pathology (see Appendix B.3.6 and C.7), including cell proliferation and mucociliary function, are discussed as mechanistic information informing MOA.

Nasal lesions (i.e., cytotoxicity, hyperplasia, and metaplasia) have been consistently reported in multiple rodent species and strains, and in monkeys. For hyperplasia and metaplasia, there were consistent indications of a concentration-response, and to a somewhat lesser extent, exposure duration-dependent relationships with inhaled formaldehyde. Somewhat surprisingly, multiple studies report that metaplasia appeared to be more sensitive, prevalent, or extensive than hyperplasia (sometimes pronounced metaplasia was observed in the absence of hyperplasia), reducing support for a strictly sequential progression of these lesions. The most informative data on squamous metaplasia (i.e., from long-term *medium* or *high* confidence studies), which is considered to be an adverse effect independent of its potential role in cancer progression, are illustrated in Figures 3-14 and 3-15.

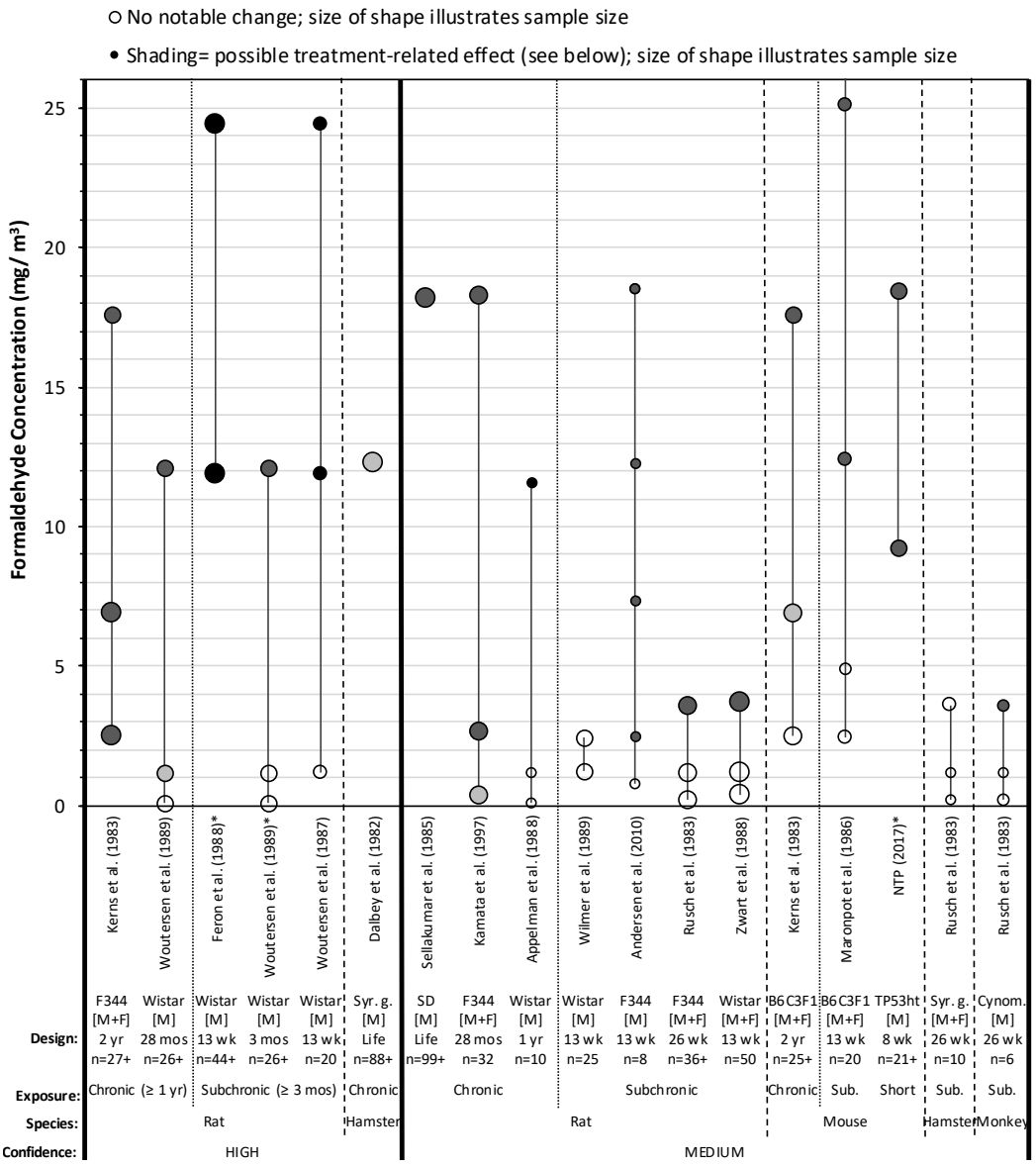


Figure 3-14. Squamous metaplasia in *medium* and *high* confidence chronic and subchronic respiratory pathology studies of inhaled formaldehyde.

Studies are organized by study evaluation confidence (see Appendix B.3.5), species, and then duration of exposure. Shading is indicated as follows: black = statistically significant effects, as indicated by study authors; gray = increases in incidence in studies without statistical analyses, with dark gray indicating pronounced changes (incidences of 50–100% were noted for many of these groups) and light gray indicating subtle changes (generally <25% change compared to controls); see Tables 3-26 through 3-28. Exposure groups with larger sample sizes are depicted as larger circles. Abbreviations: Syr. G. = Syrian golden; ht = heterozygotes; Sub. = subchronic; M + F = male and female; wk = week, mos = months, yr = year.

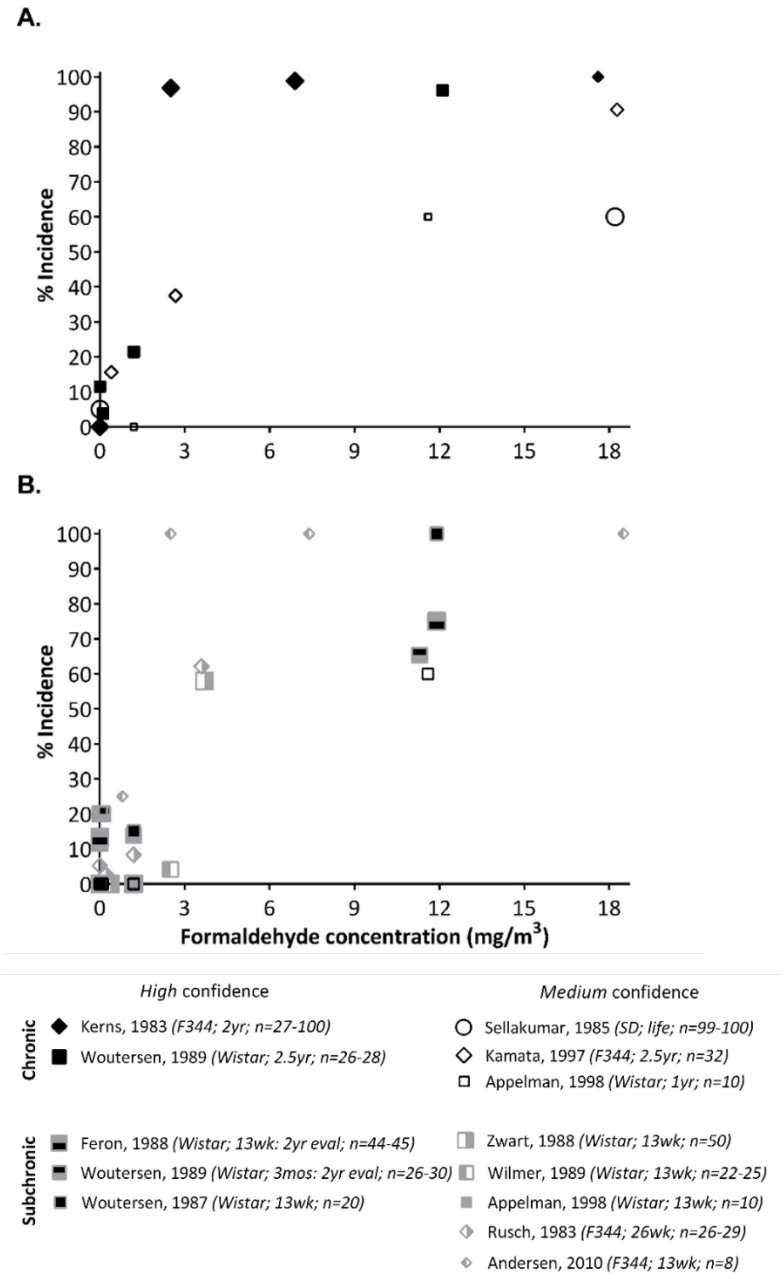


Figure 3-15. Squamous metaplasia incidence in high and medium confidence rat studies of chronic and subchronic formaldehyde exposure duration.

Incidence data for squamous metaplasia (i.e., of any severity) from the high and medium confidence studies with ≥1 year of formaldehyde exposure (Panel A, chronic exposure) or with ≥3 months of exposure (Panel B, subchronic exposure). Symbols for chronic studies are outlined in black, while subchronic studies are outlined in gray. In addition, high confidence studies include black fill, while medium confidence studies are filled in either white or a combination of white and gray. The size of the points reflects sample size for that particular exposure group (i.e., larger size = larger n). Notes: this figure does not present statistical significance; data points at 24.2 mg/m3 (Woutersen et al., 1987) and 24.6 mg/m3 (Feron et al., 1988) formaldehyde are not shown (the incidence of squamous metaplasia was approximately 100% at these levels).

Anatomical location of lesions in the upper respiratory tract

As previously mentioned, the majority of evidence for formaldehyde exposure-induced pathology in the URT of experimental animals is confined to the nasal cavity, which is discussed in greater detail in the sections below. This focus on the nasal cavity can be explained, at least in part, by the historical interest in nasal carcinogenesis.

The evidence for lesions beyond the nasal cavity in rats suggests that concentration is an important variable in long-term studies. Laryngeal lesions, including hyperplasia and squamous metaplasia, were observed in Sprague Dawley rats exposed to 18.2 mg/m^3 for a lifetime (Sellakumar et al., 1985) and in male Wistar rats exposed to 24.4 mg/m^3, but not to ≤11.9 mg/m^3, for 13 weeks (Woutersen et al., 1987). Tracheal lesions (metaplasia and hyperplasia) were reported in F344 rats after chronic exposure to 17.6 mg/m^3 formaldehyde (Kerns et al., 1983). Similar results were observed in Sprague Dawley rats in a single concentration (18.2 mg/m^3) lifetime study (Sellakumar et al., 1985). However, no laryngeal or tracheal lesions were observed in rats exposed to 11.6 mg/m^3 for 1 year (Appelman et al., 1988).

As reported in three studies, even higher concentrations of inhaled formaldehyde may be necessary for effects beyond the nose in mice. Histopathological changes were not observed in the trachea or lungs of B6C3F1 mice exposed to 17.6 mg/m^3 for 104 weeks in a study that did not provide quantitative incidence or severity information (Kerns et al., 1983), nor in the larynx of mice exposed to up to 18.5 mg/m^3 for 8 weeks and evaluated at 1 year (Morgan et al., 2017). However, a subchronic formalin study observed increases in metaplasia and hyperplasia in the trachea at ≥25.1 mg/m^3 and in the lung at ≥49.6 mg/m^3 (Maronpot et al., 1986). These high-concentration changes were also observed in a *low* confidence study with limited severity information that observed squamous metaplasia and hyperplasia in the tracheobronchial epithelium of C3H mice exposed to ≥50 mg/m^3 for 35 weeks (Horton et al., 1963).

While it is difficult to draw mechanistic inferences with confidence, these studies suggest that, in rodents, high levels of formaldehyde might be necessary to exceed the ability of the nose to scrub formaldehyde from inhaled air and allow formaldehyde to reach sites farther down the respiratory tract, which would be consistent with rodent toxicokinetic data (Appendix C.1).

Somewhat in contrast to the rodent studies, a single *medium* confidence study in rhesus monkeys, which failed to report lesion severity or incidence, observed a loss of goblet cells, hyperplasia, and metaplasia in the larynx, trachea, and carina, but not in the lungs, after exposure for ≤6 weeks to 7.4 mg/m^3 formaldehyde (Monticello et al., 1989). This might suggest that the monkey nose is less efficient than the rodent nose at scrubbing formaldehyde from inhaled air.

Overall, the evidence supports the potential for lesions in the larynx and trachea of rats at sustained high formaldehyde concentrations and in rhesus monkeys at sustained moderate concentrations. These findings are particularly interesting in the context of future research into anatomical lesion location following formaldehyde inhalation in nonrodent animal models. The

remainder of this section will highlight the far more robust evidence of respiratory tract pathology localized to the nasal cavity.

Duration dependency of nasal lesions

Data from exposed rats, supported by findings in other species, identify a clear relationship between formaldehyde exposure duration and the development of squamous metaplasia and, to a lesser extent, hyperplasia. These lesions appear to be at least partially reversible after exposure ceases (see Tables 3-26 through 3-28 for study details).

As shown in Figure 3-16, the nasal cavities of monkeys and rats are lined with four types of epithelia—squamous, transitional, respiratory, and olfactory—and there are unique structures that may be susceptible to pathological change (Young, 1981; Renne and Gideon, 2006; Renne et al., 2009; Monticello et al., 1989; Harkema et al., 2006). Due to the high reactivity and water solubility of formaldehyde, nasal metaplasia and hyperplasia have primarily been assessed (and subsequently observed) in the epithelium lining the anterior regions of rodent nasal passages (typically Levels I, II, and III) following formaldehyde inhalation exposure, mostly in regions containing respiratory epithelium.

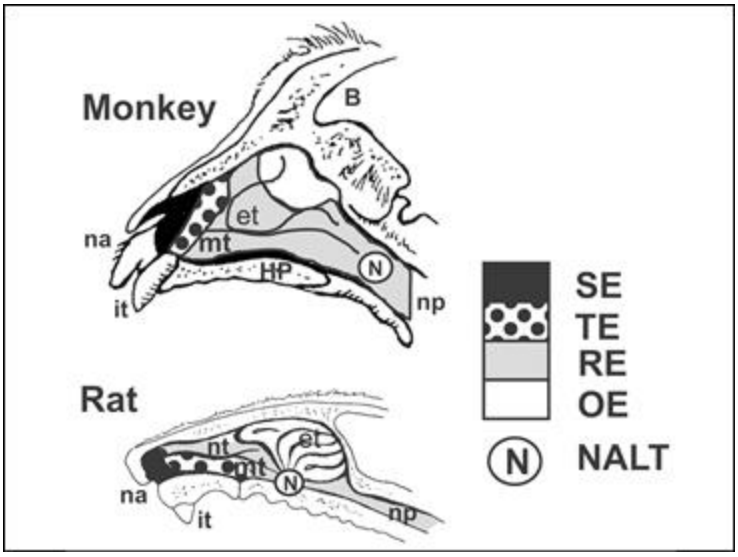


Figure 3-16. The four epithelial cell populations that line the nasal lateral wall in monkeys and rats are portrayed in this image.

The cell populations are SE = squamous epithelium, TE = transitional epithelium, RE = respiratory epithelium, OE = olfactory epithelium. Note that considerably more olfactory epithelium (OE) lines the intranasal surface in rats than in monkeys. Other abbreviations used in this image are NALT = nasal-associated lymphoid tissue, et = ethmoturbinate, mt = maxilloturbinate, nt = nasoturbinate, na = naris, it = incisor tooth, B = brain. Source: Harkema et al. (2006).

Squamous metaplasia

Squamous metaplasia has been observed to occur after chronic, subchronic, and short-term exposure to inhaled formaldehyde. Overall, the most robust responses (i.e., higher incidence or severity at lower formaldehyde concentrations) occur following chronic exposure.

Multiple chronic rat studies have reported robust increases in squamous metaplasia following exposures of approximately 2.5–2.7 mg/m^3 (Kerns et al., 1983; Kamata et al., 1997; Battelle, 1982) or 11.3–11.6 mg/m^3 (Woutersen et al., 1989; Appelman et al., 1988), although some data suggest that slight increases might be present at lower levels (i.e., 0.4–1.2 mg/m^3) (Woutersen et al., 1989; Kamata et al., 1997). In studies that compared changes in respiratory and olfactory epithelia (Woutersen et al., 1989; Appelman et al., 1988), squamous metaplasia was observed almost exclusively in the respiratory epithelium, except perhaps at the highest formaldehyde levels and with the longest exposure durations [i.e., slight increase in metaplasia at 12.1 mg/m^3 after 28 months of exposure in Woutersen et al. (1989)]. With subchronic exposure, squamous metaplasia is observed in rat noses at higher concentrations (i.e., ≥11.3 mg/m^3) in *high* confidence studies by Appelman et al. (1988), Woutersen et al. (1987), and Feron et al. (1988), the results of which are supported by consistent observations in two *medium* confidence studies (Zwart et al., 1988; Andersen et al., 2010), although these latter studies observed increases at lower exposure levels (i.e., 2.5–3.7 mg/m^3). With short-term exposures ranging from 4.4 to 18.4 mg/m^3, observations of squamous metaplasia in rats across several studies with various methodological limitations provide supporting evidence (Wilmer et al., 1987; Speit et al., 2011; Cassee and Feron, 1994; Andersen et al., 2008), although some findings were not completely consistent with a straightforward duration-dependency (e.g., Andersen et al. (2008) observed squamous metaplasia with 5 days of exposure, but not with shorter or longer exposure durations, at 7.4 mg/m^3).

The duration-dependency of these lesions in rat studies also appears to be reflected by the locations at which lesions develop, as well as their severity, possibly in parallel with the increases resulting from increasing formaldehyde concentration (see additional discussion below). The association with lesion location is demonstrated by the results of Kerns et al. (1983) which showed that, in anterior nasal regions (i.e., Level I and II) of F344 rats exposed to ≥2.5 mg/m^3, the incidence of squamous metaplasia increased from ≤20 to 100% with increasing duration (i.e., 6–24 months); however, in posterior nasal regions (i.e., Levels III–V), a duration-dependent increase in incidence was only observed at 17.6 mg/m^3 (Battelle, 1982). In some instances, noted by Kerns et al. (1983), more posterior lesions were entirely unique to longer exposure durations as compared to shorter exposures (e.g., Level III at 6.9 mg/m^3 only with 24 months of exposure). Regarding severity, squamous metaplasia was observed to increase (i.e., from slight focal lesions to metaplasia with keratinization) with exposure duration increases from 13 to 52 weeks of exposure to 11.6 mg/m^3 in Wistar rats (Appelman et al., 1988). Similarly, at ≥11.6 mg/m^3 in Wistar rats, an increase in the severity of squamous metaplasia in respiratory epithelium occurred as exposure duration increased from 4–8 to 13 weeks (Feron et al., 1988), and at very high formaldehyde levels

(24.2 mg/m^3), exposure duration was associated with an increase in the severity of focal replacement of olfactory epithelium with respiratory epithelium.

Several studies in rats confirm the important role of exposure duration in lesion development by demonstrating that the increases in lesions observed with longer-term exposure, as compared to shorter-term exposure, were not attributable to longer latencies after formaldehyde exposures began in the studies of longer-term exposure (i.e., since metaplasia, in particular, is expected to take several weeks to months to develop). In these studies of Wistar rats, nasal lesions including metaplasia and hyperplasia were consistently investigated at approximately 2 years of age following formaldehyde exposures of different durations (which began at the same ages, thus requiring longer periods of nonexposure in the shorter-term studies) (Woutersen et al., 1989; Feron et al., 1988). When animal ages at evaluation and formaldehyde exposure levels were matched, comparisons of subchronic exposure to chronic exposure (Woutersen et al., 1989) and of short-term exposure to subchronic exposure (Feron et al., 1988) revealed greater incidences or severity of these lesions with the longer exposure durations.

Rodent species other than rats also exhibit squamous metaplasia, although the duration-dependence of these lesions has not been as well established. Additionally, compared to rats, other laboratory rodents may require higher levels (i.e., mice) or exhibit a substantially reduced response (i.e., hamsters), suggesting that there may be differences in species sensitivity to formaldehyde-induced squamous metaplasia. Following chronic exposure, slight increases in the number of mice with metaplasia were observed at 6.9 mg/m^3, with more pronounced changes at 17.6 mg/m^3 (Kerns et al., 1983); however, the incidence and severity of these lesions were not quantified. Similarly, in a subchronic formalin study, squamous metaplasia was observed in all mice exposed to 12.4 mg/m^3 (Maronpot et al., 1986). Two strains of p53 deficient mice (*Trp*53 heterozygotes) also developed pronounced metaplasia at both tested concentrations (i.e., 9.23 and 18.45 mg/m^3) after only 8 weeks of exposure (Morgan et al., 2017), with changes that were dose dependent and exhibited an anterior-to-posterior gradient, similar to findings in rats. Squamous metaplasia was observed only in 5% of Syrian golden hamsters exposed to 12.3 mg/m^3 for a lifetime (Dalbey, 1982), and no changes were observed after subchronic exposure to 3.6 mg/m^3 in the same strain (Rusch et al., 1983), although these studies did not provide lesion severity.

Although the few available monkey studies did not report detailed endpoint information, squamous metaplasia was observed at 3.6 mg/m^3 in cynomolgus monkeys following subchronic, near-constant exposure (i.e., 22 hours/day for 7 day/week), and in rhesus monkeys after short-term (i.e., 1 or 6 weeks) exposure to 7.4 mg/m^3 (Monticello et al., 1989). The latter study in rhesus monkeys also supports the findings in rats of an anterior-to-posterior gradient of lesions with increasing exposure duration, and the general susceptibility of respiratory epithelium. After exposure to 7.4 mg/m^3 for 1 week, mild squamous metaplasia was observed in the respiratory epithelium of anterior regions (i.e., primarily Level A, the nasal atrium, but also including Levels B and C); however, with exposure to the same concentration for 6 weeks, the lesions were more

developed and had progressed to more posterior regions of the nasal cavity (i.e., regions of olfactory epithelium close to the olfactory/respiratory epithelial interface, and including Levels D and E) (Monticello et al., 1989). In another study (Rusch et al., 1983), monkeys exposed to formalin for 26 weeks had both squamous metaplasia and hyperplasia (these lesions were reported together) in the middle region of the nasal turbinates, with incidences of 17% at 0.23 mg/m^3 and 100% at 3.6 mg/m^3. No exposure-related effects were reported for the anterior and posterior nasal turbinates.

Although uncertainties remain, the reversibility of metaplasia may depend more on formaldehyde concentration than the duration of exposure. In general, increases in squamous metaplasia incidence appeared to be a persistent effect at higher levels of exposure (i.e., >11 mg/m^3 in rats and >9 mg/m^3 in mice), as these lesions were observed many months after formaldehyde exposure in rat recovery study comparisons by Woutersen et al. (1989) and Feron et al. (1988), and in two transgenic mouse strains (Morgan et al., 2017). However, it appears that the magnitude of this effect, particularly at lower formaldehyde levels (e.g., ≤6.9 mg/m^3), decreases with a recovery period, as evidenced by significant declines in the incidences of squamous metaplasia (and rhinitis) in F344 rats and B6C3F1 mice 3 or 6 months after 24 months of exposure (Kerns et al., 1983; Battelle, 1982).

In summary, experimental studies, primarily in rats, have demonstrated that formaldehyde exposure duration clearly influences the incidence, severity, or anatomical location of squamous metaplasia.

Hyperplasia

As with metaplasia, hyperplasia of the nasal epithelium has been observed across various durations of exposure. In some studies, hyperplasia was reported as a concurrent lesion with metaplasia (Rusch et al., 1983; Reuzel et al., 1990; Kamata et al., 1997; Cassee and Feron, 1994).

Reliable results from several studies show that chronic formaldehyde exposure of approximately 11.6–12.1 mg/m^3 induces hyperplasia in the nasal epithelium of rats (Woutersen et al., 1989; Appelman et al., 1988). Studies with more limited endpoint information also reported the formation of hyperplasia following exposure to 7.4–18.2 mg/m^3 (Sellakumar et al., 1985; Monticello et al., 1996). Subchronic exposure to formaldehyde also leads to hyperplasia in rat nasal passages after exposure to 11.9 mg/m^3 (Woutersen et al., 1987) and after exposure to approximately 3.7 mg/m^3 as reported in two studies with limited endpoint information (Zwart et al., 1988; Rusch et al., 1983). Following short-term exposures in rats to 4.4–18.5 mg/m^3, studies with methodological shortcomings also report the formation of nasal epithelium hyperplasia (Wilmer et al., 1987; Chang et al., 1983; Cassee and Feron, 1994; Andersen et al., 2008), adding support. While in nearly all cases, hyperplasia was observed in respiratory or transitional epithelium (or, in a few cases, isolated regions of olfactory epithelium), a single *medium* confidence, short-term study reported that after 4 weeks of exposure to 18.4 mg/m^3, hyperplasia of the epithelium surrounding NALT (nasal-associated lymphoid tissue) was observed in a majority (87.5%) of F344 rats, but not

B6C3F1 mice (Kuper et al., 2011). Overall, comparisons of the formaldehyde concentrations at which significant increases in hyperplasia are observed across studies of differing exposure duration do not provide a clear picture of the potential duration dependence of formaldehyde-exposure-induced hyperplasia.

However, like the results for metaplasia, several rat studies comparing exposures of differing exposure duration (e.g., chronic versus subchronic) demonstrate that increasing exposure duration results in increases in the incidence and/or severity of hyperplasia in the respiratory epithelium when testing the same formaldehyde concentrations and anatomical levels (Woutersen et al., 1989; Kerns et al., 1983; Feron et al., 1988; Appelman et al., 1988). This included two *high* confidence studies matching the age of the animals at assessment (Woutersen et al., 1989; Feron et al., 1988) to allow identical amounts of time for lesions to develop after the exposures began. Similarly, some data also indicate that duration can influence the location of the observed hyperplasia, with an increased frequency of lesions in more posterior locations (i.e., at more posterior nasal levels or in more posterior structures, such as the trachea) with longer-term exposure (Woutersen et al., 1989; Kerns et al., 1983). However, in the identified rat studies, the within-study increases in incidence or posterior location with comparatively longer exposures were generally only observed at high levels of formaldehyde (i.e., >10 mg/m^3), preventing clear interpretations regarding the duration dependence of hyperplasia at lower formaldehyde levels.

The role for duration in the development of hyperplasia in other laboratory animal species is less clear. Hyperplasia was reported in a chronic mouse study with limited endpoint information following exposure to 2.5 mg/m^3 (Kerns et al., 1983), with consistent findings in a *low* confidence, short-term study at 18.5 mg/m^3 (Chang et al., 1983); however, a *medium* confidence, short-term study in transgenic mice failed to observe significant increases in hyperplasia after exposure to 9.23–18.5 mg/m^3, despite the presence of pronounced metaplasia (Morgan et al., 2017). Interestingly, however, this short-term mouse study did observe increases in nasal osteogenesis (evidence of bone proliferation in the nasal turbinates) at 18.45 mg/m^3 in both strains tested (Morgan et al., 2017). In a lifetime study by Dalbey (1982), 5% of hamsters had hyperplasia following exposure to 12.3 mg/m^3; however, hyperplasia did not appear to develop in hamsters exposed to 3.6 mg/m^3 for 26 weeks, although hyperplasia was not specified (i.e., the authors reported no treatment-related histopathology) (Rusch et al., 1983). In cynomolgus monkeys, hyperplasia along with metaplasia was reported following subchronic exposure to 3.6 mg/m^3 (Rusch et al., 1983), and hyperplasia was also found in rhesus monkeys exposed to 7.4 mg/m^3, although lesion incidence or severity was not reported (Monticello et al., 1989). When specified, the hyperplasia observed in mice (Kerns et al., 1983) and rhesus monkeys (Monticello et al., 1989) was generally identified in the anterior nose.

Hyperplasia in rats and mice appears to persist, at least in part (Woutersen et al., 1989; Kerns et al., 1983; Feron et al., 1988; Battelle, 1982), as with observations of squamous metaplasia. However, hyperplasia generally appears to be more reversible than metaplasia, even at higher

formaldehyde concentrations, as evidenced by smaller increases in incidence with a prolonged recovery following exposure to ~11 mg/m^3 formaldehyde (Woutersen et al., 1989; Feron et al., 1988). Findings in a short-term recovery study in rats (Andersen et al., 2008), with similar results observed in a *low* confidence study in mice (Chang et al., 1983), suggest that hyperplasia may take some small amount of time to develop, as lesions progressed in incidence or severity with 18 hours of recovery after very brief (i.e., days) exposures.

Taken together, formaldehyde exposure duration does appear to have some influence on the development of hyperplasia, primarily based on studies in rats. However, considering the notable influence of exposure duration on metaplasia at formaldehyde levels ranging from 2.5 to 2.7 mg/m^3 in rat studies (Kerns et al., 1983; Kamata et al., 1997), the easier reversibility of hyperplasia, as well as the generally more robust effects of duration on the incidence of metaplasia as compared to hyperplasia across species, exposure duration appears to be more important to the development of metaplasia in laboratory animals than to the development of hyperplasia. Overall, uncertainties remain regarding the relative impact of duration on the development of hyperplasia (particularly in species other than rats), as compared to the pronounced role for concentration, particularly at low formaldehyde levels (see additional discussion below).

Necrosis, nasal damage, and cytotoxicity

Although possessing methodological limitations, numerous short-term studies and three long-term studies in rats report overt damage to the nasal epithelium following exposure to 3.9–7.4 mg/m^3 (Cassee and Feron, 1994; Cassee et al., 1996; Andersen et al., 2010), 12 mg/m^3 (Wilmer et al., 1987), or approximately 18.5 mg/m^3 (Speit et al., 2011; Chang et al., 1983), with supporting evidence from ultrastructural analyses in a short-term study (Monteiro-Riviere and Popp, 1986). Consistent observations of nasal tissue damage were reported in rhesus monkeys (Monticello et al., 1989) and in a *low* confidence, mouse study with methodological limitations (Chang et al., 1983) following short-term exposure to ≥7.4 mg/m^3. In rhesus monkeys (Monticello et al., 1989), loss of cilia and goblet cells was more severe and covered a greater surface of respiratory epithelium (including extranasal respiratory tract regions), as duration of exposure increased. As these observations of tissue cytotoxicity generally appear to occur following exposures of shorter duration than in many of the studies reporting metaplasia or hyperplasia at similar formaldehyde concentrations, these data may be consistent with the evolution of hyperplasia and metaplasia from other lesions with increasing exposure duration.

Concentration dependency of nasal lesions

The development of nasal lesions in rodents and monkeys has routinely been shown to exhibit a strong concentration dependency in terms of incidence, frequency, severity, and location of the observed lesions. This is particularly true for both squamous metaplasia and hyperplasia in the respiratory epithelium. Importantly, several studies have reported the occurrence of metaplasia in the absence of hyperplasia at a given exposure level (see Tables 3-26 and 3-27 for study details).

Squamous metaplasia

Although there is a demonstrated exposure duration dependency for the development of squamous metaplasia, formaldehyde concentration appears to be at least as important, if not more so. With increasing formaldehyde concentration, squamous metaplasia is observed in more posterior regions of the nasal tissue, and there is a marked increase in both lesion incidence and severity.

In a chronic study reporting metaplasia throughout the rat nasal passage (Kerns et al., 1983; Battelle, 1982), metaplasia was observed in the anterior nose (i.e., Level I) after exposure to 2.5 mg/m^3 and progressed in incidence toward the posterior nose, reaching Level V only after exposure to 17.6 mg/m^3. Consistent observations of the anterior-to-posterior progression of metaplasia with increasing exposure concentration were reported by another *high* confidence chronic study (Woutersen et al., 1989). These findings are supported by results from a *low* confidence chronic study with limited endpoint reporting (Monticello et al., 1996), as well as by *medium* confidence subchronic (Andersen et al., 2010) and short-term (Speit et al., 2011) studies.

With a constant duration of exposure, concentration-dependent increases for metaplasia in rat noses (Level II) after 24 months were reported in a chronic study where 1.1, 62.2, and 100% of rats were observed to have squamous metaplasia after exposure to 2.5, 6.9, or 17.6 mg/m^3, respectively (Kerns et al., 1983; Battelle, 1982). Additional studies provide support for a concentration-dependent increase in squamous metaplasia incidence following chronic and subchronic exposures in rats and mice (Woutersen et al., 1989; Maronpot et al., 1986; Kamata et al., 1997; Feron et al., 1988; Andersen et al., 2010). The incidence of squamous metaplasia and hyperplasia (lesions were reported together) also increased with concentration in rats and cynomolgus monkeys (Rusch et al., 1983).

The severity of metaplasia (e.g., from very slight to severe) also increased with concentration, as reported by subchronic studies (Woutersen et al., 1987; Feron et al., 1988; Andersen et al., 2010) and a short-term study with a relatively small sample size (Speit et al., 2011). In general, while concentration-dependent increases in more mild instances of metaplasia are typically observed at concentrations of 2.5 mg/m^3 and above (see previous section), moderate or severe lesions were only observed at the highest formaldehyde concentrations (approximately 12 mg/m^3 or more). The available studies demonstrate that formaldehyde exposure concentration occupies a central role in the development of squamous metaplasia.

Hyperplasia

Concentration-dependent increases in the incidence and severity of hyperplasia have also been observed in rats with chronic, subchronic, or short-term exposure durations (Woutersen et al., 1989; Kamata et al., 1997; Appelman et al., 1988; Andersen et al., 2008) and with subchronic exposure in F344 rats and cynomolgus monkeys (Rusch et al., 1983). Overall, the concentration dependence of these lesions, in terms of location, incidence, and severity, closely paralleled the

pattern of changes observed for squamous metaplasia, identifying a strong influence of exposure concentration on the development of hyperplasia.

Necrosis, nasal damage, and cytotoxicity

Results for concentration-dependent cytotoxicity are varied, as reported by less-than-chronic studies. A subchronic study observed no concentration-dependent increase in necrosis in the noses of Wistar rats exposed to 1.2 or 2.5 mg/m^3 for 13 weeks (Wilmer et al., 1989). Following ≤13 weeks of exposure to 0.8–18.5 mg/m^3, however, the incidence of necrosis/erosions in F344 noses generally increased with concentrations of 7.4 mg/m^3 and greater (Andersen et al., 2010). Following 4 weeks of formalin exposure from 0.63 to 18.4 mg/m^3, degeneration was observed only after exposure to the highest concentration in F344 rats (Speit et al., 2011), while focal thinning and epithelial disarrangement of the respiratory epithelium was observed in Wistar rats exposed to ≥12 mg/m^3 (Wilmer et al., 1987).

Studies comparing potential differential contributions of duration and concentration

Several animal respiratory pathology studies employed designs that compared intermittent and continuous exposure scenarios to examine the extent to which Haber's rule ($C \times t = K$; where C is concentration, t is time, and K is a constant) applies to formaldehyde-induced nasal pathology. If, for example, Haber's rule can be strictly applied, similar pathological lesions should result whether rats are exposed to 12 mg/m^3 for 3 hours (12 × 3 = 36) or to 6 mg/m^3 for 6 hours (6 × 6 = 36).

Wilmer et al. (1987) and Wilmer et al. (1989) used continuous and intermittent exposure scenarios to assess whether lesion formation appears to be influenced more by concentration or duration of exposure. In Wilmer et al. (1987), male rats were exposed to formaldehyde 5 days/week for 4 weeks. Groups of rats were either continuously exposed for 8 hours/day to target concentrations of 0, 6, or 12 mg/m^3 formaldehyde, or intermittently exposed (30 minutes of exposure followed by 30 minutes of nonexposure) to 0, 12, or 25 mg/m^3 formaldehyde (the analytical concentrations were not reported). Thus, the weekly inhaled concentrations (concentration × hours × days) were the same for the continuous and intermittent exposure groups: 0, 240, or 480 mg/m^3-hour/week. The main difference was that the intermittently exposed rats were exposed to higher concentrations than the continuously exposed rats. The rats exposed intermittently to the higher concentrations (12 or 25 mg/m^3) had greater nasal cell proliferation and histopathologic lesions, including squamous metaplasia and basal cell hyperplasia, than did the rats exposed continuously to the lower concentrations (6 or 12 mg/m^3).

Similar results were seen in a 13-week study (Wilmer et al., 1989) in which groups of male rats were either continuously exposed for 8 hours/day to target concentrations of 0, 1, or 2 mg/m^3 formaldehyde, or intermittently exposed (30 minutes of exposure followed by 30 minutes of nonexposure) to 0, 2, or 5 mg/m^3 formaldehyde (again, the analytical concentrations were not reported). The rats exposed continuously had greater incidences of diffuse disarrangement, diffuse necrosis, focal and diffuse basal cell hyperplasia, focal squamous metaplasia, keratinization, and

diffuse goblet cell hyperplasia than the rats exposed intermittently. For some of these lesions, the incidences were greater in the rats exposed continuously to 2 mg/m^3 than to 5 mg/m^3, the interpretation of which is unclear. Overall, the Wilmer et al. studies suggest that in rats exposed for 4 or 13 weeks the extent of nasal lesions and cell proliferation appears to be driven more by concentration than by duration of exposure or cumulative dose. These findings are consistent with changes in cell proliferation reported in an acute and a short-term study using similar approaches (Wilmer et al., 1987; Swenberg et al., 1983); (see Appendix C.7.1).

While the authors of another subchronic rat study reached similar conclusions, the data did not fully support a clear concentration over duration driver for the observed effects. Rusch et al. (1983) compared the findings in their 6-month rat study against the 6-month exposure phase in the 2-year rat study by Kerns et al., as reported in the supporting report by Battelle for CIIT (Kerns et al., 1983; Battelle, 1982). Rusch et al. (1983) exposed animals 22 hours/day, 7 days/week for a total of 154 hours/week, compared to 6 hours/day, 5 days/week in the (Kerns et al., 1983; Battelle, 1982) study, for a total of 30 hours/week; that is, the rats in the Rusch et al. (1983) study were exposed five times longer than in the (Kerns et al., 1983; Battelle, 1982) study. At 6 months, squamous metaplasia was observed at 2.5 mg/m^3 by (Kerns et al., 1983; Battelle, 1982) versus at 3.6 mg/m^3 in the Rusch et al. (1983) study. However, the incidence was ~60% at 3.6 mg/m^3 in Rusch et al. (1983), as compared to only 20% at 2.5 mg/m^3 in the (Kerns et al., 1983; Battelle, 1982) study. In addition, while (Kerns et al., 1983; Battelle, 1982) did not test lower formaldehyde levels, metaplasia incidence went from 2/38 in controls to 3/36 at 1.2 mg/m^3 in Rusch et al. (1983), introducing the possibility that the study may have been inadequately powered to detect an effect at lower levels. Regardless, these data do support the possibility of an increased dependence on concentration, as compared to duration, as the rats in Rusch et al. (1983) did not appear to be five-fold more sensitive.

In summary, several rat studies suggest that formaldehyde, perhaps similar to mortality responses following acute exposure to some other local irritants, may not adhere strictly to Haber's rule for the induction of nasal pathology. Although duration of exposure has a clear and substantial role for the development of these nasal lesions (see discussion above), the experiments by Wilmer et al. (1987) and Wilmer et al. (1989) suggest that a power-law function ($C^n \times t = K$) where n is >1 may better represent formaldehyde exposure-induced nasal lesions than the linear $C \times t = K$, at least when interpreting short-term or subchronic exposure (the exposure scenarios examined by Wilmer et al.). Although a value for n was not identified for formaldehyde, or for exposure-induced nasal pathology, in particular, studies of acute exposure to other local irritants and the concentration-duration dependence for mortality suggest that the value for n, on average, is approximately

1.8–1.9 (ranging from 0.5 to 4.0).[22] It is difficult to speculate where within this range a value for *n* might be most applicable to formaldehyde, particularly within the context of respiratory pathology and long-term exposures (i.e., since these *n* values are for mortality after acute exposure); however, based on the data discussed in previous sections, it might be reasonable to expect that an *n* defined for associations with hyperplasia should be higher than one defined for metaplasia.

Species and sex differences in respiratory pathology

While most respiratory pathology studies have been conducted in rats, studies conducted with mice, hamsters, and monkeys have reported interspecies differences in susceptibility (i.e., lesion incidence and severity), and in the location of lesions. Additionally, differences between sexes of the same species have also been observed.

Rats have consistently been shown to be more susceptible than mice to the formation of various nasal lesions after chronic, subchronic, and short-term exposures. A well-conducted bioassay exposing F344 rats and B6C3F1 mice to 2.5, 6.9, or 17.6 mg/m^3 formaldehyde for 24 months reported that squamous metaplasia was observed in rat noses at all exposure levels, whereas in mice metaplasia was only observed after exposure to the intermediate and high concentrations. Additionally, lesions observed in mice were less severe than in rats at the same concentration level. In fact, similar incidences of squamous cell carcinoma were observed in rats exposed at 6.9 mg/m^3 and in mice exposed at 17.6 mg/m^3 (Kerns et al., 1983). Likewise, Kuper et al. (2011) observed hyperplasia of the NALT lymphoepithelium in rats, but not in mice. A possible explanation for these species disparities is that mice have a greater reflex bradypnea response than rats and thus inhaled lower doses of formaldehyde than rats. Unfortunately, minute volume and body temperature were not measured in the 2-year Battelle study or in Kuper et al. (2011), so there is no way of knowing whether reflex bradypnea played a significant role (see Appendix C.2 for a discussion on reflex bradypnea).

Rats also show differences with other species. Rats, and, to a lesser extent, mice, appear to be more sensitive than Syrian hamsters (Rusch et al., 1983; Dalbey, 1982; Appelman et al., 1988). The comparisons to nonrodent experimental models are less clear. Squamous metaplasia and hyperplasia were specifically found in the anterior, middle, and posterior nasal turbinates of F344 rats, but lesions were predominantly in the middle nasal turbinates of cynomolgus monkeys (Rusch et al., 1983) and rhesus monkeys (Monticello et al., 1989). Monticello et al. (1989) observed lesions that extended to proximal regions of the URT (outside of the nasal cavity) at lower concentrations than in the rat studies (7.4 mg/m^3, as compared to >15 mg/m^3), likely because the monkey nose is less efficient than the rodent nose at scrubbing formaldehyde from inhaled air.

[22]Values of *n* for 11 local irritants as estimated by ten Berge et al. (1986) averaged 1.9 (range 1.0–3.5), while 21 local irritants relying on data in rats or mice, as summarized in Appendix G by California EPA (OEHHA, 2008), averaged 1.8 (range 0.5–4.0). Of potential interest to this assessment, the chemicals included ammonia (*n* = 2.0) and acrolein (*n* = 1.2).

In addition to differences between species, the formation of histopathological lesions was sometimes observed to differ between sexes, although most studies only examined male animals. A subchronic study in Wistar rats reported that males generally had more severe damage, including metaplasia, to the nasal respiratory, olfactory epithelium, and larynx (Woutersen et al., 1987). Supportive findings of increased incidence or severity of lesions in males as compared to females was also reported in a second subchronic study of Wistar rats (Zwart et al., 1988), as well as in mouse studies of subchronic (Maronpot et al., 1986) and chronic (Kerns et al., 1983; Battelle, 1982) duration. Male rats have a higher metabolic rate and oxygen demand than female rats, and therefore greater minute volumes; thus, these findings might also reflect a greater inhaled dose of formaldehyde in males as compared to females at the concentrations tested.

Table 3-26. Chronic respiratory pathology studies in animals

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Rats</td></tr>
<tr><td colspan="2">High confidence</td></tr>
<tr><td>Woutersen et al. (1989)
Wistar rats; male; 30/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for 3 or 28 months. All survivors sacrificed at 28 months.
Test article: Paraformaldehyde. Actual concentrations were 0, 0.1 (±0.07), 1.2 (±0.22), or 11.3 (±2.0) mg/m^3 for 3-month exposures and 0, 0.1 (±0.05), 1.2 (±0.14), or 12.1 (±1.60) mg/m^3 for 28-month exposures.[1]
Histopathology: 6 standard cross sections of the nose.

Note: This study also evaluated the effects of FA in a parallel group of rats that had undergone bilateral electrocoagulation (i.e., damaged nose group) prior to the initiation of FA exposure). Data presented here in the Results column are for FA-only (i.e., undamaged nose group) exposed rats.</td><td>
3 months of exposure followed by a 25-month observation period with no exposure:
FA-related histological changes generally not observed for Levels IV–VI.

Histopathological nasal changes after 3 months of exposure and 25-month recovery period
<table>
<tr><td></td><td colspan="4">Incidence of lesions in Levels I–II</td></tr>
<tr><td></td><td>0 mg/m^3</td><td>0.1 mg/m^3</td><td>1.2 mg/m^3</td><td>11.3 mg/m^3</td></tr>
<tr><td>Type of lesions (Severity NR)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Respiratory epithelium</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Disarrangement</td><td>0/26[a]</td><td>0/30</td><td>0/29</td><td>1/26</td></tr>
<tr><td>Squamous metaplasia</td><td>3/26</td><td>6/30</td><td>4/29</td><td>17/26</td></tr>
<tr><td>Keratinization</td><td>0/26</td><td>0/30</td><td>1/29</td><td>2/26</td></tr>
<tr><td>Basal cell/pseudoepithelial hyperplasia</td><td>1/26</td><td>0/30</td><td>0/29</td><td>4/26</td></tr>
<tr><td>Nest-like infolds/goblet cell hyperplasia</td><td>11/26</td><td>3/30</td><td>15/29</td><td>9/26</td></tr>
<tr><td>Invaginations</td><td>3/26</td><td>0/30</td><td>0/29</td><td>0/26</td></tr>
<tr><td>Rhinitis</td><td>5/26</td><td>4/30</td><td>3/29</td><td>13/26</td></tr>
<tr><td>Olfactory epithelium</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Thinning/disarrangement</td><td>0/26</td><td>0/30</td><td>0/29</td><td>0/26</td></tr>
<tr><td>Basal cell hyperplasia</td><td>0/26</td><td>0/30</td><td>0/29</td><td>0/26</td></tr>
<tr><td>Vacuolation/proteinaceous material/numeric atrophy</td><td>0/26</td><td>0/30</td><td>0/29</td><td>0/26</td></tr>
<tr><td>Replaced by respiratory epithelium</td><td>0/26</td><td>0/30</td><td>0/29</td><td>0/26</td></tr>
</table>
[a]Denominator represented by the effective number of animals and not the initial number of animals.

Large variation observed for nest-like infolds/goblet cell hyperplasia; due to lack of exposure-response, this change was not considered to be exposure-related.

28 months of exposure:
</td></tr>
</table>

Reference and study design	Results
	12.1 mg/m^3—Incidence of rhinitis elevated in Level I–VI; other FA-related histological changes in respiratory epithelium generally found in Level II and III; lesions observed in olfactory epithelium in Levels III and IV. *Histopathological nasal changes after 28 months of exposure period* Incidence of lesions **in Levels I–II** 0 mg/m^3 | 0.1 mg/m^3 | 1.2 mg/m^3 | 12.1 mg/m^3 Type of lesions (Severity NR) **Respiratory epithelium** Disarrangement: 0/26[a] | 0/26 | 1/28 | 1/26 Squamous metaplasia: 3/26 | 1/26 | 6/28 | 25/26 Keratinization: 0/26 | 1/26 | 0/28 | 2/26 Basal cell/pseudoepithelial hyperplasia: 0/26 | 1/26 | 2/28 | 14/26 Nest-like infolds/goblet cell hyperplasia: 5/26 | 6/26 | 14/28 | 4/26 Invaginations: 0/26 | 0/26 | 1/28 | 3/26 **Rhinitis**: 2/26 | 1/26 | 2/28 | 18/26 **Olfactory epithelium** Thinning/disarrangement: 0/26 | 0/26 | 0/28 | 0/26 Squamous metaplasia: 0/26 | 0/26 | 0/28 | 0/26 Basal cell hyperplasia: 0/26 | 0/26 | 0/28 | 0/26 Vacuolation/proteinaceous material/numeric atrophy: 0/26 | 0/26 | 0/28 | 0/26 Replaced by respiratory epithelium: 0/26 | 0/26 | 0/28 | 0/26 [a]Denominator represented by the effective number of animals and not the initial number of animals. Highest incidence for nest-like infolds/goblet cell hyperplasia observed for Level II at 1.2 mg/m^3; due to lack of exposure-response, this change was not considered to be exposure-related.
	28 months of exposure (continued): *Histopathological nasal changes after 28 months of exposure period* Incidence of lesions **in Level III** 0 mg/m^3 | 0.1 mg/m^3 | 1.2 mg/m^3 | 12.1 mg/m^3 Type of lesions (Severity NR) **Respiratory epithelium** Disarrangement: 4/26[a] | 0/26 | 2/28 | 1/26 Squamous metaplasia: 0/26 | 0/26 | 0/28 | 13/26 Keratinization: 0/26 | 0/26 | 0/28 | 1/26 Basal cell/pseudoepithelial hyperplasia: 1/26 | 0/26 | 2/28 | 7/26 Nest-like infolds/goblet cell hyperplasia: 1/26 | 2/26 | 2/28 | 1/26 Invaginations: 0/26 | 0/26 | 0/28 | 0/26 **Rhinitis**: 1/26 | 0/26 | 2/28 | 6/26 **Olfactory epithelium** Thinning/disarrangement: 1/26 | 1/26 | 1/28 | 7/26 Squamous metaplasia: 0/26 | 0/26 | 0/28 | 2/26 Basal cell hyperplasia: 3/26 | 3/26 | 4/28 | 3/26

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td></td><td>
<table>
<tr><td>Vacuolation/proteinaceous material/numeric atrophy</td><td>1/26</td><td>1/26</td><td>3/28</td><td>0/26</td></tr>
<tr><td>Replaced by respiratory epithelium</td><td>0/26</td><td>0/26</td><td>1/28</td><td>2/26</td></tr>
</table>
[a]Denominator represented by the effective number of animals and not the initial number of animals.
</td></tr>
<tr><td>Kerns et al. (1983)
Fischer 344 rats; males and females; 119 to 121/sex/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for up to 24 months. Animals sacrificed at 27 and 30 months had 3- and 6-month periods of nonexposure, respectively, after 24-months of exposure.
Test article: Paraformaldehyde. Actual concentrations were 0, 2.5 (±0.01), 6.9 (±0.02), or 17.6 (±0.05) mg/m^3.[a]
Histopathology: 5 midsagittal sections of nasal turbinates (Levels I–V; see Figure 3-14) for all animals that died or were sacrificed at scheduled intervals (i.e., at month 6, 12, 18, 24, 27, and 30).
Related studies/earlier reports: Swenberg et al. (1980a); Battelle (1981, 1982). See Battelle, 1982 for a more detailed study report.

Note: transient viral infection at 52 weeks was noted, but considered unlikely to influence these findings.</td><td>
<table>
<tr><th></th><th colspan="3">Pathological changes[a,b]</th></tr>
<tr><td>Exposure duration</td><td>2.5 mg/m^3</td><td>6.9 mg/m^3</td><td>17.6 mg/m^3</td></tr>
<tr><td>6 months</td><td>NR[c]</td><td>Levels I, II, and III: purulent rhinitis, epithelial dysplasia, and squamous metaplasia observed</td><td>Lesions first noted in anterior sections (Levels I, II, and III) of nose; changes in epithelium restricted to ventral portion of nasal septum and distal tips of nasoturbinates and maxilloturbinates</td></tr>
<tr><td>12 months</td><td>Level I[d]: purulent rhinitis, epithelial dysplasia, and squamous metaplasia observed</td><td></td><td>NR</td></tr>
<tr><td>18 months</td><td>NR</td><td></td><td>NR</td></tr>
<tr><td>24 months</td><td>Frequency of metaplasia exceeded that of prior sacrifices; dysplasia and metaplasia only observed in Level I</td><td></td><td>NR</td></tr>
<tr><td>27 months[e]</td><td>Significant decrease ($p < 0.05$) in frequency of metaplasia</td><td>Levels I, II, and III: regression ($p < 0.05$) of squamous metaplasia</td><td>Levels IV and V: regression ($p < 0.05$) of squamous metaplasia</td></tr>
</table>
[a]Severity of lesions most intense in Level I for all exposure groups. Exposure-related effects observed in Levels II, III, IV, and V for 6.9- and 17.6-mg/m^3 groups. Lesion frequency in exposed groups greater than the <15% lesion frequency observed for 0 mg/m^3 group, where lesions (e.g., dysplasia and metaplasia) only present in Level I.
[b]Authors defined squamous metaplasia as zones of altered epithelium characterized by a well-differentiated germinal cell layer (stratum germinativum) and superficial epithelial layers (stratum spinosum and stratum corneum). Authors further noted that keratin was only produced in areas of squamous metaplasia, and that in all exposure groups epithelial dysplasia was detected earlier than squamous metaplasia.
[c]Chart nine of Kerns et al. (1983) provides graphical representation of the frequency of squamous metaplasia observed for Levels I–V for all exposure groups during 24-month exposure and 3-month nonexposure period.
[d]At this location, authors observed a transition in the mucosa from normal nonciliated simple cuboidal epithelium to an epithelial lining several cells thick
</td></tr>
</table>

Reference and study design	Results
	and squamoid in appearance. The organization and polarity of the individual epithelial cells changed from vertical to horizontal with respect to the basement membrane. The authors termed such alterations as zones of epithelial dysplasia and noted that similar histomorphological alterations have been called basal cell hyperplasia and epidermoid metaplasia. [e]24 months of exposure and 3 months of nonexposure. General observations (respiratory epithelium): 17.6 mg/m^3—squamous metaplasia with zones of squamous epithelial hyperplasia and increased keratin production appeared to precede area of squamous papillary hyperplasia with foci of cellular atypia; dyspnea and death caused by excessive accumulation of keratin and inflammatory exudate in lumen of nasal cavity of rats (with and without carcinomas). General observations (tracheal pathology): 17.6 mg/m^3—rats (frequency NR) sacrificed at 18 months exhibited multifocal areas of mild epithelial hyperplasia, epithelial dysplasia, or squamous metaplasia of proximal tracheal mucosa; similar lesions at a greater frequency ($p < 0.05$) observed in rats from 24-month sacrifice and unscheduled death groups; tracheal lesions not observed in postexposure group. 0, 2.5, or 6.9 mg/m^3—no significant tracheal lesions observed

Incidence of squamous metaplasia in nasal cavity of rats

Level I[a]				
Duration	*0 mg/m^3*	*2.5 mg/m^3*	*6.9 mg/m^3*	*17.6 mg/m^3*
6 months	NA[b]	4/20	10/20	NA
12 months	NA	7/20	11/20	NA
18 months	0/40	24/40	35/40	38/39
24 months	1/101	91/94	81/82	27/27
27 months[d]	3/19	4/20[c]	8/19[c]	5/5
30 months	1/10	2/5	1/8	NR
Level II				
6 months	NA	0/20	10/20	NA
12 months	NA	0/20	8/20	NA
18 months	0/40	0/40	24/40	38/39
24 months	0/101	1/94	51/82	27/27
27 months	0/19	0/20	5/19[c]	5/5
30 months	0/10	0/5	5/8	NR
Level III				
6 months	0/20	0/20	0/20	6/20
12 months	0/20	0/20	0/20	10/20
18 months	0/40	0/40	0/40	38/39
24 months	0/101	0/94	9/82	26/27
27 months	0/19	0/20	0/19	4/5
30 months	0/10	0/5	0/8	NR
Level IV				
6 months	NA	0/20	0/20	NA
12 months	NA	0/20	0/20	NA
18 months	0/40	0/40	0/40	14/39
24 months	0/101	0/94	1/82	21/27
27 months	0/19	0/20	0/19	1/5[c]
30 months	0/10	0/5	0/8	NR
Level V				

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td></td><td>
<table>
<tr><td>6 months</td><td>NA</td><td>0/20</td><td>0/20</td><td>NA</td></tr>
<tr><td>12 months</td><td>NA</td><td>0/20</td><td>0/20</td><td>NA</td></tr>
<tr><td>18 months</td><td>0/40</td><td>0/40</td><td>0/40</td><td>11/39</td></tr>
<tr><td>24 months</td><td>0/101</td><td>0/94</td><td>0/82</td><td>19/27</td></tr>
<tr><td>27 months</td><td>0/19</td><td>0/20</td><td>0/19</td><td>0/5[c]</td></tr>
<tr><td>30 months</td><td>0/10</td><td>0/5</td><td>0/8</td><td>NR</td></tr>
</table>
[a]Data reported in part in Kerns et al. (1983) and further adapted from Battelle (1982)[b] tissue section not available for histopathology; [c]$p < 0.05$, regression of squamous metaplasia 3 months postexposure; [d]data for 27 and 30 months represent incidence after 3 and 6 months of nonexposure, respectively, following 24 months of exposure.
</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Kamata et al. (1997)
Fischer 344 rats; male; 32/group.
Exposure: Rats were exposed to FA in dynamic nose-only chambers 6 hours/day, 5 days/week for 28 months with interim sacrifices at the end of months 12, 18, and 24.
Test article: Formalin (37% FA aqueous solution containing 10% methanol). Actual concentrations were 0, 0.40 (±0.09), 2.67 (±0.40), or 18.27 (±2.73) mg/m^3.[a] The concentration of methanol in the 0 and 18.27 groups was estimated to be 5.5 mg/m^3.[b] A room control served as a no exposure group.
Histopathology: nasal region (sections from five anatomical levels, A-E; see Figure 3-14) and trachea.

Main limitations: formalin; small N for interim sacrifices; lesion severities NR</td><td>
<table>
<tr><th>Group</th><th>Squamous cell metaplasia no epithelial cell hyperplasia</th><th>Epithelial cell hyperplasia with squamous cell metaplasia</th><th>Epithelial cell hyper-keratosis</th><th>Papillary hyperplasia</th></tr>
<tr><td>Room control</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td></tr>
<tr><td>0 mg/m^3 (5.5 mg/m^3 MeOH)</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td></tr>
<tr><td>0.40 mg/m^3</td><td>1/32[a] (1/5 at 18-month)</td><td>4/32 (1/5 at 24-month, 3/11 at 28-month)</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td></tr>
<tr><td>2.67 mg/m^3</td><td>5/32[b] (2/5 at 18-month, 1/5 at 24-month, 2/7 at 28-month)</td><td>7/32[c] (2/5 at 18-month, 1/7 at 28-month, 4/10 of dead)</td><td>1/32 (1/10 of dead)</td><td>No nasal lesions observed</td></tr>
<tr><td>18.27 mg/m^3 (5.5 mg/m^3 MeOH)</td><td>NR</td><td>29/32[c] (3/5 at 12-month, 4/5 at 18-month, 2/2 at 24-month, 20/20 of dead)</td><td>26/32[c] (4/5 at 12-month, 1/5 at 18-month, ½ at 24-month, 20/20 of dead)</td><td>2/32 (2/5 at 12-month)</td></tr>
</table>
[a]data reported as group total (i.e., dead animals plus scheduled sacrifices at 12, 18, 24, and 28 months); number in parenthesis represent incidence at sacrifice; [b]$p < 0.05$, compared to 0 mg/m^3 group; [c]$p < 0.01$, compared to 0 mg/m^3 group
</td></tr>
<tr><td>Appelman et al. (1988)
SPF Wistar rat; male; 20/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for 52 weeks. Half of the rats in each group were sacrificed at 13 weeks.
Test article: Paraformaldehyde.</td><td>
Histopathological nasal changes after 13 weeks of exposure (data included for comparison with 52 weeks of exposure)
<table>
<tr><th>Type of lesion</th><th>0 mg/m^3</th><th>0.1 mg/m^3</th><th>1.2 mg/m^3</th><th>11.6 mg/m^3</th></tr>
<tr><td>Respiratory epithelium</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal squamous metaplasia:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Slight</td><td>0/10</td><td>0/10</td><td>1/10</td><td>9/10[a]</td></tr>
<tr><td>Moderate/severe</td><td>0/10</td><td>0/10</td><td>0/10</td><td>1/10</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Actual concentrations were 0, 0.1 (±0.05), 1.2 (±0.18), or 11.6 (±1.60) mg/m^3.[a]
Histopathology: nose (6 standard cross levels), larynx, trachea, and lungs.

Main limitations: small *N*; limited reporting of lesion severity (note: this 12-month study was shorter than the other available chronic studies).

Note: This study also evaluated the effects of FA in a parallel group of rats that had undergone bilateral electrocoagulation 20 to 26 hours prior to the initiation of FA exposure (not shown).</td><td>
<table>
<tr><td>**Focal basal cell hyperplasia:**</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Slight</td><td>0/10</td><td>0/10</td><td>0/10</td><td>7/10[a]</td></tr>
<tr><td>Moderate/severe</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>**Focal rhinitis**</td><td>0/10</td><td>0/10</td><td>0/10</td><td>6/10[b]</td></tr>
<tr><td>**Nest-like infolds**</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>*Olfactory epithelium*</td><td></td><td></td><td></td><td></td></tr>
<tr><td>**Focal thinning/disarrangement**</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>**Focal basal cell hyperplasia**</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>**Focal rhinitis**</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
</table>
[a]$p < 0.01$; [b]$p < 0.05$

Histopathological nasal changes after 52 weeks of exposure
<table>
<tr><th>Type of lesion</th><th>0 mg/m^3</th><th>0.1 mg/m^3</th><th>1.2 mg/m^3</th><th>11.6 mg/m^3</th></tr>
<tr><td>*Respiratory epithelium*</td><td></td><td></td><td></td><td></td></tr>
<tr><td>**Squamous metaplasia**</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>0/10</td><td>0/10</td><td>0/10</td><td>6/10[a]</td></tr>
<tr><td>Diffuse</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>Keratinization</td><td>0/10</td><td>0/10</td><td>0/10</td><td>5/10[a]</td></tr>
<tr><td>**Basal cell hyperplasia**</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>0/10</td><td>0/10</td><td>0/10</td><td>5/10[a]</td></tr>
<tr><td>Diffuse</td><td>0/10</td><td>0/10</td><td>0/10</td><td>5/10[a]</td></tr>
<tr><td>**Focal rhinitis**</td><td>2/10</td><td>0/10</td><td>0/10</td><td>10/10[a]</td></tr>
<tr><td>**Nest-like infolds**</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>6/10</td><td>2/10</td><td>3/10</td><td>4/10</td></tr>
<tr><td>Diffuse</td><td>2/10</td><td>4/10</td><td>3/10</td><td>0/10</td></tr>
<tr><td>*Olfactory epithelium*</td><td></td><td></td><td></td><td></td></tr>
<tr><td>**Thinning/disarrangement**</td><td>1/10</td><td>0/10</td><td>0/10</td><td>3/10</td></tr>
<tr><td>**Focal basal cell hyperplasia**</td><td>0/10</td><td>0/10</td><td>0/10</td><td>2/10</td></tr>
<tr><td>**Focal squamous metaplasia**</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>**Loosely arranged submucosal connective tissue**</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>**Focal rhinitis**</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
</table>
[a]$p < 0.05$

Histopathological changes in larynx, trachea, and lungs were those commonly found in this strain of rat and were about equally distributed among controls and exposed groups or were only found in one rat; these changes ultimately characterized as unrelated to FA exposure.</td></tr>
<tr><td>Sellakumar et al. (1985)
Sprague Dawley rats; male; 100/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for life.
Test article: Paraformaldehyde.
Actual concentrations were 0 and 18.2 (±2.6) mg/m^3.[a]
Histopathology: multiple (interpreted as ≥ 5 based on study description) sections of the</td><td>
<table>
<tr><th>Observation</th><th>0 mg/m^3</th><th>18.2 mg/m^3</th></tr>
<tr><td>**Larynx**</td><td></td><td></td></tr>
<tr><td>Hyperplasia</td><td>2/99</td><td>21/100</td></tr>
<tr><td>Squamous metaplasia</td><td>0/99</td><td>4/100</td></tr>
<tr><td>**Trachea**</td><td></td><td></td></tr>
<tr><td>Hyperplasia</td><td>6/99</td><td>21/100</td></tr>
<tr><td>Squamous metaplasia</td><td>0/99</td><td>7/100</td></tr>
<tr><td>**Nasal Mucosa**</td><td></td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>head (from just behind the nostril to the eye orbits) as well as sections of lung (each lobe), trachea, and larynx.
Preliminary study: Albert et al. (1982)

Main limitations: likely coexposure to paraffin oil (kerosene); lesion severities NR</td><td>
<table>
<tr><td>Rhinitis (mild to severe)</td><td>72/99</td><td>74/100</td></tr>
<tr><td>Epithelial or squamous hyperplasia</td><td>51/99</td><td>57/100</td></tr>
<tr><td>Squamous metaplasia</td><td>5/99</td><td>60/100</td></tr>
</table>
Additional observations (frequencies NR) from FA exposures included: exudation in the nasal cavity lumen; necrosis; desquamation of respiratory epithelial cells of respiratory epithelial covering of naso-maxillary turbinates and nasal septum; and inflammation of olfactory epithelium lining the ethmoidal turbinates, with seropurulent exudate in lumen.
</td></tr>
<tr><th colspan="2">Mice</th></tr>
<tr><td colspan="2">*Medium confidence*</td></tr>
<tr><td>Kerns et al. (1983)
B6C3F1 mice; males and females; 119 to 121/sex/group.
Exposure: Mice were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for up to 24 months. Animals sacrificed at 27 and 30 months had 3- and 6-month periods of nonexposure, respectively, after 24-months of exposure.
Test article: Paraformaldehyde. Actual concentrations were 0, 2.5 (±0.01), 6.9 (±0.02), or 17.6 (±0.05) mg/m^3.[a]
Histopathology: 5 midsagittal sections of nasal turbinates corresponding to the regions evaluated in rats in this study (levels I–V; see Figure 3-14) for all animals that died or were sacrificed at scheduled intervals (i.e., at month 6, 12, 18, 24, 27, and 30).
Earlier reports: Battelle (1981); Battelle (1982)

Main limitations: high mortality in all groups; limited sampling (i.e., sections); lesion incidence and severity NR</td><td>
<table>
<tr><td></td><td colspan="3">*Pathological changes*[a]</td></tr>
<tr><td>Exposure duration</td><td>2.5 mg/m^3</td><td>6.9 mg/m^3</td><td>17.6 mg/m^3</td></tr>
<tr><td>12 mos</td><td>ND</td><td>ND</td><td>Serous rhinitis in Levels III and V</td></tr>
<tr><td>18 mos</td><td>ND</td><td>Few mice[c] had dysplastic changes associated with serous rhinitis in Level II</td><td>~90% of mice had dysplastic and metaplastic alterations of nasal mucosa in Level II with a serous to purulent change in nasal exudate</td></tr>
<tr><td>24 mos</td><td>Few animals had serous rhinitis in Level II, but no significant nasal lesions; hyperplasia (minimal to moderate) of squamous epithelium lining nasolacrimal duct</td><td>Few mice had dysplasia, metaplasia, or serous rhinitis in Level II; hyperplasia (minimal to moderate) of squamous epithelium lining nasolacrimal duct; focal atrophy of olfactory epithelium lining the ethmoturbinates</td><td>>90% of mice had dysplastic and metaplastic changes associated with seropurulent rhinitis; hyperplasia (minimal to moderate) of squamous epithelium lining nasolacrimal duct, greatest frequency and distribution found in this FA level; focal atrophy of olfactory epithelium lining the ethmoturbinates, greatest frequency at this FA level</td></tr>
<tr><td>27 mos[b]</td><td>FA-related lesions ND</td><td>FA-related lesions ND; regression observed for squamous metaplasia and rhinitis for all affected Levels</td><td>Dysplastic epithelial lesions with serous exudate observed; squamous metaplasia in Level II in (~20% of mice), but not in Levels III and IV; regression observed for squamous</td></tr>
</table>
</td></tr>
</table>

Reference and study design	Results
	metaplasia and rhinitis for all affected Levels [a]Unless noted, severities NR; [b]24 months of exposure and 3 months of nonexposure; [c]Unless noted, exact frequency of lesion NR. No tracheal lesions were observed.
Hamsters	
Medium confidence	
Dalbey (1982) Syrian golden hamsters; male; 132 untreated controls and 88 exposed. *Exposure*: Hamsters were exposed to FA in dynamic whole-body chambers 5 hours/day, 5 days/week for a lifetime. *Test article*: Paraformaldehyde. Actual FA concentrations were 0 and 12.3 (±5%) mg/m^3.[a] *Histopathology*: 2 transverse sections of the nasal turbinates, longitudinal sections of larynx and trachea, and all lung lobes cut along the bronchus. **Main limitations:** lesion severities NR *Note:* this study also evaluated the effects of FA on tumorigenicity of diethylnitrosamine (DEN), either from concurrent exposures or from DEN then FA exposures (not shown).	Hamsters exposed at 12.3 mg/m^3 had slightly reduced survival ($p < 0.05$) relative to controls. Nasal epithelium: **Hyperplastic lesions** 12.3 mg/m^3–4/88 (5%) 0 mg/m^3–0/132 **Metaplastic lesions** 12.3 mg/m^3–4/88 (5%) 0 mg/m^3–0/132 **Rhinitis** 12.3 mg/m^3–21/88 (24%) 0 mg/m^3–41/132 (31%)

Organized by species, confidence, and then descending publication year. As discussed above, results from *low* confidence studies are not included given the many *high* and *medium* confidence studies (see Appendix B. 3.5).
Abbreviations: FA = formaldehyde, NA = not available, ND = not detected, NR = not reported, SD = standard deviation.
[a]Study authors originally reported FA concentrations in ppm. These values were converted based on 1 ppm = 1.23 mg/m^3, assuming 25°C and 760 mm Hg.
[b]Study authors did not report methods for specific methanol measurements but appeared to estimate the concentration based on the proportion of methanol in the formalin solutions to determine their control group methanol concentrations (see Section 2 on assessment methods and organization for relevant discussion of the uncertainties related to this assumption). Study authors originally reported methanol concentrations in ppm. These methanol values were converted based on 1 ppm = 1.31 mg/m^3.

Table 3-27. Subchronic respiratory pathology studies in animals

Reference and study design	Results		
Rats			
High confidence			
Feron et al. (1988) Wistar rats; male; 45/group. *Exposure*: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for either 4, 8, or 13 weeks followed by nonexposure periods of 126, 122, or 117 weeks, respectively. *Test article*: Paraformaldehyde.	**4 weeks of exposure followed by observation period of 126 weeks**		
	Incidence of lesions		
	0 mg/m^3	11.3 mg/m^3	24.2 mg/m^3
Focal hyperplasia of respiratory epithelium			
Very slight	0/44	0/44	0/45
Slight	0/44	3/44	8/45[c]

Reference and study design	Results			
Actual concentrations were 0, 11.3 (±0.25), or 24.2 (±0.12) mg/m^3 for the 4-week exposed groups; 0, 11.6 (±0.21), or 24.2 (±0.11) mg/m^3 for the 8-week exposed groups; and 0, 11.9 (±0.15), or 24.4 (±0.09) mg/m^3 for the 13-week exposed groups.[a] *Histopathology*: 6 standard cross levels of the nose. *Note*: only tested high formaldehyde levels	Moderate	0/44	0/44	1/45
	Focal stratified squamous metaplasia of respiratory epithelium			
	Very slight	3/44	6/44	14/45[c]
	Slight	4/44	2/44	19/45[c]
	Moderate	0/44	2/44	3/45
	Severe	0/44	0/44	0/45
	Rhinitis	7/44	7/44	18/45[b]
	Simple or stratified cuboidal or squamous metaplasia of epithelium in the dorsomedial area where respiratory and olfactory epithelium join[a]	0/44	0/44	4/45
	Focal replacement of olfactory epithelium by respiratory, respiratory-like or regenerating olfactory epithelium			
	Very slight	0/44	0/44	0/45
	Slight	1/44	0/44	6/45
	Moderate	0/44	0/44	1/45
	Severe	0/44	0/44	0/45
	[a]The changes in this area were scored separately because their origin from either respiratory or olfactory epithelium was not clear; [b]$p < 0.05$; [c]$p < 0.01$			
	8 weeks of exposure followed by observation period of 122 weeks			
		Incidence of lesions		
		0 mg/m^3	11.6 mg/m^3	24.2 mg/m^3
	Focal hyperplasia of respiratory epithelium			
	Very slight	0/45	1/44	3/43
	Slight	2/45	2/44	12/43[c]
	Moderate	0/45	1/44	0/43
	Focal stratified squamous metaplasia of respiratory epithelium			
	Very slight	8/45	16/44	17/43[b]
	Slight	2/45	1/44	20/43[c]
	Moderate	0/45	0/44	2/43
	Severe	0/45	0/44	0/43
	Rhinitis	4/45	6/44	22/43[b]
	Simple or stratified cuboidal or squamous metaplasia of epithelium in the dorsomedial area where respiratory and olfactory epithelium join	0/45	0/44	17/43[c]
	Focal replacement of olfactory epithelium by respiratory, respiratory-like or regenerating olfactory epithelium			
	Very slight	0/45	0/44	2/43
	Slight	0/45	0/44	14/43[b]
	Moderate	0/45	0/44	3/43
	Severe	0/45	0/44	1/43
	[a]See above for explanation; [b]$p < 0.05$; [c]$p < 0.01$			
	13 weeks of exposure followed by observation period of 117 weeks			
		Incidence of lesions		
		0 mg/m^3	11.9 mg/m^3	24.4 mg/m^3
	Focal hyperplasia of respiratory epithelium			
	Very slight	0/45	5/44[b]	2/44
	Slight	1/45	6/44	14/44[c]
	Moderate	0/45	0/44	4/44

Reference and study design	Results
	Focal stratified squamous metaplasia of respiratory epithelium Very slight: 2/45; 10/44[b]; 2/44 Slight: 3/45; 18/44[c]; 26/44[c] Moderate: 1/45; 5/44; 14/44[c] Severe: 0/45; 0/44; 1/44 **Rhinitis**: 8/45; 11/44; 23/44[c] **Simple or stratified cuboidal or squamous metaplasia of epithelium in the dorsomedial area where respiratory and olfactory epithelium join**[a]: 0/45; 2/44; 23/44[c] **Focal replacement of olfactory epithelium by respiratory, respiratory-like or regenerating olfactory epithelium** Very slight: 0/45; 0/44; 1/44 Slight: 0/45; 0/44; 12/44[c] Moderate: 0/45; 0/44; 12/44[c] Severe: 0/45; 0/44; 1/44 [a]See above for explanation; [b]$p < 0.05$; [c]$p < 0.01$
Woutersen et al. (1987) Wistar rats; male and female; 10/sex/group. *Exposure*: Rats were exposed to FA in dynamic whole-body chambers for 6 hours/day, 5 days/week for 13 weeks. *Test article:* Paraformaldehyde. Actual concentrations were 0, 1.2 (±0.00), 11.9 (±0.15), or 24.4 (±0.09) mg/m^3.[a] *Histopathology*: sections of the lungs, trachea, larynx (3 longitudinal) and nose (6 standard cross sections).	***[Males]*** Histological changes in the nose at 13 weeks Incidence of lesions 0 mg/m^3 | 1.2 mg/m^3 | 11.9 mg/m^3 | 24.4 mg/m^3 **Respiratory epithelial squamous metaplasia** **Diffuse** Slight: 0/10; 0/10; 0/10; 0/10 Moderate: 0/10; 0/10; 0/10; 5/10[a] Severe: 0/10; 0/10; 0/10; 5/10[a] **Focal** Very slight: 0/10; 1/10; 0/10; 0/10 Slight: 0/10; 1/10; 6/10[a]; 0/10 Moderate: 0/10; 0/10; 4/10; 0/10 **Focal respiratory epithelial hyperplasia** Very slight: 0/10; 0/10; 1/10; 1/10 Slight: 0/10; 0/10; 6/10[a]; 7/10[b] Moderate: 0/10; 0/10; 1/10; 0/10 **Focal respiratory epithelial disarrangement** Very slight: 0/10; 0/10; 1/10; 0/10 Slight: 0/10; 0/10; 3/10; 0/10 Moderate: 0/10; 0/10; 1/10; 0/10 **Focal respiratory epithelial keratinization** Very slight: 0/10; 2/10; 6/10[a]; 1/10 Slight: 0/10; 0/10; 3/10; 6/10[a] Moderate: 0/10; 0/10; 0/10; 1/10 **Focal olfactory epithelial thinning** Slight: 0/10; 0/10; 0/10; 2/10 Moderate: 0/10; 0/10; 0/10; 1/10 Severe: 0/10; 0/10; 0/10; 5/10[a] **Focal olfactory epithelial squamous metaplasia** Slight: 0/10; 0/10; 0/10; 4/10 Moderate: 0/10; 0/10; 0/10; 4/10 **Olfactory epithelial keratinization** Very slight: 0/10; 0/10; 0/10; 1/10 Slight: 0/10; 0/10; 0/10; 2/10 **Rhinitis**: 0/10; 2/10; 5/10[a]; 10/10[b]

Reference and study design	Results

Slight submucosal loosely arranged connective tissue	0/10	0/10	0/10	2/10
Pharyngeal duct mononuclear cell infiltrate	9/10	10/10	10/10	8/10
Nasolachrymal duct sinusitis	3/10	6/10	7/10	2/10
Maxillary sinus sinusitis	7/10	3/10	4/10	2/10

[a]$p < 0.05$; [b]$p < 0.01$

[Females] Histological changes in the nose at 13 weeks

	Incidence of lesions			
	0 mg/m^3	1.2 mg/m^3	11.9 mg/m^3	24.4 mg/m^3
Respiratory epithelial squamous metaplasia				
Diffuse				
Slight	0/10	0/10	0/10	3/10
Moderate	0/10	0/10	0/10	4/10
Severe	0/10	0/10	0/10	3/10
Focal				
Very slight	0/10	0/10	1/10	0/10
Slight	0/10	1/10	7/10[b]	0/10
Moderate	0/10	0/10	2/10	0/10
Focal respiratory epithelial hyperplasia				
Very slight	0/10	0/10	2/10	1/10
Slight	0/10	1/10	6/10[a]	6/10[a]
Moderate	0/10	0/10	0/10	0/10
Focal respiratory epithelial disarrangement				
Very slight	0/10	0/10	2/10	1/10
Slight	0/10	1/10	6/10[a]	6/10[a]
Moderate	0/10	0/10	0/10	0/10
Focal respiratory epithelial keratinization				
Very slight	0/10	0/10	6/10[a]	6/10[a]
Slight	0/10	0/10	2/10	4/10
Moderate	0/10	0/10	0/10	0/10
Focal olfactory epithelial thinning				
Slight	0/10	0/10	0/10	2/10
Moderate	0/10	0/10	0/10	2/10
Severe	0/10	0/10	0/10	2/10
Focal olfactory epithelial squamous metaplasia				
Slight	0/10	0/10	0/10	3/10
Moderate	0/10	0/10	0/10	1/10
Olfactory epithelial keratinization				
Very slight	0/10	0/10	0/10	0/10
Slight	0/10	0/10	0/10	0/10
Rhinitis	0/10	0/10	3/10	2/10
Slight submucosal loosely arranged connective tissue	0/10	0/10	0/10	4/10
Pharyngeal duct mononuclear cell infiltrate	10/10	10/10	10/10	10/10
Nasolachrymal duct sinusitis	3/10	5/10	2/10	4/10
Maxillary sinus sinusitis	1/10	1/10	5/10	0/10

[a]$p < 0.05$; [b]$p < 0.01$

Lung:

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td></td><td>Histological changes (e.g., focal accumulation of alveolar macrophages) in the lung were considered not to be exposure related but as common findings in this strain and rat age.

Larynx:
Squamous metaplasia (males)
24.4 mg/m^3—3/10, very slight; 1/10, slight; 1/10, moderate
11.9 mg/m^3—no lesions observed
1.2 mg/m^3—no lesions observed
0 mg/m^3—no lesions observed
Very slight keratinization (males)
24.4 mg/m^3—2/10
11.9 mg/m^3—no lesions observed
1.2 mg/m^3—no lesions observed
0 mg/m^3—no lesions observed
Squamous metaplasia (females)
24.4 mg/m^3—no lesions observed
11.9 mg/m^3—not examined
1.2 mg/m^3—not examined
0 mg/m^3—no lesions observed
Very slight keratinization (females)
24.4 mg/m^3—no lesions observed
11.9 mg/m^3—not examined
1.2 mg/m^3—not examined
0 mg/m^3—no lesions observed</td></tr>
<tr><td colspan="2">Medium Confidence</td></tr>
<tr><td>Andersen et al. (2010)
Fischer 344; male; 8/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for 1, 4, or 13 weeks. Rats sacrificed immediately after last exposure.
Test article: Paraformaldehyde. Actual concentrations reported in the Results column. Target concentrations were 0, 0.8, 2.5, 7.4, 12.3, or 18.5 mg/m^3.[a]
Histopathology: nasal sections at the nose tip and standard cross-section levels (I–V).

Main limitations: small N; data for levels III–V were not reported.</td><td>Target and Actual FA Concentrations
<table>
<tr><th></th><th colspan="3">Actual concentration (mg/m^3) for each exposure time</th></tr>
<tr><td>Target</td><td>1 week</td><td>4 weeks</td><td>13 weeks</td></tr>
<tr><td>0</td><td>0 ± 0</td><td>0 ± 0</td><td>0 ± 0</td></tr>
<tr><td>0.8</td><td>0.77 ± 0.06</td><td>0.8 ± 0.09</td><td>0.83 ± 0.07</td></tr>
<tr><td>2.5</td><td>2.5 ± 0.0</td><td>2.5 ± 0.0</td><td>2.5 ± 0.1</td></tr>
<tr><td>7.4</td><td>7.3 ± 0.2</td><td>7.4 ± 0.2</td><td>7.4 ± 0.2</td></tr>
<tr><td>12.3</td><td>12.2 ± 0.6</td><td>12.3 ± 0.7</td><td>12.3 ± 0.7</td></tr>
<tr><td>18.5</td><td>18.9 ± 0.1</td><td>18.5 ± 0.6</td><td>18.3 ± 0.5</td></tr>
</table>
Incidence and severity of nasal squamous metaplasia[a]
<table>
<tr><th></th><th colspan="6">FA (target concentrations)</th></tr>
<tr><th>Region</th><th>0 mg/m^3</th><th>0.8 mg/m^3</th><th>2.5 mg/m^3</th><th>7.4 mg/m^3</th><th>12.3 mg/m^3</th><th>18.5 mg/m^3</th></tr>
<tr><td>Level I</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 week</td><td>4[b] (1)[c]</td><td>5 (1)</td><td>8 (1.9)</td><td>8 (1.6)</td><td>8 (1.5)</td><td>6 (1.2)</td></tr>
<tr><td>4 weeks</td><td>1 (1)</td><td>6 (1)</td><td>7 (1)</td><td>8 (1.5)</td><td>8 (1.7)</td><td>8 (2.2)</td></tr>
<tr><td>13 weeks</td><td>1 (1)</td><td>2 (1)</td><td>8 (1.1)</td><td>8 (1.8)</td><td>8 (1.9)</td><td>8 (2.4)</td></tr>
<tr><td>Level II</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 week</td><td>0 (NA)</td><td>0 (NA)</td><td>0 (NA)</td><td>6 (1.1)</td><td>8 (1.5)</td><td>8 (1.5)</td></tr>
<tr><td>4 weeks</td><td>0 (NA)</td><td>0 (NA)</td><td>0 (NA)</td><td>5 (1)</td><td>8 (1.2)</td><td>8 (1.7)</td></tr>
<tr><td>13 weeks</td><td>0 (NA)</td><td>0 (NA)</td><td>0 (NA)</td><td>0 (NA)</td><td>8 (2.9)</td><td>8 (3.4)</td></tr>
</table>
Data NR for levels III, IV, and V.
[a]Squamous metaplasia diagnosed in areas with change in transitional or respiratory epithelium to squamous epithelium, with or without keratinization; [b]8 animals examined at each time point and dose; [c]Average severity score (1 = minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe).</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td></td><td>
Incidence of nasal necrosis/erosion
<table>
<tr><td></td><td colspan="4">FA (target concentrations)</td></tr>
<tr><td>Region</td><td>0 mg/m³</td><td>7.4 mg/m³</td><td>12.3 mg/m³</td><td>18.5 mg/m³</td></tr>
<tr><td>Level I</td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 week</td><td>0[a]</td><td>6</td><td>8</td><td>8</td></tr>
<tr><td>4 weeks</td><td>0</td><td>3</td><td>3</td><td>6</td></tr>
<tr><td>13 weeks</td><td>0</td><td>0</td><td>7</td><td>4</td></tr>
<tr><td>Level II</td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 week</td><td>0</td><td>0</td><td>7</td><td>7</td></tr>
<tr><td>4 weeks</td><td>0</td><td>0</td><td>5</td><td>8</td></tr>
<tr><td>13 weeks</td><td>0</td><td>0</td><td>0</td><td>6</td></tr>
</table>
Lesions ND at 0.8 and 2.5 mg/m³.
[a]8 animals examined at each time point and dose.
</td></tr>
<tr><td>
Wilmer et al. (1989)
Wistar rats; male; 25/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers either continuously for 8 hours/day, 5 days/week for 13 weeks or intermittently 8 hours/day (successive periods of 0.5 hour of exposure and 0.5 hour of nonexposure), 5 days/week for 13 weeks.
Test article: Paraformaldehyde.
Actual concentrations were not determined. Target concentrations were 0, 1.23, or 2.46 mg/m³ for continuous exposures and 0, 2.46, or 4.92 mg/m³ for intermittent exposures.[a]
Histopathology: 6 standard cross sections of the nose [note: same as Woutersen et al. (1989)]

Main limitations: analytical concentrations and lesion severities were not reported.
</td><td>
Histopathological changes in respiratory epithelium (cross section II) observed after 13 weeks of exposure
<table>
<tr><td></td><td colspan="5">Incidence of lesions</td></tr>
<tr><td></td><td>A</td><td>B</td><td>C</td><td>D</td><td>E</td></tr>
<tr><td></td><td>Control</td><td>1.23 mg/m³ Contin.</td><td>2.46 mg/m³ Contin.</td><td>2.46 mg/m³ Inter.</td><td>4.92 mg/m³ Inter.</td></tr>
<tr><td>Disarrangement</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>12/25</td><td>4/22</td><td>8/24</td><td>3/23[a]</td><td>8/25</td></tr>
<tr><td>Diffuse</td><td>1/25</td><td>1/22</td><td>0/24</td><td>15/23[c]</td><td>11/25[b]</td></tr>
<tr><td>Necrosis</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>4/25</td><td>3/22</td><td>0/24</td><td>2/23</td><td>3/25</td></tr>
<tr><td>Diffuse</td><td>0/25</td><td>0/22</td><td>0/24</td><td>2/23</td><td>2/25</td></tr>
<tr><td>Basal cell hyperplasia</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>9/25</td><td>4/22</td><td>6/24</td><td>11/23</td><td>10/25</td></tr>
<tr><td>Diffuse</td><td>4/25</td><td>0/22</td><td>0/24</td><td>4/23</td><td>11/25</td></tr>
<tr><td>Squamous metaplasia</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>5/25</td><td>0/22</td><td>1/24</td><td>7/23</td><td>16/25[b]</td></tr>
<tr><td>Keratinization</td><td>0/25</td><td>0/22</td><td>1/24</td><td>0/23</td><td>3/25</td></tr>
<tr><td>Nest-like infolds</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>5/25</td><td>4/22</td><td>11/24</td><td>14/23[b]</td><td>7/25</td></tr>
<tr><td>Diffuse</td><td>0/25</td><td>3/22</td><td>1/24</td><td>0/23</td><td>1/25</td></tr>
<tr><td>Goblet cell hyperplasia</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>0/25</td><td>1/22</td><td>1/24</td><td>2/23</td><td>1/25</td></tr>
<tr><td>Diffuse</td><td>5/25</td><td>2/22</td><td>8/24</td><td>13/23[a]</td><td>10/25</td></tr>
<tr><td>Rhinitis</td><td>3/25</td><td>2/22</td><td>3/24</td><td>16/23[c]</td><td>8/25</td></tr>
</table>
A = 0 mg/m³; B = 1.23 mg/m³ continuous (9.8 mg/m³ h/d); C = 2.46 mg/m³ continuous (19.7 mg/m³ h/d); D = 2.46 mg/m³ intermittent (9.8 mg/m³ h/d); E = 4.92 mg/m³ intermittent (19.7 mg/m³ h/d).
[a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.001$.
</td></tr>
<tr><td>
Zwart et al. (1988)
Wistar rats; male and female; 50/group/sex.
Exposure: Rats were exposed to FA in dynamic whole-body chambers
6 hours/day, 5 days/week for 13 weeks.
Test article: Paraformaldehyde.
Actual concentrations were 0, 0.37 (±0.02), 1.2 (±0.10), or 3.7 (±0.27) mg/m³.[a]
</td><td>
[Data only reported for cross sections II and III]
3 days:
Nose:
3.7 mg/m³—Focal basal cell hyperplasia concomitant with loss of cilia observed at section III, number of rats and sex NR.
Histological changes NR for other groups.

13 weeks:
Nose:
</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Histopathology: 6 standard cross sections of the nose [note: same as Woutersen et al. (1989)]

Main limitations: failed to completely report lesion incidence and lesion severities were not reported.</td><td>3.7 mg/m^3—Histological changes including epithelial disarrangement to epithelial hyperplasia and squamous metaplasia (with or without keratinization) found in 37/50 males and 21/50 females. Changes localized to the anterior part of section II that is normally covered by respiratory epithelium.
Histological changes NR for other exposure groups at section II.
No histological changes in respiratory epithelium observed in section III for any rat exposed to FA. Statistically significant differences in the incidences of inflammatory lesions (e.g., rhinitis, sinusitis, and aggregates of mononuclear cell infiltrates) in the pharyngeal ducts observed between control and treatment groups, although quantitative data NR and exposure-related response was absent.
3.7 mg/m^3—Electron microscopic evaluation revealed: changes in nasal septa epithelium including loss of cilia, but not slender microvilli; strongly indented and disarranged epithelial cell nuclei; the presence of small blood vessels; interdigitations between epithelial cells and the presence of cilia in intracellular spaces; foci of keratinized squamous epithelium; and glandularization of goblet cells, which were arranged in gland-like structures.
0.37 and 1.2 mg/m^3—Electron microscopic evaluation of section II showed no differences except for irregularly shaped and strongly indented nuclei when compared to controls.</td></tr>
<tr><td>Rusch et al. (1983)
Fischer 344 rats; male and female; 20/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers for 22 hours/day, 7 days/week for 26 weeks.
Test article: Unstabilized 5% solution of formaldehyde (0.03% methanol). Actual concentrations were 0.23 (±0.02), 1.2 (±0.1), or 3.6 (±0.22) mg/m^3.[a] Controls exposed to 0.011 (±0.009) mg/m^3.
Histopathology: Four sections of lung, one section of trachea, and three transverse sections of nasal turbinates (anterior, middle, and posterior regions) and one transverse section of ethmoturbinate.

Main limitations: lesion severities were NR; data only reported for one section; metaplasia and hyperplasia reported together.</td><td>Microscopic evaluation of lungs and trachea for Groups I, III, V, and VI showed lesions frequently observed in laboratory animals but not considered exposure-related. Electron microscopic evaluation for Group I and II animals (5/sex) did not reveal turbinate, tracheal, or pulmonary ultrastructure changes associated with treatment.

Observations in middle region of nasal turbinate
<table><tr><th>Group</th><th>Exposure</th><th>Squamous metaplasia and hyperplasia</th><th>Basal cell hyperplasia</th></tr><tr><td>I (control for II and III)</td><td>0 mg/m^3</td><td>2/38</td><td>0/38</td></tr><tr><td>II</td><td>0.23 mg/m^3</td><td>1/38</td><td>0/38</td></tr><tr><td>III</td><td>1.2 mg/m^3</td><td>3/36</td><td>0/36</td></tr><tr><td>V (control for VI)</td><td>0 mg/m^3</td><td>3/39</td><td>4/39</td></tr><tr><td>VI</td><td>3.6 mg/m^3</td><td>23/37</td><td>25/37</td></tr></table>For anterior nasal turbinates, no evidence of exposure-related effects with the possible exception for Group VI. When comparing to Group V, fourfold increase for the incidences of squamous metaplasia/hyperplasia and basal cell hyperplasia in Group VI; for posterior nasal turbinates, only Group VI showed evidence of squamous metaplasia (3/37); no evidence of exposure-related effects in ethmoturbinates; level of rhinitis comparable in Groups I, II, and III, but most frequent in Group VI.</td></tr>
<tr><td colspan="2">Mice</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Maronpot et al. (1986)
B6C3F1 mice; male and female; 10/sex/group.
Exposure: Mice were exposed to FA in dynamic whole-body chambers for 6 hours/day, 5 days/week for 13 weeks.</td><td>Lesions after 13 weeks of exposure:
<table><tr><th>mg/m^3:</th><th colspan="2">0</th><th colspan="2">5.02</th><th colspan="2">12.4</th><th colspan="2">25.1</th><th colspan="2">49.6</th></tr><tr><th>Nasal cavity</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr><tr><td>Metaplasia, squamous</td><td>0/10</td><td>0/10</td><td>1/10</td><td>0/10</td><td>10/10</td><td>10/10</td><td>10/10</td><td>10/10</td><td>10/10</td><td>10/10</td></tr></table></td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>*Test article*: Formalin (9.2% w/v), assumed to contain methanol.
Actual concentrations were 2.41 (±0.25), 5.02 (±0.62), 12.4 (±0.80), 25.1 (±1.1), or 49.6 (±3.2) mg/m^3.
Histopathology: sections of the nasal turbinates (3 sections), larynx, trachea, and lung.

Main limitations: formalin; small *N*</td><td>
<table>
<tr><td>Inflammation, seropurulent</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td><td>4/10</td><td>0/10</td><td>10/10</td><td>8/10</td><td>10/10</td><td>10/10</td></tr>
</table>
No lesions observed after exposure to 2.41 mg/m^3.
<table>
<tr><th>mg/m^3:</th><th colspan="2">0</th><th colspan="2">25.1</th><th colspan="2">49.6</th></tr>
<tr><th></th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td colspan="7">Larynx</td></tr>
<tr><td>Metaplasia, squamous</td><td>0/8</td><td>0/8</td><td>6/9</td><td>3/9</td><td>10/10</td><td>7/8</td></tr>
<tr><td colspan="7">Trachea</td></tr>
<tr><td>Metaplasia, squamous</td><td>0/10</td><td>0/9</td><td>3/10</td><td>5/10</td><td>10/10</td><td>10/10</td></tr>
<tr><td>Hyperplasia, epithelial</td><td>0/10</td><td>0/9</td><td>4/10</td><td>2/10</td><td>2/10</td><td>0/10</td></tr>
<tr><td>Inflammation, purulent</td><td>0/10</td><td>0/9</td><td>0/10</td><td>0/10</td><td>8/10</td><td>5/10</td></tr>
<tr><td>Fibrosis, submucosal</td><td>0/10</td><td>0/9</td><td>0/10</td><td>0/10</td><td>9/10</td><td>5/10</td></tr>
<tr><td colspan="7">Lung</td></tr>
<tr><td>Bronchus, metaplasia squamous</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td><td>4/10</td><td>3/10</td></tr>
<tr><td>Bronchus, inflammation</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td><td>3/10</td><td>2/10</td></tr>
<tr><td>Bronchus, fibrosis, submucosal</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td><td>2/10</td><td>0/10</td></tr>
</table>
No laryngeal lesions observed after 2.41, 5.02, or 12.4 mg/m^3; no tracheal lesions observed after 2.41, 5.02, or 12.4 mg/m^3, except 1/10 females (squamous metaplasia) after 12.4 mg/m^3; no lung lesions after 12.4 mg/m^3; data were NR for 2.41 and 5.02 mg/m^3.
</td></tr>
<tr><td colspan="2">Hamsters</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Rusch et al. (1983)
Syrian golden hamsters; male and female; 10/sex/group.
Exposure: Hamsters were exposed to FA in dynamic whole-body chambers for 22 hours/day, 7 days/week for 26 weeks.
Test article: Unstabilized 5% solution of formaldehyde (0.03% methanol).
Actual concentrations were 0.23 (±0.02), 1.2 (±0.1), or 3.6 (±0.22) mg/m^3.[a] Controls were exposed to 0.011 (±0.009) mg/m^3.
Histopathology: 4 sections of lung, 1 section of trachea, and the hamster equivalent of the rat turbinate sections (i.e., 3 transverse sections of nasal turbinates [anterior, middle, and posterior regions] and one transverse section of ethmoturbinate).

Main limitations: lesion incidences NR (note: only metaplasia was investigated).</td><td>Microscopic evaluation of lungs and trachea for Groups I (controls for Groups II and III), III (1.2 mg/m^3), V (controls for Group VI), and VI (3.6 mg/m^3) showed lesions frequently observed in laboratory animals but not considered exposure related. Histopathological data for Group II (0.23 mg/m^3) not reported.

No evidence of exposure-related effects for the incidence of squamous metaplasia even at 3.6 mg/m^3 exposure level.</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Monkeys</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Rusch et al. (1983)
Cynomolgus monkeys; male; 6/group.
Exposure: Monkeys were exposed to FA in dynamic whole-body chambers for 22 hours/day, 7 days/week for 26 weeks.
Test article: Unstabilized 5% solution of formaldehyde (0.03% methanol).
Actual concentrations were 0.23 (±0.02), 1.2 (±0.1), or 3.6 (±0.22) mg/m^3. Controls exposed to 0.011 (±0.009) mg/m^3.[a]
Histopathology: 4 sections of lung, 1 section of trachea, and the monkey equivalent of the rat turbinate sections (i.e., 3 transverse sections of nasal turbinates [anterior, middle, and posterior regions] and one transverse section of ethmoturbinate).

Main limitations: lesion severities NR; incidence of squamous metaplasia and hyperplasia reported together; data reported for only one nasal section.</td><td>Microscopic evaluation of lungs and trachea for Groups I (controls for Groups II and III), III (1.2 mg/m^3), V (controls for Group VI), and VI (3.6 mg/m^3) showed lesions frequently observed in laboratory animals but not considered exposure related. Histopathological data for Group II (0.23 mg/m^3) not reported.

Observations in middle region of nasal turbinate
<table><tr><th>Group</th><th>Exposure</th><th>Squamous metaplasia and hyperplasia</th></tr><tr><td>I (control for II and III)</td><td>0 mg/m^3</td><td>0/6</td></tr><tr><td>II</td><td>0.23 mg/m^3</td><td>0/6</td></tr><tr><td>III</td><td>1.2 mg/m^3</td><td>1/6</td></tr><tr><td>V (control for VI)</td><td>0 mg/m^3</td><td>0/6</td></tr><tr><td>VI</td><td>3.6 mg/m^3</td><td>6/6</td></tr></table>For anterior and posterior nasal turbinates, no exposure-related effects reported.
Rhinitis observed in numerous animals from all Groups but with no apparent exposure-response.
For Group VI, observations of hoarseness, congestion, and nasal discharge were reported.</td></tr>
</table>

Organized by species, then confidence, then descending publication year. As discussed above, results from *low* confidence studies are not included given the many *high* and *medium* confidence studies (see Appendix B.3.5).

Abbreviations: FA = formaldehyde; NR = not reported, SD = standard deviation.

[a]Study authors originally reported FA concentrations in ppm. These values were converted based on 1 ppm = 1.23 mg/m^3, assuming 25°C and 760 mm Hg.

Table 3-28. Selected short-term respiratory pathology studies in animals (see Appendix C.6.1 for others)

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Rats</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Kuper et al. (2011)
Fischer rats; males; 8/group.
Exposure: Mice were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 day/week for 4 weeks.
Test article: Formalin (10.21% FA; although NR, the description supports the assumption that it was freshly prepared). Actual concentrations were 0, 0.63 (±0.06), 1.23 (±0.14), 2.48 (±0.18), 7.53 (±0.42), 12.3 (±0.48), and 18.4 (±0.06) mg/m^3.[a]
Histopathology: 2 sections of nasopharynx-associated lymphoid tissues (NALT) and one section of an upper respiratory tract-draining lymph node (i.e., posterior, and superficial cervical lymph nodes).

Main limitations: small N; unclear test article</td><td>
Incidence of lesions/changes after 4 weeks
<table>
<tr><td></td><td colspan="7">FA (mg/m^3)</td></tr>
<tr><td>NALT</td><td>0</td><td>0.63</td><td>1.23</td><td>2.48</td><td>7.53</td><td>12.3</td><td>18.4</td></tr>
<tr><td>Size</td></tr>
<tr><td>Very small</td><td>1</td><td>0</td><td>0</td><td>1</td><td>0</td><td>2</td><td>1</td></tr>
<tr><td>Small</td><td>2</td><td>1</td><td>2</td><td>2</td><td>3</td><td>3</td><td>6</td></tr>
<tr><td>Medium</td><td>2</td><td>7</td><td>5</td><td>5</td><td>5</td><td>3</td><td>1</td></tr>
<tr><td>Large</td><td>3</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Decreased cellularity</td></tr>
<tr><td>Slight</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Moderate</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>Germinal center development</td></tr>
<tr><td>Very slight</td><td>1</td><td>5</td><td>3</td><td>3</td><td>3</td><td>3</td><td>0</td></tr>
<tr><td>Moderate</td><td>3</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Score expanded total</td><td>4</td><td>5</td><td>3</td><td>3</td><td>3</td><td>3</td><td>0</td></tr>
<tr><td>Epithelial hyperplasia</td></tr>
<tr><td>Slight</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>Moderate</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>5</td></tr>
<tr><td>Score expanded total</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>7[a]</td></tr>
</table>
[a]$p < 0.01$.

Incidence of lesions/changes after 4 weeks
<table>
<tr><td></td><td colspan="7">FA (mg/m^3)</td></tr>
<tr><td></td><td>0</td><td>0.63</td><td>1.23</td><td>2.48</td><td>7.53</td><td>12.3</td><td>18.4</td></tr>
<tr><td>Posterior cervical lymph nodes</td></tr>
<tr><td>Germinal center development</td></tr>
<tr><td>Very slight</td><td>3</td><td>3</td><td>2</td><td>4</td><td>4</td><td>5</td><td>5</td></tr>
<tr><td>Slight</td><td>0</td><td>1</td><td>2</td><td>1</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>Moderate</td><td>1</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Marked</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Very marked</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>Score expanded totals</td><td>5</td><td>5</td><td>5</td><td>5</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>Superficial cervical lymph nodes</td></tr>
<tr><td>Germinal center development</td></tr>
<tr><td>Very slight</td><td>5</td><td>3</td><td>2</td><td>0</td><td>3</td><td>1</td><td>0</td></tr>
<tr><td>Very marked</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Score expanded totals</td><td>5</td><td>3</td><td>3</td><td>0[a]</td><td>3</td><td>1</td><td>0[a]</td></tr>
</table>
[a]$p < 0.05$.
</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Wilmer et al. (1987)
Wistar rats; male; 10/group.
Exposure: Rats were exposed to FA in a dynamic whole-body chamber either continuously for 8 hours/day, 5 days/week for 4 weeks or intermittently 8 hours/day (successive periods of 0.5 hour of exposure and 0.5 hour of nonexposure), 5 days/week for 4 weeks.
Test article: Paraformaldehyde.
Actual concentrations were not determined. Target concentrations were 0, 6.2, or 12.3 mg/m^3 for continuous exposures and 0, 12.3, or 24.6 mg/m^3 for intermittent exposures.[1]
Histopathology: 6 standard nasal cross sections.

Main limitations: analytical concentrations NR; lesion incidence and severities NR</td><td>Respiratory epithelium:
Focal thinning and disarrangement of mainly the lateral wall observed in all animals exposed to 24.6 mg/m^3.
Squamous metaplasia and basal cell hyperplasia observed mainly in 12.3 and 24.6 mg/m^3.
Rhinitis (minimal to moderate) observed in all groups.

Severity of nasal lesions<table><tr><td>intermittent exposure to 24.6 mg/m^3 (98.4 mg/m^3-h/day)</td><td>></td><td>continuous exposure to 12.3 mg/m^3 (98.4 mg/m^3-h/day)</td></tr><tr><td>intermittent exposure to 12.3 mg/m^3 (49.2 mg/m^3-h/day)</td><td>></td><td>continuous exposure to 6.2 mg/m^3 (49.6 mg/m^3-h/day)</td></tr><tr><td>intermittent exposure to 12.3 mg/m^3 (49.2 mg/m^3-h/day)</td><td>=</td><td>continuous exposure to 12.3 mg/m^3 (98.4 mg/m^3-h/day)</td></tr></table></td></tr>
<tr><td colspan="2">Mice</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Morgan et al. (2017)
C3B6.129F1-Trp53^{tm1Brd} (C3B6 TP53±) and B6.129-Trp53^{tm1Brd} (B6 TP53±) mice; males; 24-35/group
Exposure: Mice were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 day/week for 8 weeks.
Test article: Paraformaldehyde
Nominal concentrations were 0, 9.23, or 18.45 mg/m^3.[a]
Histopathology: 3 sections of the nasal cavity and one section of the larynx

Main limitations: somewhat limited sampling and minor reporting limitations; potentially short duration (however, lesions are observed)</td><td>Incidence (and severity) of noncancer nasal lesions at 32 weeks post-exposure<table><tr><td></td><td>FA (mg/m^3)</td><td></td><td></td></tr><tr><td></td><td>0</td><td>9.23</td><td>18.45</td></tr><tr><td colspan="4">C3B6 TP53± mice</td></tr><tr><td>Squamous Metaplasia (respiratory epithelium)</td><td>0/21</td><td>14/21 (1.2)</td><td>22/23 (1.5)</td></tr><tr><td>Hyperplasia (respiratory epithelium)</td><td>0/21</td><td>0/21</td><td>1/23 (1.0)</td></tr><tr><td>Osteogenesis (turbinate)</td><td>0/21</td><td>0/21</td><td>3/23 (3.0)</td></tr><tr><td colspan="4">B6 TP53± mice</td></tr><tr><td>Squamous Metaplasia (respiratory epithelium)</td><td>0/22</td><td>13/27 (1.0)</td><td>17/26 (1.5)</td></tr><tr><td>Osteogenesis (turbinate)</td><td>0/22</td><td>1/27 (1.0)</td><td>1/26 (1.0)</td></tr></table>Average severity score based on 1= minimal; 2= mild; 3= moderate; 4= marked
No laryngeal lesions were reported</td></tr>
<tr><td>Kuper et al. (2011)
B6C3F1 mice; females; 6/group.
Exposure: Mice were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 day/week for 4 weeks.
Test article: Formalin (10.21% FA; although NR, the description supports the assumption that it was freshly prepared).</td><td><table><tr><td>Group</td><td>Observation</td></tr><tr><td>Controls</td><td>NALT: varied in size from small to large; scarce germinal centers</td></tr><tr><td>Exposed</td><td>Posterior and cervical lymph nodes: no FA-related changes

NALT: no FA-related changes; no significant change in size compared to controls; scarce germinal centers</td></tr></table></td></tr>
</table>

Reference and study design	Results	
Actual concentrations were 0, 0.63 (±0.06), 1.23 (±0.14), 2.48 (±0.18), 7.53 (±0.42), 12.3 (±0.48), and 18.4 (±0.06) mg/m^3.[a] *Histopathology:* 2 sections of nasopharynx-associated lymphoid tissues (NALT) and one section of an upper respiratory tract-draining lymph node (i.e., posterior and superficial cervical lymph nodes). **Main limitations**: small N; unclear test article		
Monkeys		
Medium confidence		
Monticello et al. (1989) Rhesus monkeys; males; 3/group. *Exposure:* Monkeys were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for 1 or 6 weeks. *Test article:* Paraformaldehyde. Actual concentrations were not determined. Target concentration was 0 or 7.4 mg/m^3.[a] *Histopathology*: 5 transverse sections of the nasal passages (A-E) extending from the nares to the soft palate. The evaluation also included cross sections of larynx and mid-trachea, a frontal section of the carina, and sections of all lung lobes, which were trimmed mid-sagitally to include airway bifurcations. **Main limitations:** analytical concentrations NR; lesion incidence and severities NR	Exposure	Observations (truncated from original article)
	Control	Nasal passages Four types of epithelium lining rhesus nasal passages were identified: (1) stratified squamous in the vestibule (Level A); (2) transitional (Level A), present in narrow zone just posterior to vestibule; (3) olfactory in mid-dorsal region (Levels B−D); and (4) respiratory, the most extensive (Levels B−E) and present throughout remaining areas. Extranasal respiratory tract Typical pseudostratified columnar respiratory epithelium observed for the larynx, trachea, and major bronchi; mild inflammatory changes from pulmonary acariasis in one monkey
	7.4 mg/m^3 1-week	Nasal passages Characteristic changes in respiratory epithelium described as generally being bilaterally symmetrical and consistent in nature and severity for all three monkeys in group Changes included loss of goblet cells and cilia, minimal-to-mild epithelial hyperplasia with or without early stages of squamous metaplasia, and an accompanying neutrophilic inflammatory response Squamous metaplasia present in various stages; metaplastic epithelium eroded (mild) in some areas;

Reference and study design	Results	
		neutrophils occasionally found in metaplastic epithelium; maxillary sinuses exhibited no treatment-related lesions Extranasal respiratory tract Lesions of larynx, trachea, and carina were considered mild and included multifocal loss of cilia; extent of lesions covering surface area of larynx/trachea of 1-week group (3.0 ± 1.3%) was minimal compare to 6-week group (26.0 ± 10.0%); no treatment-related lesions in lungs
	7.4 mg/m^3 6-week	Erosions absent; mild squamous metaplasia (more developed than in 1-week group); maxillary sinuses exhibited no treatment-related lesions; in two monkeys, olfactory epithelium exhibited small discrete areas of mild squamous metaplasia close to olfactory/respiratory epithelial interface Extranasal respiratory tract Lesions included multifocal areas of respiratory mucosa with loss of cilia and goblet cells, mild epithelial hyperplasia, and early squamous metaplasia with occasional squamous cell formation on the surface; no treatment-related lesions in lungs
	Exposure	Morphometric analysis of monkey nasal passages
	7.4 mg/m^3 1-week	Anterio-posterior severity gradient for percentage of surface area with treatment-related lesions
	7.4 mg/m^3 6-week	Of all nasal passage regions, middle turbinate had greatest percentage of surface area affected Greater respiratory epithelium surface area with treatment-related lesions compared with 1-week group ($p \leq 0.05$) More extensive lesions in the posterior nasal passages (Levels D−E) and larynx/trachea compared with same locations in 1-week group ($p \leq 0.05$)
	7.4 mg/m^3 1- and 6-week	Anterior regions (Levels B−C) had highest percentage of nasal mucosal surface area with treatment-related lesions

Organized by species, then confidence, then descending publication year. As discussed above, results from *low* confidence studies are not included given the many *high* and *medium* confidence studies (see Appendix B.3.5).

Abbreviations: FA = formaldehyde, NA = not applicable, ND = not detected, NR = not reported, SD = standard deviation, SE = standard error of the mean.

[a]Study authors originally reported FA concentrations in ppm. These values were converted based on 1 ppm = 1.23 mg/m^3, assuming 25°C and 760 mm Hg.

Summary of Animal Evidence Synthesis Judgments

The available animal studies on respiratory tract pathology provide *robust* evidence of formaldehyde exposure-induced effects. The evidence is clear and convincing across multiple factors, as summarized for the most influential factors below.

- *Consistency and Study Confidence*: Across numerous *high* and *medium* confidence studies formaldehyde exposure resulted in squamous metaplasia and hyperplasia in the respiratory epithelium. This effect was observed across animal species, from rodents to monkeys.
- *Strength and Precision:* Severe lesions were observed at higher formaldehyde concentrations, including observations of overt nasal tissue damage.
- *Dose-Response*: Multiple studies demonstrated a clear progression in lesion incidence, severity and anatomical location (moving deeper into the respiratory tract) with increasing formaldehyde exposure.
- *Coherence:* Multiple mechanistically related lesion types were observed following exposure.
- *Biological Plausibility*: Strong mechanistic evidence supports a progression of cellular and tissue-level changes that can lead to the development of the observed lesions.

In addition to the judgment above, several general inferences can be drawn based on the animal studies. Specifically, the animal data suggest that lesion development appears to be driven more by concentration than duration, particularly for the respiratory lesion of hyperplasia, and males may be more sensitive than females. In addition, studies of intentional damage to the nasal epithelium indicate that pre-existing nasal injury is likely to be a condition that would make individuals more susceptible to formaldehyde exposure-induced respiratory tract pathology.

Evidence on Mode of Action

Based primarily on studies in experimental animals or acutely exposed human volunteers (most of these endpoints are difficult to examine in long-term observational epidemiology studies), induction of histopathological lesions in the respiratory tract following formaldehyde exposure appears to result, at least in part, from a series of increasingly severe effects, including altered mucociliary function, damage to the nasal epithelium (e.g., sustained cytotoxicity), and sustained reparative cell proliferation culminating in a hyperplastic epithelium, or transitioning to an adaptive, metaplastic tissue (see Figure 3-17; see Appendix C.7 for additional details). Consistent with observations of metaplasia without hyperplasia in many of the rodent health effect studies, this pathway illustrates that metaplasia may develop following damage to the epithelium in the absence of hyperplasia (i.e., hyperplasia may not be an essential precursor). All the mechanistic events and relationships between events in the proposed pathway are based on robust or moderate evidence, indicating that this is likely a mechanism by which formaldehyde exposure causes squamous metaplasia. However, because modification of epithelial cell health and function in the URT can occur via multiple direct and indirect mechanisms following formaldehyde inhalation, which are expected to vary due to differences in both exposure duration and intensity, there are

likely to be other plausible mechanisms by which formaldehyde exposure could cause this health effect. The current understanding provides strong biological support for an association between formaldehyde exposure and respiratory tract pathology. Additionally, as many of the mechanistic events in this pathway have been observed in both humans (sometimes indirectly) and experimental animals, including effects on mucociliary function and cell proliferation, as well as evidence of elevated oxidative stress, findings from experimental animals are considered relevant to humans.

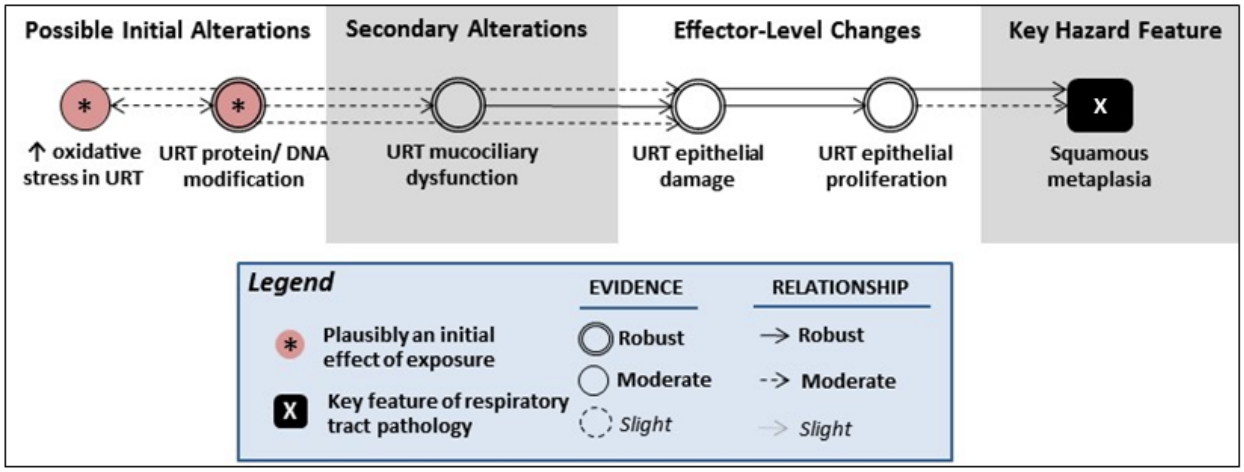


Figure 3-17. Possible mechanistic associations between formaldehyde exposure and respiratory tract pathology.

An evaluation of the formaldehyde exposure-specific mechanistic evidence informing the potential for formaldehyde exposure to cause respiratory health effects (see Table 3-29 and Appendix C.7) identified this sequence of mechanistic events as likely to be a mechanism by which formaldehyde inhalation could cause respiratory tract pathology, specifically squamous metaplasia, although it is assumed that other plausible pathways explaining this association have yet to be defined.

Some uncertainties remain regarding this pathway. Effects on the mucociliary system are likely secondary to the production of reactive byproducts in the URT or covalent modification to mucosal structural components following physical interactions of formaldehyde with proteins in the mucus, the latter of which at least would be expected to be driven largely by concentration. The nasal mucociliary apparatus cleans the airways by moving contaminant-laden mucus out of the URT. When damage to the cilia slows or disrupts the movement of the mucus, formaldehyde or other reactive molecules dissolved into the mucus may accumulate to a concentration that may be overtly toxic to the cells beneath the mucus. Thus, alterations to this normally protective apparatus could allow for greater access of inhaled formaldehyde (and other inhaled chemical and nonchemical substances) to epithelium lining the nasal passages (Harkema et al., 2006). Conversely, gradual tissue changes following exposure might also lead to resilience (e.g., increases in epithelial cell barrier function). Unfortunately, animal studies of mucociliary function and other detailed mechanistic studies characterizing the initial molecular interactions of formaldehyde in the

URT following long-term exposure are unavailable. However, given the formaldehyde removal and metabolism processes in the nasal respiratory epithelium (see Appendix C.1), it would generally be expected that low levels of formaldehyde would be rapidly detoxified in healthy tissues, noting that changes in mucus flow patterns have been observed at lower formaldehyde levels than those eliciting URT epithelial lesions (i.e., at ≤0.3 mg/m^3 in exposed humans and >0.6mg/m^3 in animals).

Relatedly, while both hyperplasia and metaplasia, which generally represent attempts to protect the nasal epithelium from further insult, are often correlated with areas of cell proliferation (see Appendix C.7), similar evaluations were not identified for lesions such as necrosis. Although cell proliferation can occur in response to tissue damage, the concentrations at which cytotoxicity and tissue damage begin to occur are poorly defined compared to other respiratory tract lesions (i.e., hyperplasia; metaplasia), partly due to differences in methodology and reporting across studies. This complicates the interpretation of the potential progression (at least in terms of concentration) of these URT changes. Regardless, since increases in cell proliferation are largely adaptive responses to replace damaged and dying cells within the epithelial tissue layer, and proliferation is typically not observed below 1.23 mg/m^3 (note: while proliferation is clearly increased above ~3.7 mg/m^3, results across studies are mixed between 1.23 and 3.7 mg/m^3; see Appendix C.7.1), cellular damage-induced proliferation at similar levels is assumed to represent an important mechanistic component for the development of URT pathology.

Interestingly, cellular proliferation "rates" (i.e., the available studies labeled dividing cells only during the last few days of exposures that varied in duration) did not appear to be strongly influenced by exposure duration (see Appendix C.7.1). Although differences exist, the general pattern of proliferation was similar across sets of studies exposing rats for either ≤1 week, 1–6 weeks, or ≥12 weeks. This similarity adds further support that cellular damage or pathology resulting in cell proliferation (i.e., hyperplasia) may not be highly dependent on exposure duration; it remains unclear whether the cumulative proliferative potential (i.e., proliferative events across the entire duration of exposure) might vary more strongly as a function of exposure duration, or to what extent this association might hold for lesions that may not be as dependent on proliferation (e.g., metaplasia). The broader implications of this relationship are discussed elsewhere (see Sections 3.2.5 and 5.2.1).

In addition, there are potential modifying factors that are not illustrated in Figure 3-17. One significant uncertainty relates to the potential for inflammatory and immunological changes in the upper airways (see Sections 3.2.2 and 3.2.3), which generally have been observed only after longer formaldehyde exposures, to modify the pattern or progression of mechanistic changes leading to the development of respiratory tract pathology. This understanding is further complicated because the available data are limited both in terms of understanding the specific initiating events leading to upper airway inflammatory changes, as well as their ability to clearly define the concentration and duration requirements for effects on URT immunological processes. As with the other examined health effects, uncertainties also exist regarding interindividual sensitivity to these effects, with

respiratory health status and sensitivity to allergens expected to be strong modifiers of these effects. Nasal lesions are far more severe in rodents with prior nasal damage (e.g., (Woutersen et al., 1989; Appelman et al., 1988)), and similar observations have been made in exposed humans (Falk et al., 1994), while changes in mucus flow and related nasal features in allergic individuals would be expected to modify the more direct effects of formaldehyde on the mucociliary apparatus. Genetics may also play a role. For example, possibly complementing the hypothesized role of p53 in nasal genotoxicity (see Appendix C.3), two strains of p53 deficient mice (*Trp53* heterozygotes) exhibited pronounced metaplasia after short-term (8-week) exposure (Morgan et al., 2017); however, this study did not include metaplasia rates in wild-type mice for comparison[23] and there are no corresponding rat models, which would be presumed to be even more sensitive.

Overall, although uncertainties remain, the mechanistic evidence supports the conclusion that metaplasia and hyperplasia are likely to result, at least in part, from direct or indirect (e.g., through disruption of normal mucociliary function) effects on epithelial cell health, which often appears to involve sustained cellular proliferation, particularly for hyperplasia.

Table 3-29. Mechanistic evidence most informative to the development of respiratory tract pathology after formaldehyde inhalation

Endpoint		Study-specific findings and confidence	Summary of evidence	Conclusion
The majority of these mechanistic changes have been discussed in previous sections. *See Table 1-3 for presentation of the evidence for:* ↑ **URT oxidative stress** (moderate) *See Table 1-10 for presentation of the evidence for:* **URT protein/DNA modification** (robust); **URT mucociliary dysfunction** (robust); and **URT epithelial damage** (robust)				
↑ **URT Cellular (epithelial) Proliferation** (see Appendix C.7 for additional detail and discussion)	*High or Medium*	*Human*: None (note: indirect data from human studies indicating an increase in histopathological scores that included hyperplasia were not specific enough to independently evaluate proliferation). *Animal*: Acute dose-dependent increases in cell proliferation in rats, measured primarily by DNA labeling during the final days of exposure, were consistently observed following acute, short-term, and subchronic exposure, and generally with a similar magnitude of responses across durations. Proliferation was typically highest in anterior regions (e.g., "level 2"), with little evidence of proliferation at ≤1.23 mg/m^3, mixed findings between 1.24 and 3.5 mg/m^3, and studies generally reporting increases with exposure at higher levels, particularly with longer exposure duration. These data are supported by consistent observations of formaldehyde exposure-induced increases in hyperplasia in pathology studies, some of which provided	Increased cell proliferation in rats at all tested durations. Proliferation increases were typically observed in the anterior nasal cavity at tested levels ≥~3.5–4 mg/m^3, and were generally not observed at ≤1.23 mg/m^3. Sites of proliferation correlated with the development of hyperplasia and metaplasia, although the temporal and	Robust

[23]Lesion frequency or severity in the study by NTP (2017) was not noticably different from the other available studies of wild-type mice similarly exposed to >9 mg/m^3 (i.e., 12.4 and 17.6 mg/m^3) for subchronic [e.g., (Maronpot et al., 1986)] or chronic [e.g., (Kerns et al., 1983)] duration.

Endpoint		Study-specific findings and confidence	Summary of evidence	Conclusion
		information showing a correlation between acute proliferation and hyperplasia and metaplasia. The only rat study that measured exposure longer than 13 weeks suggests that increases in acute proliferation may begin to decrease in magnitude with chronic exposure at ≥6 mg/m^3 (Monticello et al., 1996). A few studies suggest that mice may exhibit less robust responses than rats, while monkeys may exhibit proliferation in more posterior nasal regions at >7 mg/m^3.	exposure levels specifics of this association are unclear. Indirect data from observations of hyperplasia in exposed animals and humans are consistent with these data.	
	Low	N/A: Sufficient information for 'robust' from *high or medium* confidence studies.		

Summary of Inferences Regarding Mode of Action

Robust or moderate evidence for mechanistic events based predominantly on experimental animal studies supports a biological progression of changes that appears to include mucociliary dysfunction, epithelial damage, and often cellular proliferation, leading to the eventual development of nasal lesions, including squamous metaplasia. Thus, although it may be incomplete, a MOA involving effects on mucociliary function and epithelial cell health is well supported and considered to be a major contributor to these effects.

Evidence Integration Summary

The literature on formaldehyde effects on respiratory tract pathology in animals provides *robust* evidence that inhaled formaldehyde exposure can induce histopathologic lesions in the URT of animals, primarily in the nasal cavity, in a manner dependent on both the concentration and, to a lesser extent (particularly for hyperplasia), duration of exposure. Based on numerous *high* and *medium* confidence studies of chronic and subchronic exposure duration, formaldehyde exposure resulted in lesions in the respiratory epithelium, including goblet and basal epithelial cell hyperplasia, necrosis, and squamous metaplasia (see Tables 3-26 and 3-27). These lesions have been observed across experimental animal species, including monkeys, mice, and hamsters, but primarily in rats. In general, rats appear to be more sensitive than mice or hamsters, while the limited data in monkeys suggest a similar sensitivity to rats with possible differences in lesion location. While these lesions consistently develop in rodents of both sexes, several studies suggest an increased susceptibility of males as compared to females, potentially due to differences in breathing patterns. Presumably due to the high reactivity and water solubility of formaldehyde, these pathological lesions have been primarily assessed (and subsequently observed) in the epithelium lining the anterior regions of the rodent nasal passages following formaldehyde inhalation exposure, mostly in regions containing respiratory epithelium. Generally, at higher concentrations or longer durations, similar effects are seen in more posterior sections of the nasal cavity (and sometimes beyond), as well as in the olfactory epithelium. Additionally, lesions progress

in severity (e.g., slight to moderate) at specific anatomical locations (e.g., cross-section level) with increasing concentration or duration of exposure, indicating cumulative effects. While several studies support that an increased incidence of nasal lesions such as hyperplasia and metaplasia persists after cessation of exposure, partial regression (e.g., a reduced severity or smaller increase in incidence) of these lesions appears to occur, at least in mice and rats.

Although the evidence is more equivocal in one study (Boysen et al., 1990), the four human epidemiology studies examining histopathology found that participants exposed to average formaldehyde levels between 0.05 and 0.6 mg/m^3 had a higher average histopathology score than their respective comparison group (Holmstrom et al., 1989c; Edling et al., 1988; Ballarin et al., 1992). Although the studies were limited by probable survival bias, and in some cases other limitations that resulted in a bias toward the null, a consistent association with histopathological endpoints, including squamous metaplasia, was observed. Therefore, the observational human data provide *moderate* evidence that inhaled formaldehyde induces histopathological lesions in the URT.

Mechanistic insights based on a large amount of animal data (some similar effects were observed in humans, although the data were sparse) indicate a likely role for altered mucociliary function or cellular proliferation in the occurrence of these exposure-induced lesions (see Appendix C.7). Overall, the strength of the evidence for hyperplasia and squamous metaplasia includes *robust* evidence from animal studies and *moderate* human evidence from observational epidemiology studies, and strong support for a plausible MOA based largely on mechanistic evidence in animals (supported by more limited, coherent findings in human mechanistic studies), Therefore, the **evidence demonstrates** that inhalation of formaldehyde causes respiratory tract pathology in humans given the sufficient exposure conditions. The primary basis for this conclusion is rat bioassays of chronic exposure that consistently observed squamous metaplasia at formaldehyde exposure levels ≥2.5 mg/m^3.

Table 3-30. Evidence integration summary for effects of formaldehyde inhalation on respiratory pathology

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Respiratory Pathology					
Human	*Consistency and Study Confidence*	• Three of the four *medium* confidence occupational studies observed a higher prevalence of abnormal nasal histopathology, including loss of ciliated cells, hyperplasia, and squamous metaplasia at concentrations ranging from 0.1–2 mg/m^3; the remaining (1) study had more equivocal findings.		*Moderate* Based on consistent observations of abnormal histopathology, including squamous metaplasia in exposed workers.	The **evidence demonstrates** that inhalation of formaldehyde causes respiratory tract pathology in humans, given sufficient exposure conditions[a] This judgment is primarily based on rat bioassays of chronic exposure which consistently observed squamous metaplasia at formaldehyde exposure levels ≥2.5 mg/m^3. *Potential Susceptibilities:* Variation in sensitivity may depend on differences in URT immunity, allergen sensitivity, and nasal structure or past injury (e.g., studies support increased sensitivity of rodents with intentionally damaged nasal cavities), and males may be more sensitive than females.
	Strength and Precision	N/A			
	Dose-Response	N/A			
	Coherence	N/A			
	Biological Plausibility	• Mechanistic changes in one *medium* confidence and one *low* confidence study in humans provides evidence of changes in mucociliary clearance and mucus flow beginning at formaldehyde concentrations of 0.25−0.3 mg/m^3. This provides some minimal additional support for biological plausibility.			
Animal	*Consistency and Study Confidence*	• Consistent evidence of squamous metaplasia and hyperplasia in the nasal respiratory epithelium across		*Robust* Based on consistent, dose-dependent, and	

		numerous independent *high* and *medium confidence* studies. • Consistent evidence of both metaplasia and hyperplasia in monkeys, rats, mice, and hamsters; the data were more limited for monkeys, while mice and hamsters exhibited less sensitivity.		coherent evidence of pathological changes in numerous studies across multiple species, with strong support for biological plausibility. Generally, the most sensitive effects were metaplasia observed after chronic exposure to ≥2.5 mg/m^3 formaldehyde.	
	Strength and Precision	• At higher concentrations, lesions were more severe, including some with evidence of overt nasal tissue damage.			
	Dose-Response	• Multiple studies provided clear evidence of a concentration dependence for lesion development, as demonstrated by increases in the incidence, severity, and anatomical location of the observed lesions with increasing exposure.			
	Coherence	• Multiple mechanistically related lesion types were consistently observed.			
	Biological Plausibility	• Robust or moderate evidence for mechanistic events based predominantly on experimental animal studies supports a biological progression of changes that appears to include mucociliary dysfunction, epithelial damage, and often cellular proliferation, leading			

		to the eventual development of nasal lesions, including squamous metaplasia.			
Other inferences	• *Relevance to humans*: Similarities in the function and properties of the nasal epithelium across species, as well as similar mechanistic and apical effects observed in both humans and animals, provide strong support for the relevance of the findings in animals to humans. • *MOA*: Although it may be incomplete, a MOA involving effects on mucociliary function and epithelial cell health is well supported and considered to be a major contributor to these effects. • *Other*: Data from animal studies suggest that lesion development may be driven more by concentration than duration, particularly for hyperplasia. While estimates for formaldehyde were not identified, estimates for other irritants indicate that concentration is ~1.8- to 1.9-fold (on average) more influential than duration regarding exposure-induced mortality after acute exposure.				

N/A = indicates the factor was not applicable to (i.e., did not influence) the judgment drawn.
[a]The "sufficient exposure conditions" are more fully evaluated and defined through dose-response analysis in Section 5.1.

3.2.5. Respiratory Tract Cancers

This section examines the evidence pertaining to the carcinogenic effect of formaldehyde exposure on the upper respiratory tract (URT) of humans and animals. The specific endpoints considered in this section include diagnoses of nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx and hypopharynx, and laryngeal cancer in exposed humans; experimental animal studies examining the potential for cancers of the nasal cavity and proximal regions of the URT (note: the results of several studies that also included examinations of more distal regions of the respiratory tract are discussed); and mechanistic studies relevant to interpreting potential carcinogenic effects on the URT. In humans, URT cancers were reviewed independently of one another based on primary data from case-control and cohort studies (the approximate structural delineations referred to in the section on human evidence are shown below in Figure 3-18).

Epidemiological findings provide *robust* evidence for nasopharyngeal cancers (NPCs), and sinonasal cancer, based on groups with occupational exposure. Epidemiological evidence is *slight* for oropharyngeal/hypopharyngeal cancers, and *indeterminate* for laryngeal cancers, respectively. Evidence for a carcinogenic effect in the URT of humans is further supported by experimental animal studies. Precancerous lesions (e.g., dysplasia) and tumors (primarily squamous cell carcinomas) were observed in the nasal cavities of multiple species/strains of rodents. Such observations in animals were concentration and duration dependent. Mechanistic data suggest that URT cancers are likely the result of genotoxicity and mutagenicity, cytotoxicity, and cell proliferation. Together, genotoxicity, cellular proliferation, and cytotoxicity-induced regenerative proliferation exhibit multiple layers of coherence as a function of species, anatomy, temporality, concentration, and duration of exposure, and when these factors are integrated, they form a biologically relevant MOA for formaldehyde-induced URT carcinogenesis.

The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer (NPC) in humans, based on *robust* epidemiological evidence of an increased risk of the occurrence of NPCs from studies of occupational formaldehyde exposure in several geographic locations among different occupational populations representing diverse exposure settings; *robust* evidence from long-term bioassays in two animal species providing consistent and reliable evidence of nasal cancers following exposure; and reliable and consistent mechanistic evidence in both animals and humans supporting causality. The nasopharynx, although not typically specified in animal studies, is the region adjacent to the nasal cavity, where the animal evidence was predominantly observed, providing plausible coherence between the animal and human data (and thus, the animal evidence is reflected as *robust* for the purpose of interpreting human NPC). The evidence is sufficient to conclude that a mutagenic mode of action of formaldehyde is operative in formaldehyde-induced nasopharyngeal carcinogenicity.

The **evidence demonstrates** that formaldehyde inhalation causes sinonasal cancer (SNC) in humans, based on *robust* epidemiological evidence of an increased risk of the occurrence of sinonasal cancer from studies of occupational formaldehyde exposure in several geographic

locations among different occupational populations representing diverse exposure settings. This evidence is supported by the apical and mechanistic evidence for nasal cancers across multiple animal species, although some uncertainty remains in the interpretation of the animal nasal data as wholly applicable to interpreting sinonasal cancer (and thus, the animal evidence is reflected as *moderate* for the purpose of interpreting human SNC). Despite some uncertainty in the applicability of the animal data to human SNC, the identified nasal cancer MOA, including mutagenicity, is interpreted as relevant to this cancer type.

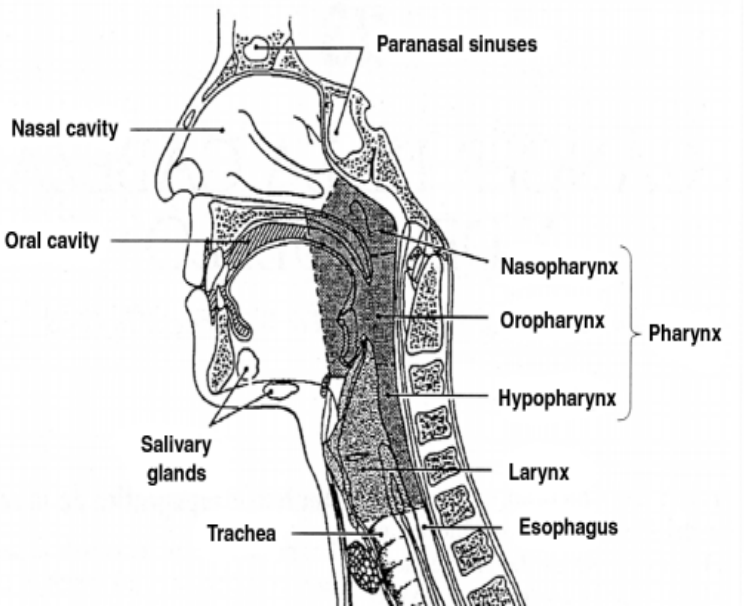


Figure 3-18. Schematic diagram of the human upper respiratory tract (i.e., nose, nasal cavity, paranasal sinuses, pharynx, larynx), as well as neighboring structures (from Vokes et al. (1993)).

Upper Respiratory Tract Cancers in Human Studies

Each specific type of upper respiratory tract (URT) cancer (nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx and hypopharynx, and laryngeal cancer) is reviewed and evaluated independently in the sections below. For each type of URT cancer, the evidence is organized by considerations that inform the strength of evidence (e.g., consistency, exposure-response) and evaluation of the potential for bias and insensitivity in individual studies to affect the estimates of relative risk. Evidence tables for each type of URT cancer (Tables 3-32 through 3-35) are included and are organized first by the study evaluation conclusions (i.e., *high, medium, low*) and then by publication year.

Nasopharyngeal cancer

Epidemiological evidence

The most specific classification of nasopharyngeal cancer diagnosis that is commonly reported on death certificates across the epidemiological literature has been based on the first three digits of the Seventh (i.e., nasopharyngeal cancer ICD-7: 146), Eighth, or Ninth Revision of the ICD code (i.e., nasopharyngeal cancer ICD-8/9: 147) although some studies did report the histological type of cancer (i.e., squamous cell carcinoma and nonkeratinizing or undifferentiated cancer), the histological type is infrequently reported on death certificates.

Evidence describing the association between formaldehyde exposure and the risk of developing or dying from nasopharyngeal cancer is available from 20 epidemiological studies—12 case-control studies (Yu et al., 2004; Yang et al., 2005; West et al., 1993; Vaughan et al., 1986a, b; Vaughan, 1989; Vaughan et al., 2000; Roush et al., 1987b; Olsen et al., 1984; Li et al., 2006; Hildesheim et al., 2001; Armstrong et al., 2000) and eight cohort studies (Siew et al., 2012; Meyers et al., 2013; Malker et al., 1990; Hauptmann et al., 2009; Hansen and Olsen, 1995; Dell and Teta, 1995; Coggon et al., 2014; Beane Freeman et al., 2013). These are the only primary studies that provide evidence of the effect of formaldehyde exposure on the risk of dying from nasopharyngeal cancer. The outcome-specific evaluations of confidence in the precise effect estimate of an association from each study are provided in Appendix B.3.9. Note that the confidence judgments are for the confidence in the precise effect estimate of an association from each study—and not a confidence judgment in the overall study. The distinction here is important in that a study of adequate quality overall may still report an effect estimate judged to be of *low* confidence due to the rarity of the cancer outcome, the rarity of the exposure, or noncritical biases that are expected to yield effect estimates that underestimate any true effect. The results from Li et al. (2006) were classified as *not informative* due to the rarity of exposure in both the case and control groups; for details see Appendix B.3.9. The reported result from a case-control study by Armstrong et al. (2000) was classified as *not informative* due, primarily, to the rarity of relevant exposure data as only 8/564 subjects (1.4%) had more than 10 years of potential exposure beyond a 10-year latency period, and thus the study lacked sensitivity to detect any true effect (see Appendix B.3.9). The results from Dell et al. (1995) were classified as *not informative* due to the rarity of exposure in the cohort with 111 men exposed to formaldehyde out of 5932 (1.9%) and there were no observed cases of nasopharyngeal cancer; for details see Appendix B.3.9. Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for nasopharyngeal cancer (see Table 3-32) following the causal evaluation.

Consistency of the observed association

Seventeen informative studies reported risks of nasopharyngeal cancer among subjects with formaldehyde exposure based on occupational or residential history. These studies examined different populations, in different geographical locations, under different exposure settings and

employing different study designs. Importantly, for nasopharyngeal cancer, these studies were conducted in low background risk populations (e.g., Europe and the United States) and high background risk populations (e.g., China and Taiwan). Table 3-31 provides the incidence rates of nasopharyngeal cancer per year by country/region based on the IARC publication *Cancer Incidence in Five Continents* (Curado et al., 2007) for each of the 17 studies.

Table 3-31. Age-standardized (world) incidence rates of nasopharyngeal cancer per 100,000 people per year

Study	Country	Region	Incidence rate/year (per 100,000)
Siew et al. (2012)	Finland		0.3
Coggon et al. (2014)	England and Wales	South and Western	0.4
Hansen and Olsen (1995)	Denmark		0.4
Malker et al. (1990)	Sweden		0.4
Olsen et al. (1984)	Denmark		0.4
Vaughan et al. (2000)	United States	CT, Detroit, IA, Seattle, UT	0.4–0.7
Meyers et al. (2013)	United States	Georgia and Pennsylvania	0.5–0.6
Beane Freeman et al. (2013)	United States	National Cancer Registries	0.6
Hauptmann et al. (2009)	United States	National Cancer Registries	0.6
Vaughan (1989)	United States	Washington	0.6
Roush et al. (1987a)	United States	Connecticut	0.6
Vaughan et al. (1986a)	United States	Washington	0.6
Vaughan et al. (1986b)	United States	Washington	0.6
Yang et al. (2005)	Taiwan[a]		3.5–8.3
Hildesheim et al. (2001)	Taiwan[a]		3.5–8.3
West et al. (1993)	Philippines		5.8
Yu et al. (2004)	China	Hong Kong	17.8

[a]Taiwan is not included in the IARC publication of cancer incidence rate so data were obtained from Chen et al. (2002).

Also important for nasopharyngeal cancer is the consideration of histological subtype, which may be of a keratinizing or nonkeratinizing cell type as the proportion of each cell type varies in low and high-risk populations. The study results presented in Table 3-32 (by confidence level and publication date) detail all of the reported associations. Results are plotted in Figure 3-19; results are grouped by population background risk and arrayed from lowest to highest by the percentage of cases in each study's results, which were considered likely to be squamous cell carcinomas.

Fourteen out of 17 studies reported increased risks of nasopharyngeal cancer with at least one metric of formaldehyde exposure—often with both clear statistical significance and exposure-response relationships. These included the results of large cohort study of 25,619 U.S. workers (Beane Freeman et al., 2013) classified with *high* confidence, and all four sets of results classified with *medium* confidence (see Table 3-32). Nine studies in eight independent populations reported relative effect estimates greater than three-fold. Yang et al. (2005) reported an OR of 4.29 (95% CI 2.45, 7.51) among cases with the highest cumulative formaldehyde exposure; Yu et al. (2004) reported a mortality odds ratio (MOR) of 3.75 (95% CI 1.12, 12.54) for restaurant workers

in Hong Kong; West et al. (1993) reported an OR = 4.0 (95% CI 1.3,12.3) among Philippine cases with greater than 25 years of time since first exposure (TSFE); Roush et al. (1987a) reported an OR = 4.0 (95% CI 1.3, 12.0) among Connecticut cases aged 68+ years with the highest duration of exposure and 20+ years TSFE; Beane Freeman et al. (2013) reported an RR = 11.54 (95% CI 1.38, 96.81) for workers with the highest average intensity of exposure; Malker et al. (1990) reported a standardized incidence ratio (SIR) of 3.9 (95% CI 1.24, 9.40) among workers employed in fiberboard plants; Vaughan et al. (1986b) reported an OR = 6.7 (95% CI 1.2, 38.9) for cases living and working in a mobile home; Vaughan (1989) reported an OR = 31.8 (no CI provided) for the highest duration of working as a carpenter; and Vaughan et al. (2000), after excluding undifferentiated and nonkeratinizing histological types, reported an OR = 13.3 (95% CI 2.5, 70) for cases with the highest likelihood of formaldehyde exposure.

Results showing increased risks were consistently reported in populations from high-risk areas with endemic Epstein-Barr infection such as Hong Kong (Yu et al., 2004), Taiwan (Yang et al., 2005; Hildesheim et al., 2001), the Philippines (West et al., 1993) as well as in populations from low/medium-risk areas such as the United States (Vaughan et al., 1986a, b; Vaughan, 1989; Vaughan et al., 2000; Roush et al., 1987a; Beane Freeman et al., 2013). Results showing increased risks were also consistently reported across study populations with different proportions of squamous cell carcinomas (SCC) (i.e., Hildesheim et al. (2001) and Yang et al. (2005) reported only 9% of their cases were keratinizing SCC), more heterogeneous mixes of keratinizing and nonkeratinizing carcinomas [i.e., Malker et al. (1990), (48% keratinizing SCC); Vaughan et al. (2000), (60%); (Vaughan et al., 1986a, b), (78%)], and study populations restricted to only squamous cell carcinomas (Vaughan, 1989; Vaughan et al., 2000) (100% keratinizing SCC)].

Of these 17 studies, all but three reported increased risks of nasopharyngeal cancer that appeared to be associated with exposure to formaldehyde; the three exceptions were the results from the large occupational cohort studies by Siew et al. (2012), Coggon et al. (2014), and Meyers et al. (2013)—all of which were classified with *low* confidence. One additional study (Andjelkovich et al., 1995) reported zero cases of NPC among 3,929 U.S. workers exposed to formaldehyde over 83,064 person-years but reported no data on the number of expected cases and thus was not included here.[24] An additional study (Edling et al., 1987b) reported one case of NPC among 521 Swedish workers exposed to formaldehyde over 7,011 person-years but reported no data on the number of expected cases and was not included here.[25] One possible explanation for the inconsistency is the rarity of NPC in the populations studied by Siew and by Coggon. Table 3-32 shows that the Finnish population studies by Siew et al. (2012) had a background incidence rate of 0.3 cases per year for each 100,000 people—the lowest of all the available populations reviewed

[24]For Andjelkovich et al. (1995), assuming a rate of NPC for U.S. workers of 0.6 per 100,000 person-years (Curado et al., 2007), the expected number of cases would have been 0.33 and the ~SMR = 0 (95% CI 0, 5.99).
[25]For Edling et al. (1987b), assuming a rate of NPC for Swedish workers of 0.4 per 100,000 person-years (Curado et al., 2007), the expected number of cases would have been 0.028 and the ~SMR = 35.71 (95% CI 1.79, 176.1).

here. The English and Welch population studied by Coggon et al. (2014) had the second lowest incidence rate at 0.4 cases per year for each 100,000 people.[26] The very low national incidence rates of NPC can make studies of these populations lack the statistical sensitivity to detect any true association—even when the number of people being followed appears to be large.

It is important to understand that the statistical power of these cohort studies depends directly on the number of observed and expected cases. While there are exact methods to compute the variance of the standardized mortality ratio, the general formula illustrates the dependence on the case counts. The variance of the standardized mortality ratio is generally a function of the inverse of the observed and expected case count, specifically, *var*(SMR) = [# observed cases/(# of expected cases)^2]. Smaller case counts produce larger statistical variances and wider confidence intervals. Because the SMR is a measure of relative effect bounded between zero and infinity, it may be more straightforward to consider the width of confidence intervals on the scale of the natural logarithm, which bounds the estimates symmetrically between negative infinity and positive infinity. Coggon et al. (2014) expected only 1.7 deaths from nasopharyngeal cancer in the exposed workers and observed just one resulting in an unstable estimated RR = 0.38 (95% CI 0.02, 1.90); on the natural log scale the ln(RR) = −0.97 (95% CI −3.91, to 0.64). Meyers et al. (2013) expected only 1.33 deaths and did not observe any deaths, resulting in an SMR = 0 (95% CI 0, 2.77); on the natural log scale, the ln(RR) = negative infinity (95% CI negative infinity to +1.99). These effect estimates result in wide confidence intervals. For comparison, the other large cohort study (Beane Freeman et al., 2013) expected 4.89 deaths and observed nine deaths from NPC, resulting in a SMR = 1.84 (95% CI 0.84, 3.49); on the natural log scale, the ln(RR) = negative infinity (95% CI −0.17, 1.25). The NPC results from the Coggon et al. (2014), Meyers et al. (2013) and Siew et al. (2012) studies were all considered to lack sensitivity to detect any true effect, which contributed to their classifications of *low* confidence.

In summary, the majority of studies from different populations, in different locations, exposure settings, and using different study designs reported increased risks of nasopharyngeal cancer associated with formaldehyde exposure. There are reasonable alternative explanations for the three studies that did not observe an increased risk.

Strength of the observed association

While reported relative effect estimates were consistently elevated above the null value of one across 14 of the 17 studies, the magnitude of the relative risk estimates varied with the quality of the exposure assessment. Studies with higher quality exposure data that were capable of stratifying subjects by exposure level, exposure probability, and timing of exposure (including lagged exposures) generally reported higher relative effect estimates. Nine studies reported greater

[26]For comparison, the background incidence rate in the United States is 0.6 cases per year for each 100,000 people and ranges from 3.5 to 17.8 cases per year for each 100,000 people in the Philippines, Taiwan, and Hong Kong (see Table 3-31).

than three-fold increased risks of nasopharyngeal cancer that appeared to be associated with exposure to formaldehyde (Yu et al., 2004; Yang et al., 2005; West et al., 1993; Vaughan et al., 1986b; Vaughan, 1989; Vaughan et al., 2000; Roush et al., 1987a; Malker et al., 1990; Beane Freeman et al., 2013). Three studies reported greater than 10-fold increased risks of nasopharyngeal cancer in the highest exposure categories. These increased risks appeared to be associated with duration of exposure to formaldehyde after accounting for a latency period (Vaughan, 1989; Vaughan et al., 2000; Beane Freeman et al., 2013). Results from the studies with higher quality exposure data were judged with greater confidence.

Temporal relationship of the observed association

Two related aspects of time are encompassed in the consideration of temporality. One aspect is the necessity for the exposure to precede the onset of the disease. In each of the studies, the formaldehyde exposures among the study participants started before their diagnoses of NPC, and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and done in a blinded fashion with respect to outcome status.

The second aspect involves the time course of formaldehyde exposures in relation to the incidence of NPC and death from NPC. From the epidemiological literature, it is known that there can be an induction/latency period for some environmental agents and that the induction period may exceed 10 years. Three studies provided analyses of this temporal relationship showing some evidence of the effect of time since first exposure on the risk of dying from nasopharyngeal cancer (West et al., 1993; Roush et al., 1987b; Hildesheim et al., 2001); however, none of them did so by histological subtype. Hildesheim et al. (2001) reported conflicting evidence of lower risks among all NPC cases for first exposure to formaldehyde more than 20 years earlier, but higher risks with greater time since first exposure (TSFE) when analyses were limited to only those who were positive for Epstein-Barr virus. Roush et al. (1987b) reported somewhat greater risks among those first exposed more than 20 years and a stronger such pattern among those considered to be highly exposed more than 20 years prior to dying of nasopharyngeal cancer. Even higher risks were found among those with high early exposures and who were 68 years or older at death (OR = 4.0; 95% CI 1.3, 12.0), which may imply that TSFE much greater than 20 years carries greater risk. The results from West et al. (1993) support this assertion; in multivariate analyses, they reported a low odds ratio for TSFE less than 25 years but higher risks for greater than 25 years (OR = 4.0; 95% CI 1.3, 12.3). In separate analyses controlling only for TSFE to formaldehyde, dust, and exhaust fumes, West et al. (1993) reported even higher risk among those first exposed to formaldehyde more than 35 years earlier (OR = 5.6; 95% CI 0.58, 52.9).

The histological subtype and background rate of nasopharyngeal cancer is important in considering latency as the population studied by Hildesheim et al. (2001) resided in Taiwan (a high background risk population), and cases were more than 90% nonkeratinizing. In contrast, the population Roush et al. (1987b) studied was from Connecticut (a low background risk population), which may have only ~28% nonkeratinizing cases, if consistent with a U.S. study of nasopharyngeal

cancer that included cases from Connecticut (Vaughan, 1989). West et al. (1993) studied subjects from the Philippines where the background rate is intermediate to the high rates of some East Asians and the low rates in populations of European descent (Hildesheim et al., 1993).

The association between exposure to formaldehyde and risk of nasopharyngeal cancer may be weaker for nonkeratinizing cases (Vaughan et al., 2000). This may explain the apparent lack of a clear latency effect in the Hildesheim et al. (2001) study, which has more than 90% of cases diagnosed with nonkeratinizing cases. The remaining limited evidence on the time course of death following initial formaldehyde exposure is consistent with expectation of a lengthy latency period for cancer development and subsequent deaths.

Exposure-response relationship

In their large population-based case-control study including 196 cases of nasopharyngeal cancer, Vaughan et al. (2000) clearly demonstrated two important points: (1) that there was an exposure-response relationship between increased formaldehyde exposure and increased risk of nasopharyngeal cancer, and (2) that the exposure-response differed by nasopharyngeal cancer subtype in the U.S. population. Vaughan et al. (2000) reported statistically significant trends for differentiated squamous cell carcinomas ($p = 0.033$) and for cases of epithelial carcinoma without specification of histological type ($p = 0.036$). However, there was no trend with duration of exposure to formaldehyde among cases with undifferentiated/nonkeratinizing histology ($p = 0.82$). Grouping of all histological subtypes appeared to mask the underlying relationship seen in squamous cell carcinoma in this study. Excluding nasopharyngeal cancer cases with undifferentiated or nonkeratinizing histology, Vaughan et al. (2000) reported a clear exposure-response with increased probability of exposure to formaldehyde with the highest risks seen in subjects with the highest probability of occupational exposure to formaldehyde (OR = 13.3; 95% CI 2.5, 70; $p = 0.0007$). Among those subjects considered to be "definitely exposed," there were increasing risks of nasopharyngeal cancer with increasing duration of formaldehyde exposure ($p < 0.001$) and with increased cumulative formaldehyde exposure ($p < 0.001$).

Further evidence of exposure-response relationships was reported by Beane Freeman et al. (2013) for peak formaldehyde exposures ($p = 0.005$), and, to a lesser degree, for cumulative exposures ($p = 0.06$) and with average intensity of formaldehyde exposure ($p = 0.09$)[27]. Other supporting evidence of an exposure-response relationship between increased exposure to formaldehyde and increased risk of NPC come from three reports on the same study population in Washington state (Vaughan et al., 1986a, b; Vaughan, 1989). These studies reported higher risks with increasing occupational exposures but did not report tests of trend (Vaughan et al., 1986a); for

[27]Möhner et al. (2019) argued that there might have been a diagnostic bias in coding the specific and non-specific pharyngeal cancer in the NCI cohort study which could have affected the pharyngeal cancer SMRs; however, potential administrative miscoding of cancer mortality on death certificates would be independent of the quantitative estimates of workers' exposures, and any misclassification of diagnostic codes would not be expected to yield evidence of exposure-response relationships.

example, with a 15-year lag, compared to the lowest exposure score, those in the second level had an OR = 1.7 (95% CI 0.5, 5.7), while those in the third level had an OR = 2.1 (95% CI 0.4, 10.0). These researchers also reported increased risks with length of residence in mobile homes with the risk peaking among those with more than 10 years of occupancy (OR = 5.5; 95% CI 1.6, 19.4) (Vaughan et al., 1986b). The majority (84%) of mobile homes in the United States at this time were reported to have mean formaldehyde exposures in excess of 100 ppb, with 22% having mean exposures in excess of 500 ppb (Breysse, 1984) as cited in WHO (IPCS, 1989). A qualitative exposure-response relationship was shown for overall mobile home exposures with the risk of nasopharyngeal cancer for working in a mobile home but not living in a mobile home (OR = 1.7; 95% CI 0.5, 5.7) being exceeded by the risk of living in a mobile home (OR = 2.8; 95% CI 1.0, 7.9). However, the greatest risk was reported for living and working in a mobile home (OR = 6.7; 95% CI 1.2, 38.9). Vaughan (1989) also reported increasing risk with duration of employment as a carpenter after lagging exposures by 15 years to account for cancer latency (χ^2 trend = 8.65; p = 0.01 with 2 df)—especially as a carpenter in the construction industry (χ^2 trend = 14.86; p = 0.0006 with 2 df). Carpentry is considered to be a formaldehyde-related job since many products used in construction and building trades involve exposure to formaldehyde (Vaughan et al., 1986a; Hildesheim et al., 2001). Carpentry also involves coexposure to wood dust, which is likely to be a potential confounder for NPC, as it is a potent risk factor. The potential for confounding by wood dust is evaluated in the following section. Other evidence generally consistent with an exposure-response relationship was reported by Yu et al. (2004), Hildesheim et al. (2001), and West et al. (1993). Yu et al. (2004) reported mortality Ors (MORs) for three levels of increasing cumulative exposure based on years of union membership compared to none and report MORs of 2.5, 3.41, and 3.75 (95% CI 1.12, 12.54). Hildesheim et al. (2001) reported an OR = 1.3 for less than 25 years of cumulative exposure and OR = 1.5 for more than 25 years of cumulative exposure (95% CI 0.88, 2.7, p-trend = 0.10); West et al. (1993) reported that daily use of antimosquito coils [which have been shown in experiments to emit formaldehyde concentrations of between 0.87 and 25 μg/m^3; see (Liu et al., 2003)] had an OR = 5.9 (95% CI 1.7, 20.1), while less than daily use had an OR = 1.4.

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias may alter epidemiological findings when participation or follow-up rates are related to the probability of exposure or the outcome. However, this is an unlikely bias in the epidemiological studies of nasopharyngeal cancer, as the case-control studies evaluated exposure status without regard to outcome status and had participation levels of 85–100%. Each of the cohort studies included at least 72% of eligible participants and lost relatively few participants over the course of mortality follow-up.

The issue of potential selection bias was relevant to the results from two study populations —all classified with *low* confidence (Yang et al., 2005) and the three Vaughan papers (Vaughan et al., 1986a, b; Vaughan, 1989). Both Yang et al. (2005) and Vaughan (1989) with (Vaughan et al.,

1986a, b) used more than 40% of case interviews completed by next of kin due to cancer mortality among cases and no proxy respondent was included for the controls. When next-of-kin is used to provide proxy information on cases, measurement error is likely to be present to some degree. If the quality of those data differs between cases and controls, this can result in selection bias if any differences are related to exposure. Hence, EPA considers that there is some risk of selection bias in the results of these studies (e.g., (Yang et al., 2005; Vaughan et al., 1986a, b; Vaughan, 1989).

Information bias may distort findings when subjects' true personal exposures are inaccurately assigned. Differential misclassification, in which exposure status influences disease classification (or disease status influences exposure classification), can lead to bias toward or away from the null (i.e., spurious or "false positive" associations). This scenario is considered unlikely among these studies of nasopharyngeal cancer mortality because the likelihood of differential misclassification based on these study designs is low. The assignment of exposure status or calculation of exposure measures in the case-control and cohort studies was done independently of knowledge of the cause of death. Therefore, an exposure-related bias in subjects' recall or reconstruction of their occupational histories seems unlikely.

Another aspect of information bias stems from random measurement error or nondifferential misclassification. This type of error typically will bias the risk estimate toward the null, thereby obscuring real effects by underestimating their magnitude. Given the difficulty in accurately estimating personal exposure over time or in the use of proxies to represent exposure to formaldehyde, the likelihood of random measurement error is almost certain in many studies. The implication of such information bias is that the consistently reported increases in risks of formaldehyde-related mortality may be underestimates and the true risk could be larger than was demonstrated in these epidemiological studies.

A third possible scenario for information bias could arise from systematic measurement error that is nondifferential with respect to disease. Such a scenario would be unusual in a study with exposure assessment based in industrial settings with extensive industrial hygiene data used to determine levels of exposure (Beane Freeman et al., 2013). However, a claim was made by (Marsh et al., 2002; Marsh et al., 2007a) that the exposure assessment used for the NCI formaldehyde cohort reported on by Beane Freeman et al. (2013) was 10-fold higher than those estimated by (Marsh et al., 2002; Marsh et al., 2007a). If this were true, then the same amount of observed risk in Beane Freeman et al. (2013) would be apportioned to one-tenth the same exposure, which would yield an exposure-response 10-fold greater in magnitude. The claim by (Marsh et al., 2002; Marsh et al., 2007a) suggests a one-sided uncertainty in the exposure-response reported by Beane Freeman et al. (2013), which may be 10 times more potent than reported.

Confounding is a potential bias that could arise if another cause of nasopharyngeal cancer was also associated with formaldehyde exposure. There does not appear to be any evidence of a common confounder that would provide an alternative explanation for the consistently observed association of formaldehyde exposure with increased risk of nasopharyngeal cancer seen across

these studies. Chemicals and other coexposures that have not been independently associated with nasopharyngeal cancer are not expected to confound results. Other known risk factors for nasopharyngeal cancer include childhood consumption of Chinese salted fish (Yu et al., 1986), wood dust (Hildesheim et al., 2001), smoking, and alcohol consumption (Vaughan, 1996). While these other exposures may be independent risk factors for nasopharyngeal cancer, consumption of Chinese salted fish (or other dietary exposures to nitrosamines) and alcohol are unlikely to be generally related to formaldehyde exposures, and therefore, these other exposures are not expected to be consistent confounders across all of the studies. Additionally, Epstein-Barr virus is thought to be a cause of nasopharyngeal cancer due to its ubiquitous presence in nasopharyngeal cancer cases, but Hildesheim (2001) described Epstein-Barr virus as an effect modifier of the association between formaldehyde and nasopharyngeal cancer, and not as a confounder.

Wood dust may be an independent risk factor for nasopharyngeal cancer, but three studies specifically controlled for the potential confounding of the effects of wood dust on the risk of nasopharyngeal cancer and did not find wood dust to be a confounder (West et al., 1993; Vaughan et al., 2000; Hildesheim et al., 2001). Similarly, smoking was specifically controlled for in a number of studies (West et al., 1993; Vaughan et al., 1986a, b; Vaughan, 1989; Vaughan et al., 2000) and was not likely to have been a major confounder of the formaldehyde-associated results. Marsh et al. (2005) re-evaluated the association between formaldehyde exposure and NPC in the NCI cohort and reported that the majority of the cases of NPC arose in one of the 10 plants included in the cohort and that this finding suggested that there might be something specific to the experience in Plant 1 (in Wallingford , CT) that may have given rise to the excess of NPC cases there – perhaps a confounder. Marsh et al. (2007a) suggests that silversmithing may be a cause of NPC in Plant 1 and that the reported association between formaldehyde and NPC may be due to confounding; however, Beane Freeman et al. (2013) noted that the reported association for formaldehyde on the risks of NPC did not decrease when analyses adjusted for silversmithing (see Table 5 of (Marsh et al., 2007a)). The details of Table 1 in (Marsh and Youk, 2005) show the SMRs for NPC for each of the 10 plants. The two plants with the highest average intensity of formaldehyde exposure had the two highest SMR estimates for NPC. It is plausible that the observation that the majority of the cases of NPC in the NCI cohort come from Plant 1 reflects generally higher formaldehyde exposures and a larger number of people at that plant than at other plants. This overall evidence does not indicate confounding of the formaldehyde association with increased risk of NPC.

Consistency across multiple studies is demonstrated by a pattern of increased risk in different populations, exposure scenarios, and time periods. Such consistency makes unmeasured confounding an unlikely alternative explanation for the observed associations. This consistency also reduces the likelihood of chance as an alternative explanation by increasing the statistical strength of the findings through the accumulation of a larger body of similar evidence. The observations of multiple instances of very strong associations, as well as exposure-response trends with increased

formaldehyde exposure using multiple metrics of exposure similarly reduce the likelihood that chance, confounding, or other biases can explain the observed association.

Summary of Human Evidence Synthesis Judgments, Causal Evaluation, and Conclusion

Summary of human evidence synthesis judgments

The following factors were most influential to the causal evaluation and synthesis conclusion:

- *Consistency and Study Confidence*: Consistent increases in risk observed across several studies—including results classified with *high*, *medium*, and *low* confidence; with higher risks among Asian populations that have higher background rates of nasopharyngeal cancer and reasonable explanations for the lack of findings in a few studies with very low background rates of nasopharyngeal cancer.

- *Strength and Precision*: The magnitude of the relative effect estimates varied with the quality of the exposure assessment. Nine studies out of 17 reported at least a 3-fold increase in risk and three studies reported greater than 10-fold increased risks in the highest exposure categories.

- *Coherence*: Biologically coherent temporal relationship consistent with a pattern of exposure to formaldehyde and subsequent death from nasopharyngeal cancer, allowing time for cancer induction, latency, and mortality.

- *Dose-Response:* Reported exposure-response relationships showed that multiple measures of increased exposure to formaldehyde were repeatedly associated with increased risk of dying from nasopharyngeal cancer—especially among studies primarily focused on squamous cell carcinomas.

Causal evaluation

The human evidence synthesis judgments strongly support a causal conclusion and are further supported by a judgment of reasonable confidence that alternative explanations are ruled out, including chance, bias, and confounding within individual studies or across studies. Although the cancer incidence and mortality data alone are sufficient for the causal conclusion supported by the human evidence synthesis judgments described above, consistent observations of genotoxicity in exfoliated buccal cells or nasal mucosal cells across several occupational studies involving diverse exposure settings (discussed under MOA below) strengthens *biological plausibility*, providing further support.

Conclusion

- The available epidemiological studies provide *robust* evidence of an association consistent with causation between formaldehyde exposure and increased risk of nasopharyngeal cancer.

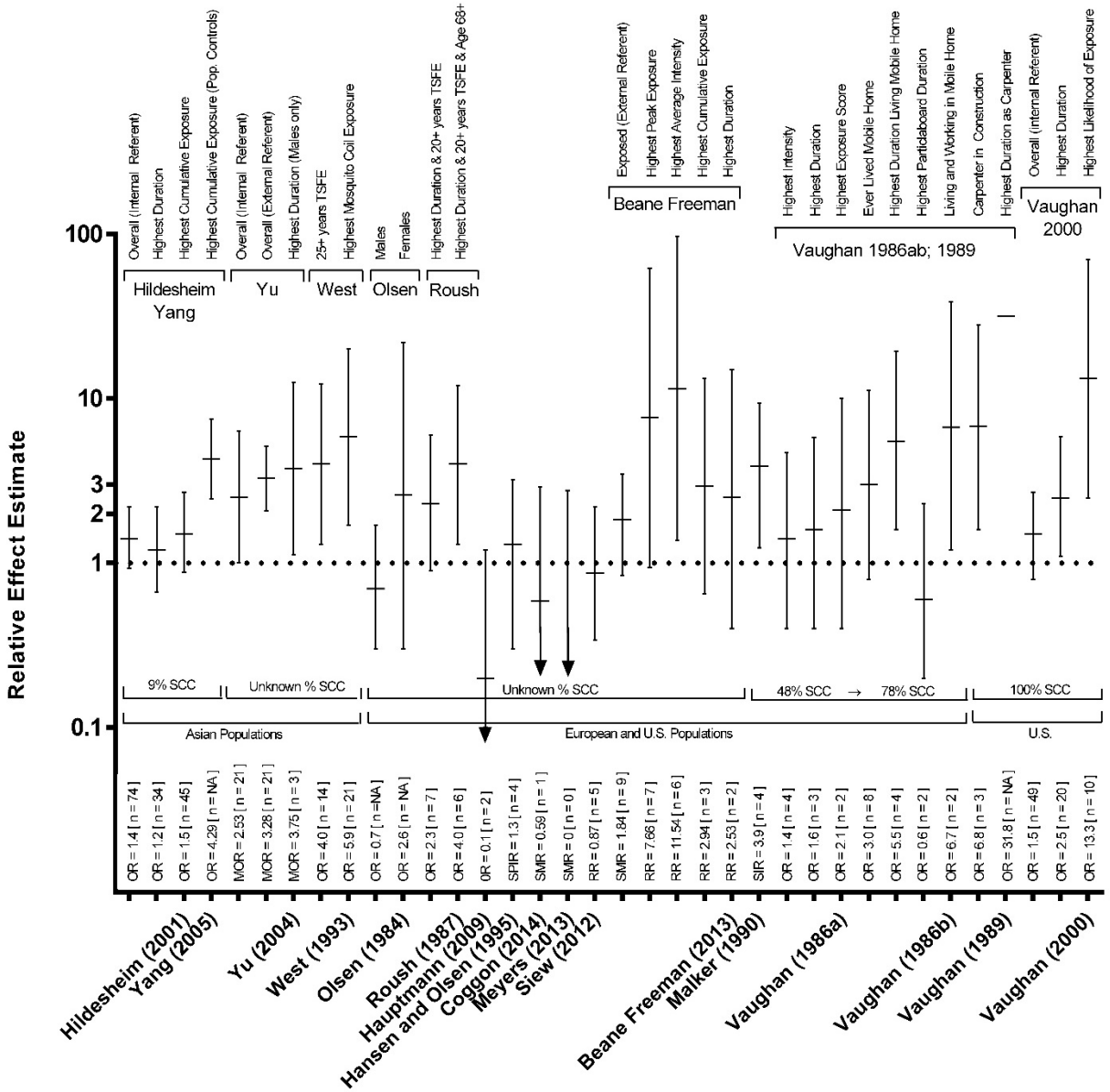


Figure 3-19. Epidemiological studies reporting nasopharyngeal cancer risk estimates.

Results are grouped by population background risk and arrayed from lowest to highest by the percentage of cases in each study's results that were considered likely to be squamous cell carcinomas (SCC). Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for

nasopharyngeal cancer (see Table 3-32). SMR: standardized mortality ratio. PMR: proportionate mortality ratio. SPIR: Standardized Proportional Incidence Ratio. RR: relative risk. OR: odds ratio. MOR: mortality odds ratio. TSFE: time since first exposure. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 74]). For studies reporting results on multiple metrics of exposure, only the highest category of each exposure metric is presented in the figure.

Table 3-32. Epidemiological studies of formaldehyde exposure and risk of nasopharyngeal cancers

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]

Reference: Beane Freeman et al. (2013)
Population: 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the United States followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. 676 workers (3%) were lost to follow-up. Vital status was 97.4% complete and only 2.6% lost to follow-up.
 	
Outcome definition: Death certificates used to determine underlying cause of death from nasopharyngeal cancer (ICD-8: 147). Histological typing not reported.
 	
Design: Prospective cohort mortality study with external and internal comparison groups.
 	
Analysis: RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. Results were presented for 15-year lag.
 	
SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates.
 	
Related studies:
Blair et al. (1986)
Hauptmann et al. (2004)
Beane Freeman et al. (2009)
 	
Confidence in effect estimates:[a]
HIGH (No appreciable bias)
	Exposure assessment: Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists who took 2,000 air samples from representative job, and monitoring data from 1960 through 1980.
	Median TWA (over 8 hours) = 0.3 ppm (range 0.01−4.3). Median cumulative exposure = 0.6 ppm-years (range 0−107.4).
	
	Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data.
	
	Duration and timing: Exposure period from <1946 to 1980. Median length of follow-up: 42 years. Median length of employment was 2.6 years (range 1 day−47.7 years). Duration and timing since first exposure were not evaluated.
	Variation in exposure:
	Peak exposure:
	Level 1 (>0 to <2.0 ppm)
	Level 2 (2.0 to <4.0 ppm)
	Level 3 (≥4.0 ppm)
	Average intensity:
	Level 1 (>0 to <0.5 ppm)
	Level 2 (0.5 to <1.0 ppm)
	Level 3 (≥1.0 ppm)
	Cumulative exposure:
	Level 1 (>0 to <1.5 ppm-years)
	Level 2 (1.5 to <5.5 ppm-years)
	Level 3 (≥5.5 ppm-years)
	Duration of exposure:
	Level 1 (0 years)
	Level 2 (>0 to <5 years)
	Level 3 (5 to <15 years)
	Level 4 (≥15 years)
	
	Coexposures: Exposures to 11 other compounds were identified and evaluated as potential confounders and
		Internal comparisons:
		Peak exposure
		Unexposed RR = 4.39 (0.36−54.05) [2]
		Level 1 RR = 1.00 (Ref. value) [1]
		Level 2 RR = NA [0]
		Level 3 RR = 7.66 (0.94−62.34) [7]
		p-trend (exposed) = 0.005;
		p-trend (all) = 0.10
		
		Average intensity
		Unexposed
		RR = 6.79 (0.55−83.64) [2]
		Level 1 RR = 1.00 (Ref. value) [1]
		Level 2 RR = 2.44 (0.15−39.07) [1]
		Level 3 RR = 11.54 (1.38−96.81) [6]
		p-trend (exposed) = 0.09;
		p-trend (all) = 0.16
		
		Cumulative exposure
		Unexposed RR = 1.87 (0.30−11.67) [2]
		Level 1 RR = 1.00 (Ref. value) [4]
		Level 2 RR = 0.86 (0.10−7.70) [1]
		Level 3 RR = 2.94 (0.65−13.28) [3]
		p-trend (exposed) = 0.06;
		p-trend (all) = 0.07
		Duration of exposure
		Level 1 RR = 1.00 (Ref. value) [4]
		Level 2 RR = 0.86 (0.10−7.70) [1]
		Level 3 RR = 2.94 (0.65−13.28) [3]
		Level 4 RR = 2.53 (0.4−15.0) [not given]
		p-trend (all) = 0.4
		
		External comparisons:
		$SMR_{Unexposed}$ = 1.45 (0.17−5.25) [2]
		$SMR_{Exposed}$ = 1.84 (0.84−3.49) [9]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
	found not be confounders. [As noted in Appendix B.3.9: There was no information on smoking, however, according to Blair et al. (1986), "The lack of a consistent elevation for tobacco-related causes of death, however, suggests that the smoking habits among this cohort did not differ substantially from those of the general population." Beane Freeman et al. (2013) report that among a sample of 379 cohort members, they "found no differences in prevalence of smoking by level of formaldehyde exposure."]	
Reference: Hauptmann et al. (2009) **Population:** 6,808 embalmers and funeral directors who died during 1960−1986. Identified from registries of the National Funeral Directors' Association, licensing boards and state funeral directors' associations, NY State Bureau of Funeral Directors, and CA Funeral Directors and Embalmers. Deaths were identified from the National Death Index. Next of kin interviews conducted for 96% of cases and 94% of controls. **Outcome definition:** Death certificates used to determine UCOD from nasopharyngeal cancer (ICD-8: 147). **Design:** Nested case-control study within a prospective cohort mortality study using two internal comparison groups; the first composed of those who had never embalmed (1 case and 55 controls) and the second composed of those who had fewer than 500 embalmings (five cases and 83 controls). **Analysis:** Ors calculated using unconditional logistic regression adjusted for date of birth, age at death, sex, data source, and smoking. Lagged exposures were evaluated to account for cancer latency. These results are shown in table 3 of Hauptmann et al. (2009).	**Exposure assessment:** Occupational history obtained by interviews with next of kin and coworkers using detailed questionnaires. Exposure was assessed by linking questionnaire responses to an exposure assessment experiment providing measured exposure data. Exposure levels (peak, intensity, and cumulative) were assigned to each individual using a predictive model based on the exposure data. The model explained 74% of the observed variability in exposure measurements. Multiple exposure metrics including duration (mean = 31.3 years in cases), # of embalming, peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1932 through 1986. Duration of exposure was evaluated. Duration is also a surrogate for time because first exposure since dates of death was closely related to cessation of workplace exposures. **Variation in exposure:** Level 1 Never embalmed Level 2 Ever embalmed **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde,	**Internal comparisons:** Never embalming: OR = 1.00 (Ref. value) [2] Ever embalming: OR = 0.1 (0.01–1.2) [2]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Results from the second internal comparison group with <500 embalmings were selected to increase statistical stability. These results are shown in table 4 of Hauptmann et al. (2009) **Related studies:** Hayes et al. (1990) Walrath and Fraumeni (1983) Walrath and Fraumeni (1984) **Note:** The original cohorts from these three original studies were combined in Hauptmann et al. (2009) and follow-up was extended so the case-series overlap and are not independent. However, the three original cohorts used external reference groups for comparison while Hauptmann et al. (2009) selected internal controls, which were independent of the reference groups used in the original studies. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Low sensitivity (few cases).	mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	
Reference: Hildesheim et al. (2001) **Population:** Male and female Taiwanese aged <75 years newly diagnosed with nasopharyngeal cancer identified between July 1991 and January 1995 from two hospitals. Participation of eligible cases was 99 and 87% for controls. **Outcome definition:** Diagnosis of nasopharyngeal was confirmed by histological review with >90% diagnosed with nonkeratinizing and undifferentiated carcinomas and 9% with squamous cell carcinoma. **Design:** Population-based case-control study of 375 cases of nasopharyngeal cancer. 325 controls identified from a random sample of households from a national household registration system and matched by age, sex, and area of residence.	**Exposure assessment:** Occupational history obtained from interviews of cases and controls for jobs held for ≥1 year since age 16 and identified job title, typical activities/duties, type of industry, and tools and/or materials used. Industrial hygienist assigned Standard Industry Classification/Standard Occupational Classification codes to jobs, assigning each a probability and intensity of exposure on a 0 (not exposed) to 9 (strong) scale. Cumulative exposure defined as the product of average intensity and duration. Multiple exposure metrics including average intensity, average probability, cumulative, years since first exposure, and age at first exposure were evaluated.	**Internal comparisons:** All cases and controls Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. value) [301] Level 2 OR = 1.4 (0.93–2.2) [74] Duration (overall): Level 1 OR = 1.0 (Ref. value) [301] Level 2 OR = 1.3 (0.69–2.3) [31] Level 3 OR = 1.6 (0.91–2.9) [43] *p*-trend (exposed) = 0.08 Duration (excluding 10 years before diagnosis): Level 1 OR = 1.0 (Ref. value) [307] Level 2 OR = 1.6 (0.89–3.0) [34] Level 3 OR = 1.2 (0.67–2.2) [34] Cumulative exposure: Level 1 OR = 1.0 (Ref. value) [301] Level 2 OR = 1.3 (0.70–2.4) [29] Level 3 OR = 1.5 (0.88–2.7) [45] *p*-trend (exposed) = 0.10 Time since first exposure:

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Analysis: RRs estimated by Ors calculated by logistic regression and adjusted for age, sex, education, and ethnicity. An induction period of 10 years was also utilized to account for latency in evaluating duration of exposure. All subjects were tested for the EBV; subset analysis based on EBV positivity (360 cases and 94 controls). EBV seropositives defined as positive for one of the following anti-EBV antibodies known to be associated with nasopharyngeal cancer: viral capsid antigen IgA, EBV nuclear antigen one IgA, early antigen IgA, DNA binding protein IgG, and anti-Dnase IgG. **Related studies:** Yang et al. (2005); Hildesheim et al. (1997); Cheng et al. (1999) **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group B) with attenuation of association.	**Duration and timing:** Duration and timing of exposure were evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (no) Level 2 (yes) Duration (overall): Level 1 (none) Level 2 (≤10 years) Level 3 (>10 years) Duration (excluding 10 years before diagnosis): Level 1 (none) Level 2 (≤10 years) Level 3 (>10 years) Cumulative exposure: Level 1 (none) Level 2 (<25 years) Level 3 (≥25 years) Time since first exposure: Level 1 (none) Level 2 (<20 years) Level 3 (≥20 years) Age at first exposure: Level 1 (none) Level 2 (<25 years) Level 3 (≥25 years) **Other exposures:** wood dust, solvents, and smoking. [As noted in Appendix B.3.9: The observed associations were not materially affected when controlling for wood dust, solvent exposure, or smoking.]	Level 1 OR = 1.0 (Ref. value) [301] Level 2 OR = 2.3 (0.95–5.8) [19] Level 3 OR = 1.2 (0.76–2.0) [55] Age at first exposure: Level 1 OR = 1.0 (Ref. value) [301] Level 2 OR = 1.3 (0.80–2.0) [62] Level 3 OR = 3.4 (0.94–12) [12] No notable findings were reported between formaldehyde exposure and the risk of nasopharyngeal cancer when considering an induction period of 10 years. Authors reported that the observed associations were not materially affected when analyses additionally controlled for wood dust and solvent exposure.
Reference: Hildesheim et al. (2001)	**Exposure assessment:** Occupational history obtained from interviews of cases and controls for jobs held for ≥1 year since age 16 and identified job title, typical activities/duties, type of industry, and tools and/or materials used. Industrial hygienist assigned Standard Industry Classification/Standard Occupational Classification codes to jobs, assigning each a probability and intensity of exposure on a 0 (not exposed) to 9 (strong) scale. Cumulative exposure defined as the product of average intensity and duration.	**Internal comparisons:** EBV positive subjects (based on 360 cases and 94 controls) Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 2.7 (1.2–6.2) [# not given] Duration (overall): Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 2.8 (0.83–9.7) [# not given] Level 3 OR = 2.6 (0.87–7.7) [# not given] Duration (excluding 10 years before diagnosis): Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 4.7 (1.1–20) [# not given] Level 3 OR = 1.7 (0.65–6.0) [# not given] Cumulative exposure:

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
	Multiple exposure metrics including average intensity, average probability, cumulative, years since first exposure, and age at first exposure were evaluated. **Duration and timing:** Duration and timing of exposure were evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (no) Level 2 (yes) Duration (overall): Level 1 (none) Level 2 (≤10 years) Level 3 (>10 years) Duration (excluding 10 years before diagnosis): Level 1 (none) Level 2 (≤10 years) Level 3 (>10 years) Cumulative exposure: Level 1 (none) Level 2 (<25 years) Level 3 (≥25 years) Time since first exposure: Level 1 (none) Level 2 (<20 years) Level 3 (≥20 years) Age at first exposure: Level 1 (none) Level 2 (<25 years) Level 3 (≥25 years) **Other exposures**: wood dust, solvents, and smoking.	Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 4.0 (0.92–17) [# not given] Level 3 OR = 2.2 (0.80–5.8) [# not given] Time since first exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 2.3 (0.52–10) [# not given] Level 3 OR = 2.8 (1.1–7.6) [# not given] Age at first exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 2.6 (1.1–6.5) [# not given] Level 3 OR = 3.1 (0.39–24) [# not given] No notable findings were reported between formaldehyde exposure and the risk of nasopharyngeal cancer when considering an induction period of 10 years.
Reference: Vaughan et al. (2000) **Population:** Males and females between the ages of 18 and 74 who were diagnosed with nasopharyngeal cancer between April 1987 and July 1993 and identified from five population-based cancer registries in the United States. Interviews were completed for 82% of eligible cases and 76% of eligible controls. **Outcome definition:** Diagnosis of nasopharyngeal (any histological type) was based on clinical records from cancer registries. Histological typing was reported and included for analysis with 28% diagnosed with undifferentiated and nonkeratinizing	**Exposure assessment:** Occupational histories obtained from interviews of cases and controls and identified job title, typical activities/duties, type of industry, and start and stop dates. Exposure was estimated by industrial hygienists by linking occupational history with participants' self-reported exposure information. Probability of exposure: definitely not or unlikely (<10%), possible (≥10 and <50%), probable (≥50 and <90%), and definite (≥90%). Jobs with potential exposure assigned estimated concentration levels based	**Internal comparisons:** **All histological types:** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. value) [117] Level 2 OR = 1.3 (0.8–2.1) [79] Maximum exposure: Level 1 OR = 1.4 (0.8–2.4) [60] Level 2 OR = 0.9 (0.4–2.3) [14] Level 3 OR = 1.6 (0.3–7.1) [5] *p*-trend (exposed) = 0.57 Duration: Level 1 OR = 0.8 (0.4–1.6) [24] Level 2 OR = 1.6 (0.7–3.4) [26] Level 3 OR = 2.1 (1.0–4.5) [29] *p*-trend (exposed) = 0.07 **Epithelial (NOS)** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. value) [12]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
carcinomas, 60% with differentiated squamous cell carcinomas, and 12% with epithelial carcinomas (not otherwise specified [NOS]). **Design:** Population-based case-control study of 196 cases of nasopharyngeal cancer. 244 controls identified from random digit dialing in the same geographic regions and frequency matched by age, sex, and cancer registry. **Analysis:** Ors calculated by logistic regression and adjusted for age, sex, race, SEER site, cigarette usage, proxy status, and education. An induction period of 10 years was also utilized to account for latency in evaluating duration and cumulative exposure. Results with and without this 10-year lag period were similar. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group B) with attenuation of association.	on TWA8: low (<0.10 ppm), moderate (≥0.10 and <0.50 ppm), and high (≥0.50 ppm). Multiple exposure metrics including probability of exposure and cumulative exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (never) Level 2 (ever) Maximum exposure: Level 1 (<0.10 ppm) Level 2 (0.10 to 0.50 ppm) Level 3 (>0.50 ppm) Duration: Level 1 (1 to 5 years) Level 2 (6 to 17 years) Level 3 (>18 years) **Other exposures:** Wood dust. [As noted in Appendix B.3.9: Wood dust evaluated as an independent risk factor for NPC controlling for formaldehyde and it was not a risk factor in this data set.]	Level 2 OR = 3.1 (1.0–9.6) [12] Maximum exposure: Level 1 OR = 4.0 (1.2–13.1) [11] Level 2 OR = 1.5 (0.2–13.9) [1] Level 3 no cases *p*-trend (exposed) = 0.46 Duration: Level 1 OR = 2.0 (0.4–9.8) [4] Level 2 OR = 4.0 (0.9–18.6) [3] Level 3 OR = 4.2 (0.8–21.5) [5] *p*-trend (exposed) = 0.036 **Differentiated Squamous Cell** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. value) [69] Level 2 OR = 1.5 (0.8–2.7) [49] Maximum exposure: Level 1 OR = 1.6 (0.8–3.0) [35] Level 2 OR = 1.2 (0.4–3.3) [10] Level 3 OR = 2.1 (0.4–12.3) [4] *p*-trend (exposed) = 0.32 Duration: Level 1 OR = 0.8 (0.3–2.0) [12] Level 2 OR = 1.8 (0.7–4.3) [17] Level 3 OR = 2.5 (1.1–5.9) [20] *p*-trend (exposed) = 0.033 **Undifferentiated and nonkeratinizing** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. value) [36] Level 2 OR = 0.9 (0.4–2.0) [18] Maximum exposure: Level 1 OR = 1.0 (0.4–2.4) [14] Level 2 OR = 0.5 (0.1–3.1) [3] Level 3 OR = 1.5 (0.2–14.7) [1] *p*-trend (exposed) = 0.72 Duration: Level 1 OR = 0.7 (0.3–2.2) [8] Level 2 OR = 1.0 (0.2–3.9) [6] Level 3 OR = 1.2 (0.3–4.8) [4] *p*-trend (exposed) = 0.82
Reference: Vaughan et al. (2000)	**Exposure assessment:** Occupational histories obtained from interviews of cases and controls and identified job title, typical activities/duties, type of industry, and start and stop dates. Exposure was estimated by industrial hygienists by linking occupational history with participants' self-reported exposure information. Probability of exposure: definitely not or unlikely (<10%), possible (≥10 and <50%), probable (≥50 and <90%), and	**Internal comparisons:** **Excluding undifferentiated and nonkeratinizing histological types** **Possible, probable or definite exposure** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. Value [# not given] Level 2 OR = 1.6 (1.0–2.8) [61] Duration: Level 1 OR = 0.9 (0.4–2.1) [16] Level 2 OR = 1.9 (0.9–4.4) [20] Level 3 OR = 2.7 (1.2–6.0) [25] *p*-trend (exposed) = 0.014 Cumulative exposure:

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
	definite (≥90%). Jobs with potential exposure assigned estimated concentration levels based on 8-h TWA: low (<0.10 ppm), moderate (≥10 and <50 ppm), and high (≥50 ppm). Multiple exposure metrics including probability of exposure and cumulative exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (never) Level 2 (ever) Duration: Level 1 (1 to 5 years) Level 2 (6 to 17 years) Level 3 (>18 years) Cumulative exposure: Level 1 (0.05 to 0.40 ppm-years) Level 2 (>0.4 to 1.10 ppm-years) Level 3 (>1.10 ppm-years) **Other exposures**: Wood dust was evaluated but not found to be a confounder.	Level 1 OR = 0.9 (0.4–2.0) [15] Level 2 OR = 1.8 (0.8–4.1) [22] Level 3 OR = 3.0 (1.3–6.6) [24] *p*-trend (exposed) = 0.033 **Probable or definite exposure** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. Value) [# not given] Level 2 OR = 2.1 (1.1–4.2) [27] Duration: Level 1 OR = 2.0 (0.8–5.0) [12] Level 2 OR = 3.3 (0.9–11.8) [9] Level 3 OR = 1.6 (0.5–5.6) [6] *p*-trend (exposed) = 0.069 Cumulative exposure: Level 1 OR = 1.9 (0.7–4.9) [12] Level 2 OR = 2.6 (0.7–9.5) [7] Level 3 OR = 2.2 (0.7–7.0) [8] *p*-trend (exposed) = 0.13 **Definite exposure** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. Value) [# not given] Level 2 OR = 13.3 (2.5–70) [10] Duration: Level 1 OR = not reported [5] Level 2 OR = not reported [2] Level 3 OR = not reported [3] *p*-trend (exposed) <0.001 Cumulative exposure: Level 1 OR = not reported [4] Level 2 OR = not reported [2] Level 3 OR = not reported [4] *p*-trend (exposed) <0.001 Results with and without this 10-year lag period were similar.
Reference: West et al. (1993) **Population:** Male and female Filipinos between the ages of 11 and 83 years recruited from the Philippine General Hospital and diagnosed prior to 1992. Among 234 suspicious cases, 9% refused biopsy and were excluded and 104 were pathologically confirmed as cases (Hildesheim et al., 1992), of which 100% agreed to participate. All 104 hospital controls agreed to participate while only 77% of community controls agreed to participate (Hildesheim et al., 1992). **Outcome definition:** Diagnosis of nasopharyngeal was confirmed by	**Exposure assessment:** Occupational history obtained by interview for all participants. Occupational exposure to formaldehyde classified by industrial hygienist as likely or unlikely. Multiple exposure metrics including analysis by length of exposure, length of exposure lagged 10 years, TSFE, and age at first exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Time since first exposure: Level 1 (never) Level 2 (<25 years) Level 3 (≥25 years)	**Internal comparisons:** Multivariate results from Table 4 in West et al. Time since first exposure: Level 1 OR = 1.0 (Ref. value) [75] Level 2 OR = 1.2 (0.41–3.6) [12] Level 3 OR = 4.0 (1.3–12.3) [14] Antimosquito coil exposure: Level 1 OR = 1.0 (Ref. value) [59] Level 2 OR = 1.4 (0.64–2.8) [24] Level 3 OR = 5.9 (1.7–20.1) [21] **Additional:** Bivariate results adjusted only for dust/exhaust from Table 1 Length of exposure (bivariate): Level 1 OR = 1.0 (Ref. value) [75]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
histological review for all cases. Histological typing not reported. **Design:** Hospital-based case-control study of 104 predominantly non-Chinese cases of nasopharyngeal cancer. 205 controls (104 hospital and 101 community cases) matched on gender, age, and hospital or neighborhood. **Analysis: RRs estimated by** Ors were calculated by conditional logistic regression and adjusted for education, years since first exposure to dust and exhaust fumes, smoking, antimosquito coils, herbal medicines, and diet including processed meats and fresh fish. **Related studies:** Hildesheim et al. (1992) **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) with attenuation of association.	Antimosquito coil exposure: Level 1 (never) Level 2 (<daily) Level 3 (≥ daily) Length of exposure: Level 1 (never) Level 2 (<15 years) Level 3 (≥15 years) Length of exposure lagged 10 years: Level 1 (no) Level 2 (<15 years) Level 3 (≥15 years) Time since first exposure: Level 1 (never) Level 2 (<25 years) Level 3 (≥25 years) Level 4 (≥35 years) Age at first exposure: Level 1 (never) Level 2 (<25 years) Level 3 (≥25 years) **Other exposures:** dust and exhaust exposure, fresh or salted fish consumption, smoking, antimosquito coils, and herbal medicines. Note: Independent testing of six brands of East Asian mosquito coils evaluated the emission rates of carbonyl compounds in the mosquito smoke and reported that formaldehyde and acetaldehyde had the highest emission rates (Liu et al., 2003). Among the three experiments on each of the six brands, the range of formaldehyde concentrations was from 0.87 µg/m^3 (0.7 ppb) to 25 µg/m^3 (20 ppb). [As noted in Appendix B.3.9, Control for mosquito coils may have underestimated the estimated effect of formaldehyde.]	Level 2 OR = 2.7 (1.1–6.6) [19] Level 3 OR = 1.2 (0.48–3.2) [8] Length of exposure lagged 10 years (bivariate): (Reference value included eight cases and three controls exposed only in the 10 years before diagnosis) Level 1 OR = 1.0 (Ref. value) [83] Level 2 OR = 1.6 (0.65–3.8) [11] Level 3 OR = 2.1 (0.70–6.2) [8] Age at first exposure (bivariate): Level 1 OR = 1.0 (Ref. value) [75] Level 2 OR = 2.7 (1.1–6.6) [16] Level 3 OR = 1.2 (0.47–3.3) [11] Time since first exposure (bivariate): Level 1 OR = 1.0 (Ref. value) [75] Level 2 OR = 1.3 (0.65–3.8) [12] Level 3 OR = 2.9 (1.1–7.6) [14] Time since first exposure (bivariate): Level 4 OR = 5.6 (0.58–52.9) [5] Authors noted that stronger effects were not evident among those considered most likely to have been exposed or most likely to have been exposed to high doses.
Reference: Roush et al. (1987b) **Population:** Males identified from the Connecticut Tumor Registry who died of any cause during 1935–1975. **Outcome definition:** Diagnosis of nasopharyngeal cancer based on case registration by the Connecticut Tumor Registry. Clinical records reviewed for >75% of cases. Histological typing not reported.	**Exposure assessment:** Occupational history obtained by city directories and death certificates, which yielded information on job, industry, employer, and year of employment. Exposure classification scheme based on potential for formaldehyde exposure, probability of exposure for each participant and each job-industry pair, and level of exposure.	Exposure level and timing of exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.0 (0.6–1.7) [21] Level 3 OR = 1.3 (0.7–2.4) [17] High exposure level and timing of exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.4 (0.6–3.1) [9] Level 3 OR = 2.3 (0.9–6.0) [7] **Additional:** Age of Death 68+

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Design: Population-based case-control study of 173 male cases of nasopharyngeal cancer. Controls were 605 males dying in Connecticut during the same time period, randomly selected from state death certificates. **Analysis:** Ors calculated by logistic regression and adjusted for age at death, year at death, and availability of occupational information. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) with attenuation of association.	Probability of exposure defined as unexposed, possibly exposed, probably exposed, or definitely exposed. Level of exposure estimated as zero, low (<1 ppm), and high (≥1 ppm). Among those probably exposed to some level of formaldehyde for most of their working lifetime, the extent and level of exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure level and timing of exposure: Level 1 (unexposed) Level 2 (probably exposed most of working life) Level 3 (probably exposed most of working life and probably exposed 20+ years before death) High exposure level and timing of exposure: Level 1 (unexposed) Level 2 (probably exposed most of working life and probably to high level in some year) Level 3 (probably exposed most of working life and probably exposed to high level 20+ years before death) **Other exposures:** Not evaluated as potential confounders. [As noted in Appendix B.39: Exposure to wood dust was not found to be a risk factor for all nasal cancers (NPC + SNC). This suggests a lower potential for confounding by wood dust.]	High exposure level and timing of exposure: Level 3 OR = 4.0 (1.3–12.0) [6]
Reference: Olsen et al. (1984) **Population:** Male and females linked to the Danish Cancer Registry during 1970–1982. **Outcome definition:** Diagnosis of cancer of the nasopharynx based on ICD code 146 from Registry data. 9% of nasopharyngeal cases were sarcomas and 91% were carcinomas. Sarcomas were excluded but	**Exposure assessment:** Employment histories from 1964 maintained by Danish Cancer Registry. Occupational exposures estimated by industrial hygienists based on industries or occupations considered to have certain or probably exposure. Authors reported that 4.2 and 0.1% of control males and females, respectively, were exposed to formaldehyde.	**Internal comparisons:** Occupational exposure: Men [≈196 (91% of 215)] Level 1 RR = 1.0 (Ref. value) [# not given] Level 2 RR = 0.7 (0.3–1.7) [# not given] Women [≈90 (91% of 99)] Level 1 RR = 1.0 (Ref. value) [# not given] Level 2 RR = 2.6 (0.3–21.9) [# not given] Time since first exposure: No evidence of association (data not shown).

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
gender-specific case counts were not provided for carcinomas. **Design:** Population-based case-control study of 266 cases of nasopharyngeal cancer. Three controls per case were selected for the same distributions of age, sex, and year of diagnosis as cases. **Analysis:** OR calculated using programs developed by Rothman and Boice (1979). **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) with attenuation of association.	**Duration and timing:** Exposure period starting at 1964. Exposure to formaldehyde may have been between 0 and 20 years depending on when first exposed during the define exposure period. **Variation in exposure:** Occupational exposure: Level 1 (no exposure) Level 2 (ever exposed) Time since first exposure: Level 1 (≤10 years) Level 2 (>10 years) **Coexposures:** Coexposure evaluated included: wood dust, paint, lacquer, and glue. [As noted in Appendix B.3.9 Wood dust is associated with SNC and was evaluated as a potential confounder of NPC but was not a risk factor.]	
Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories which produced formaldehyde. Cohort mortality followed from 1941 through 2012. Cause of deaths was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378 deaths through 2012. Vital status was 98.9% complete through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from nasopharyngeal cancer. **Design:** Cohort mortality study with external comparison group with a nested case-control study. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003)	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941–1982. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. [As noted in Appendix B.3.9: Styrene is associated with LHP cancers but not URT cancers. Asbestos is associated with URT cancers, but not this outcome. Other coexposures are not known risk factors for this outcome.]	**External comparisons:** Exposed: Observed: 1 deaths Expected: 1.7 deaths $SMR_{Exposed}$ = 0.59 (0.03–2.90) [†] [1] [†]EPA derived confidence intervals for the SMRs using Fischer's Exact method (See Armitage and Cullis (1971); Snedecor and Cochran (1980) for nonzero SMRs and using the Mid-P method See Rothman and Boice (1979).

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Confidence in effect estimates:[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency analysis with attenuation of association. Low sensitivity (few cases).		
Reference: Meyers et al. (2013) **Population:** 11,043 workers in 3 U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion. **Outcome definition:** Death certificates used to determine the underlying cause of death from nasopharyngeal cancer (ICD code in use at time of death). Histological typing not provided. **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Stayner et al. (1985) Stayner et al. (1988) Pinkerton et al. (2004) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984 with 12–73 within each department. Formaldehyde levels across all departments and facilities were similar. Geometric TWA8 exposures ranged from 0.09–0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm, (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 to 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were not evaluated for this cancer. **Variation in exposure:** Not evaluated. **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	**External comparisons:** SMR = 0 (0–2.77) [0]
Reference: Siew et al. (2012) **Population:** All Finnish men born during 1906–1945 who participated in census and were employed in 1970 (*n* = 1.2 million). Vital status was "virtually complete."	**Exposure assessment:** Individual-level exposure estimates based on matching occupations listed in the census to the Finnish job-exposure matrix which covers major occupational exposures and provided exposure estimates for formaldehyde.	**Internal comparisons:** Exposure to formaldehyde: Level 1 RR = 1.00 (Ref. value) [144] Level 2 RR = 0.87 (0.34–2.20) [5]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Outcome definition: Diagnosis of cancer reported to the Finnish Cancer Registry. **Design:** Prospective national cohort incidence study with internal comparison groups. **Analysis:** RRs calculated controlling for sex, age, socioeconomic status, period of follow-up, and smoking. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association. Low sensitivity (low background rate of cancer).	**Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (none) Level 2 (any) **Coexposures:** Wood dust exposures were controlled for in analyses.	
Reference: Yang et al. (2005) **Population:** Taiwanese men and women from 325 families which had two or more nonparent-offspring family members diagnosed with nasopharyngeal cancer (other first-, second-, or third-degree relatives). Cases were identified from the national tumor registry. **Outcome definition:** Diagnosis of incident nasopharyngeal cancer was confirmed by histological review for all cases (*n* = 502). An earlier report on 375 cases from the same series reported >90% diagnosed with nonkeratinizing and undifferentiated carcinomas and 9% with squamous cell carcinoma Hildesheim et al. (2001) **Design:** Family-based case-control study of nasopharyngeal cancer. Cases from high-risk families were compared to two controls groups. Initial set of 375 cases reported by Cheng et al. (1999) had a 99% occupational questionnaire response rate. Similar data were available for 60% of new cases (*n* = 127) with the remainder considered to be missing at random. Overall case response rate is 85%. The Family control groups consisted of up to five unaffected siblings, the	**Exposure assessment:** Occupational history obtained from interviews of cases and controls for jobs held for ≥1 year since age 16 and identified job title, typical activities/duties, type of industry, and tools and/or materials used. Industrial hygienist assigned Standard Industry Classification/Standard Occupational Classification codes to jobs, assigning each a probability and intensity of exposure on a 0 (not exposed) to 9 (strong) scale. Cumulative exposure defined as the product of average intensity and duration. **Duration and timing:** Duration was evaluated as a component of the cumulative exposure score. The timing of exposure was not evaluated. **Variation in exposure:** Intensity scored 0–9 Duration in years Cumulative exposure (Intensity*duration): Level 1 (none) Level 2 (<25) Level 3 (≥25)	**Internal Comparisons:** Familial cases (*n* = 502) compared to Family controls (*n* = 1,944) Cumulative exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.03 (0.60–1.76) [# not given] Level 3 OR = 1.31 (0.87–1.97) [# not given] Familial cases (*n* = 502) compared to population controls (*n* = 327) Cumulative exposure (Intensity*duration): Level 1 OR = 1.00 (Ref. value) [# not given] Level 2 OR = 1.30 (0.70–2.39) [# not given] Level 3 OR = 4.29 (2.45–7.51) [# not given]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
parents of affected subjects, or spouses of affected cases' children (*n* = 1,944; participation rate not given). Population controls (*n* = 327; 88% response rate) were originally matched to a subset of cases accrued at an earlier time (*n* = 375) matched on age, sex and residence (Cheng et al., 1999). The same population controls and cases were later augmented with additional cases to encompass the total of 502 cases. **Analysis:** For the Family controls, Ors were calculated by conditional logistic regression matched on family. For the Population controls, OR's were calculated by unconditional logistic regression controlling for age and sex; however, while population controls were originally matched on residence, residence was not controlled for in this later analysis. **Related studies:** Hildesheim et al. (1997); Hildesheim et al. (2001); Cheng et al. (1999) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association. Confounding possible.	**Other exposures:** smoking, betel nut use, wood exposure, and salted fish consumption which were not controlled for in the analysis. [As noted in Appendix B.3.9: In this study, smoking was inversely associated with NPC. Since smoking is positively associated with formaldehyde, there may be negative confounding by smoking in this study.]	
Reference: Yu et al. (2004) **Population:** Deceased male and female restaurant workers who died during 1986–1995 and were registered as union members by four major Chinese-style restaurant workers' unions in Hong Kong (*n* = 1,225). **Outcome definition:** Underlying cause of death from nasopharyngeal cancer (ICD-9: 147) obtained from the Hong Kong Census and Statistics Department (*n* = 29). Cause of death available for more than 80% of restaurant workers. Histological typing not reported.	**Exposure assessment:** Occupational history obtained from union records. Waiters, waitresses and kitchen workers presumed to be exposed to formaldehyde based on independent studies of air quality from the kitchen exhausts of Hong Kong restaurants (Ho et al., 2006b; EHS Consultants Ltd., 1999) Note: Ho et al. (2006b) reported time-averaged formaldehyde concentrations at Chinese restaurants in Hong Kong were reported as high as 249 ppb (306 μg/m^3). The Hong Kong Environmental Protection Department survey of indoor air at local restaurants reported	**Internal Comparisons:** Male and female (Waiters and waitresses) Wait staff cases compared to kitchen worker controls MOR = 2.53 (1.01–6.36) [21] Male only (Waiters) Wait staff cases compared to kitchen worker controls MOR = 2.61 (1.02–6.69) [17] **External Comparisons:** Male and female (Waiters and waitresses) Wait staff cases compared to general Hong Kong male and female population controls MOR = 3.28 (2.08–5.16) [21]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Design: Mortality odds ratio where cases are deaths from nasopharyngeal cancer and controls are deaths from all other causes of death after excluding cancer. Internal control group composed of other deceased kitchen workers. External control group composed of all noncancer deaths from the general population in Hong Kong. **Analysis:** Mortality odds ratios (MORs) based on the internal control group were calculated by logistic regression controlling for sex, age at death, year of death, and place of origin. For the external control group, MORs were calculated by logistic regression controlling for sex, age at death, and year of death. **Related studies:** Ho et al. (2006a) EHS Consultants Ltd. (1999) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group C) and lack of latency analysis with attenuation of association. Confounding possible.	a mean formaldehyde concentration of 162 µg/m^3 with a high value of 975 µg/m^3 (EHS Consultants Ltd., 1999). **Duration and timing:** Duration of exposure was evaluated based on length of restaurant union membership. **Variation in exposure:** Cumulative exposure: Level 1 (none) Level 2 (<15 years union membership) Level 3 (16–24 years union membership) Level 4 (≥25 years union membership) **Other exposures:** not evaluated. Wait staff exposed to other sources of formaldehyde such as environmental tobacco smoke, furniture, carpeting, and room partitions made of plywood and fiberboard, which are not shared by kitchen staff. [As noted in Appendix B.3.9: Smoking was evaluated as a potential confounder because 49% of staff smoked compared to 27% of population, but it was insufficient to explain the observed effects.]	Male only (Waiters) Wait staff cases compared to general Hong Kong male population controls MOR = 3.02 (1.82–5.00) [17] Male only (Waiters) Cumulative exposure: Level 1 MOR = 1.00 (Ref. Value) [3,225] Level 2 MOR = 2.50 (1.14–5.49) [7] Level 3 MOR = 3.41 (1.56–7.45) [7] Level 4 MOR = 3.75 (1.12–12.54) [3] Female only (Waitresses) Wait staff cases compared to general Hong Kong female population controls MOR = 4.58 (1.63–12.86) [4]
Reference: Hansen and Olsen (1995) **Population:** 2,041 men with cancer who were diagnosed during 1970–1984 and whose longest work experience occurred at least 10 years before cancer diagnosis. Identified from the Danish Cancer Registry and matched with the Danish Supplementary Pension Fund. Ascertainment considered complete. Pension record available for 72% of cancer cases. **Outcome definition:** Nasopharyngeal cancer (ICD-7: 146) listed on Danish Cancer Registry file. Histological typing not reported. **Design:** Proportionate incidence study with external comparison group.	**Exposure assessment:** Individual occupational histories including industry and job title established through company tax records to the national Danish Product Register. Subject were considered to be exposed to formaldehyde if: (1) they had worked in an industry known to use more than 1 kg formaldehyde per employee per year and (2) subject's longest single work experience (job) in that industry since 1964 was ≥10 years prior to cancer diagnosis. **Duration and timing:** Exposure period not stated. Based on date of diagnosis during 1970–1984, and the requirement of exposure more than 10 years prior to diagnosis, the approximate period was 1960–1974.	**External comparisons:** Overall (exposure to formaldehyde ≥10 years prior to cancer diagnosis) SPIR = 1.3 (0.3–3.2) [4]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Analysis: Standardized proportionate incidence ratio calculated as the proportion of cases for a given cancer in formaldehyde-associated companies relative to the proportion of cases for the same cancer among all employees in Denmark. Adjusted for age and calendar time. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association. Low sensitivity for NPC (few cases).	**Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated for potential confounding [As noted in Appendix B.3.9: While other coexposures were not evaluated, the overall correlation between coexposures in multiple occupational industries is likely to be low.]	
Reference: Malker et al. (1990) **Population:** Employed Swedish men newly diagnosed with nasopharyngeal cancer identified during 1961–1979 registered by the Swedish Cancer-Environment Registry. **Outcome definition:** Microscopic confirmation obtained for 99.6% of nasopharyngeal cases. Squamous cell carcinomas constituted 48% of cases with 37% classified as unspecified carcinomas, 5% transitional cell carcinomas, and 3% adenocarcinomas. **Design:** Population-based standardized incidence ratio study of 471 incidence cases of nasopharyngeal cancer compared to expected number of cases among men in occupational groups defined by employment in 1960. **Analysis:** SIRs calculated as the ratio of observed to expected cases of nasopharyngeal cancer. **Confidence in effect estimates:**[a] **Low ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) and lack of latency analysis with attenuation of association.	**Exposure assessment:** Occupations presumed to be exposed to formaldehyde. **Duration and timing:** Duration and timing of exposure were not evaluated. **Variation in exposure:** Occupation and industry **Coexposures:** Not evaluated as potential confounders. [As noted in Appendix B.3.9: Wood dust is associated with URT cancers and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.	**External comparisons:** Occupation Glassmakers SIR = 6.2 (1.58–16.87)[†] [3] Bookbinders SIR = 6.1 (1.55–16.59)[†] [3] Shoemakers SIR = 3.8 (1.39–8.42)[†] [5] Industry Shoe repair SIR = 4.0 (1.47–8.87)[†] [5] Fiberboard plant SIR = 3.9 (1.24–9.40)[†] [4] [†]EPA derived Cis using the Mid-P Method (See (Rothman and Boice, 1979))

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Confounding possible. Low sensitivity (few exposed cases).		
Reference: Vaughan (1989) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System during 1980−1983. Participation for all cases was 68.7 and 80.0% for controls. **Outcome definition:** Diagnosis of nasopharyngeal cancer based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates. Nonsquamous cell cancers were excluded from the study. **Design:** Population-based, case-control study of 21 cases with nasopharyngeal cancer. 552 controls were identified by random digit dialing in same geographic area. **Analysis:** Ors were calculated by logistic regression and adjusted for age, gender, and race. Induction periods were evaluated. **Related studies:** Vaughan et al. (1986a, 1986b) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association. Low sensitivity (rare exposure).	**Exposure assessment:** Presumed exposure to formaldehyde. Interview-based information on lifetime occupational history by job type and industry. Occupations evaluated for both no lag and 15-year lag time between recent exposure and diagnosis. **Duration and timing:** Duration and timing of exposure were evaluated. **Variation in exposure:** Occupation and industry Duration: Level 1 (unexposed) Level 2 (1 to 9 years) Level 3 (>10 years) **Other exposures:** Not evaluated as potential confounders. [As noted in Appendix B.3.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. ~50% of cases interviews completed by next of kin. May result in poorer quality exposure data and a bias toward the null.]	**Internal comparisons:** Carpenter (lagged 15 years) All Industries: OR = 4.5 (1.1−18.7) [3] All Industries by Duration: Level 1 OR = 1.0 (Ref. value) Level 2 OR = 1.6 (not provided) Level 3 OR = 12.4 (not provided) Chi^2 trend = 8.65 (p = 0.01)[†] Carpenter (lagged 15 years) Construction industry: OR = 6.8 (1.6−28.2) [3] Construction by Duration: Level 1 OR = 1.0 (Ref. value) Level 2 OR = 2.1 (not provided) Level 3 OR = 31.8 (not provided) Chi^2 trend = 14.86 (p = 0.0006)[†] Food Service (lagged 15 years) All Industries: OR = 1.8 (0.6−5.7) [4] All Industries by Duration: Level 1 OR = 1.0 (Ref. value) Level 2 OR = 1.6 (not provided) Level 3 OR = 4.0 (not provided) Chi^2 trend = 1.65 (p = 0.44)[†] Food Service (lagged 15 years) Retail Trade: OR = 1.9 (0.5−6.9) [3] Retail Trade by Duration: Level 1 OR = 1.0 (Ref. value) Level 2 OR = 1.4 (not provided) Level 3 OR = 9.3 (not provided) Chi^2 trend = 2.21 (p = 0.33)[†] [†]EPA computed p-value assuming 2 d.f.
Reference: Vaughan et al. (1986a) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System during 1980−1983. Participation for all cases was 68.7 and 80.0% for controls.	**Exposure assessment:** Interview-based information on lifetime occupational exposure to formaldehyde with cases, next of kin, and controls. Exposure from available hygiene data, NIOSH and other data, and NCI job-exposure linkage system. Multiple exposure metrics including intensity, # of years exposed, and exposure score based on the sum of	**Internal comparisons:** Intensity of exposure: Level 1 OR = 1.0 (Ref. value) [16] Level 2 OR = 1.2 (0.5−3.3) [7] Level 3 OR = 1.4 (0.4−4.7) [4] Number of years exposed: Level 1 OR = 1.0 (Ref. value) [16] Level 2 OR = 1.2 (0.5−3.1) [8] Level 3 OR = 1.6 (0.4−5.8) [3]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Outcome definition: Diagnosis of nasopharyngeal cancer based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates. Histological typing not reported; however, according to Vaughan (1989), 6 cases were nonsquamous cell cancers. **Design:** Population-based, case-control study of 27 cases with nasopharyngeal cancer. 552 controls were identified by random digit dialing in same geographic area. **Analysis:** Ors were calculated by logistic regression and adjusted for cigarette smoking and ethnic origin. Induction periods were evaluated. **Related studies:** Vaughan et al. (1986b); Vaughan (1989) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association.	# years spent per job weighted by estimated formaldehyde level were evaluated. Exposure score calculated for both no lag and 15-year lag time between recent exposure and diagnosis. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Intensity of exposure: Level 1 (background) Level 2 (low) Level 3 (medium or high) Number of years exposed: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years) Exposure score (no lag): Level 1 (0 to 4) Level 2 (5 to 19) Level 3 (≥20) Exposure score (15-year lag): Level 1 (0 to 4) Level 2 (5 to 19) Level 3 (≥20) **Other exposures:** Not evaluated as potential confounders. [As noted in Appendix B.3.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. However, as this is a case-control study the correlation between formaldehyde and wood dust is expected to be small and thus wood dust would not be expected to be a confounder.]	Exposure score (no lag): Level 1 OR = 1.0 (Ref. value) [21] Level 2 OR = 0.9 (0.2–3.2) [3] Level 3 OR = 2.1 (0.6–7.8) [3] Exposure score (15-year lag): Level 1 OR = 1.0 (Ref. value) [21] Level 2 OR = 1.7 (0.5–5.7) [4] Level 3 OR = 2.1 (0.4–10.0) [2] **Additional:** Excluding Next of Kin Interviews [15] Exposure score (no lag): Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.1 (0.2–5.5) [# not given] Level 3 OR = 2.2 (0.4–10.8) [# not given] Exposure score (15-year lag): Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.4 (0.3–7.3) [# not given] Level 3 OR = 3.1 (0.6–15.4) [# not given]
Reference: Vaughan et al. (1986b) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System between 1980 and 1983. Participation for all cases was 68.7 and 80.0% for controls. **Outcome definition:** Diagnosis of nasopharyngeal cancer based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates. Histological typing	**Exposure assessment:** Interview-based information on lifetime occupational history and residential history from cases, next of kin, and controls. Multiple exposure metrics including type of dwelling (i.e., mobile home) and use of particleboard or plywood were evaluated. **Duration and timing:** Exposure period since 1950. Duration of exposure was evaluated. **Variation in exposure:**	**Internal comparisons:** Lived in mobile home: Level 1 OR = 1.0 (Ref. value) [19] Level 2 OR = 3.0 (1.2–7.5) [8] Lived in mobile home (lagged 15 years): Level 1 OR = 1.0 (Ref. value) [24] Level 2 OR = 3.0 (0.8–11.2) [3] Years of residence in mobile home: Level 1 OR = 1.0 (Ref. value) [19] Level 2 OR = 2.1 (0.7–6.6) [4] Level 3 OR = 5.5 (1.6–19.4) [4] Years of exposure to particleboard or plywood:

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
not reported; however, according to Vaughan (1989), 6 cases were nonsquamous cell cancers. **Design:** Population-based, case-control study of 27 cases with nasopharyngeal cancer. 552 controls were identified by random digit dialing in same geographic area. **Analysis:** Ors were calculated by multiple logistic regression and adjusted for cigarette smoking and ethnic origin. **Related studies:** Vaughan et al. (1986a, 1986b); Vaughan (1989) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association. Low sensitivity (rare exposure).	Lived in a mobile home: Level 1 (no) Level 2 (yes) Lived in a mobile home (lagged 15 years): Level 1 (no) Level 2 (yes) Years of residence in mobile home: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years) Years of exposure to particleboard or plywood: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years) Mobile home exposures (lagged 15 years): Level 1 (none) Level 2 (occupation only) Level 3 (mobile home only) Level 4 (both) Note: The majority (84%) of mobile homes in the United States at about this time were reported to have mean formaldehyde exposures in excess of 100 ppb, with 22% having mean exposures in excess of 500 ppb (Breysse (1984) as cited in IPCS (1989). **Coexposures:** Not evaluated. Information on occupational exposures provided in Vaughan et al. (1986a). [As noted in Appendix B.3.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. However, as this is a case-control study the correlation between formaldehyde and wood dust is expected to be small and thus wood dust would not be expected to be a confounder.]	Level 1 OR = 1.0 (Ref. value) [17] Level 2 OR = 1.4 (0.5–3.4) [6] Level 3 OR = 0.6 (0.2–2.3) [4] Mobile home exposures (lagged 15 years): Level 1 OR = 1.0 (Ref. value) [15] Level 2 OR = 1.7 (0.5–5.7) [4] Level 3 OR = 2.8 (1.0–7.9) [6] Level 4 OR = 6.7 (1.2–38.9) [2] **Additional:** Excluding Next of Kin Interviews [15] Lived in mobile home: Level 1 OR = 1.0 (Ref. value) [10] Level 2 OR = 2.8 (0.9–8.8) [5]

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.9. SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Sinonasal cancer

Epidemiological evidence

The most specific classification of sinonasal cancer diagnosis commonly reported across the epidemiological literature has been based on the first three digits of the Seventh, Eighth or Ninth Revision of the ICD code (i.e., Malignant neoplasm of nose, nasal cavities, middle ear and accessory sinuses ICD-7/8/9: 160), although some studies did report the histological type of cancer (i.e., squamous cell carcinoma and adenocarcinoma).

Evidence of an association between formaldehyde exposure and the risk of developing or dying from sinonasal cancer was available from 20 epidemiological studies—7 case-control studies (Teschke et al., 1997; Roush et al., 1987b; Pesch et al., 2008; Olsen and Asnaes, 1986; Mayr et al., 2010; Luce et al., 2002; D'Errico et al., 2009) and 13 cohort studies (Stroup et al., 1986; Siew et al., 2012; Meyers et al., 2013; Jakobsson et al., 1997; Hayes et al., 1990; Hansen and Olsen, 1995; Coggon et al., 2014; Bertazzi et al., 1986; Beane Freeman et al., 2013);(Walrath and Fraumeni, 1983, 1984; Levine et al., 1984a; Harrington and Oakes, 1984). One additional study, (Luce et al., 2002), combined 12 other case-control studies in a pooled analysis of occupational exposures using a common protocol of standardized questionnaires and standardized exposure classifications.[28] The results of this pooled analysis of original primary data across studies (Luce et al., 2002) are included in place of those from the 12 individual studies that are listed under "Related studies" in Table 3-33 for Luce et al. (2002). The outcome-specific evaluations of confidence in the precise effect estimate of an association from each study are provided in Appendix B.3.9. Three sets of reported results from Mayr et al. (2010), d'Errico et al. (2009), and Harrington and Oakes (1984) were classified as *not informative* due to multiple biases and uncertainties; for details see Appendix B.3.9. Details of the reported results of these studies are provided in the evidence table for sinonasal cancer (see Table 3-33) following the causal evaluation.

Consistency of the observed association

Seventeen informative studies reported risks of sinonasal cancer among study subjects with formaldehyde exposure based on occupational history. These studies examined different populations, in different locations, under different exposure settings, and used different study designs. For sinonasal cancer, it is important to consider the histological subtype or types in each report (squamous cell carcinoma, adenocarcinoma, or mixed). The study results presented in Table 3-33 (by confidence level and publication date) detail all of the reported associations. One

[28]Note the pooled study by Luce et al. (2002) includes data from 12 publications and thus represents substantially more information than a single result. The references for the source data are: Zheng et al. (1992); Vaughan et al. (1986a, 1986b); Vaughan (1989); Vaughan and Davis (1991); Merler et al. (1986); Magnani et al. (1993); Luce et al. (1992); Luce et al. (1993); Leclerc et al. (1994); Hayes et al. (1986b); Hayes et al. (1986a); Hardell et al. (1982); Comba et al. (1992a); Comba et al. (1992b); Bolm-Audorff et al. (1990); Mack and Preston-Martin (Unpub. Data presented in Luce et al. (2002)); Brinton et al. (1984); Brinton et al. (1985).

additional study (Andjelkovich et al., 1995) reported zero cases of SNC among 3,929 U.S. workers exposed to formaldehyde over 83,064 person-years but reported no data on the number of expected cases and thus was not included here.[29]

Sinonasal cancer is exceedingly rare with expected rates of 0.6 cases per 100,000 people each year (Curado et al., 2007). Many of these cohort studies lacked the statistical sensitivity to detect an association with formaldehyde; 8 of 12 cohort studies reported zero cases in their study populations and all but 1 cohort study (Beane Freeman et al., 2013) were classified with low confidence. For such rare cancers, case-control studies can often be the most informative study design.

Of the nine studies that did observe cases of sinonasal cancer, results from six reported increased risks of sinonasal cancer that appeared to be associated with exposure to formaldehyde—four of six sets of results had been classified with *medium* confidence (Roush et al., 1987b; Olsen and Asnaes, 1986; Luce et al., 2002; Beane Freeman et al., 2013) and two with *low* confidence (Teschke et al., 1997; Hansen and Olsen, 1995). Each of the other three sets of results that did not report some increase in risk associated with formaldehyde exposure had been in the group classified with *low* confidence, in part due to their lack of sensitivity to detect a true effect (Siew et al., 2012; Pesch et al., 2008; Coggon et al., 2014).

As discussed in a following section on the potential for confounding, wood dust is a very strong risk factor for sinonasal cancer and because coexposure to wood dust may also be correlated with formaldehyde exposures (e.g., in carpentry and other woodworking occupations), wood dust could have been a potent confounder that might have caused the reported effects of formaldehyde to appear inflated due to positive confounding. However, the evaluation of studies in Appendix B.3.9 screened each set of results for potential confounding by wood dust and retained only those results that either controlled for coexposures to wood dust using statistical adjustment in regression analyses or by restricting analyses to workers without coexposure to wood dusts (Teschke et al., 1997; Roush et al., 1987b; Olsen and Asnaes, 1986; Luce et al., 2002; Hansen and Olsen, 1995; Beane Freeman et al., 2013), or those results from studies that were unlikely to have had occupational coexposure to wood dusts (Teschke et al., 1997; Siew et al., 2012; Coggon et al., 2014).

As can be seen in Table 3-33, and in Figure 3-20, which shows the *medium* confidence studies, associations were stronger for adenocarcinomas than for squamous cell carcinomas. However, both histological cell type groupings, and a mixed-type group, yielded results which were consistently elevated—with a clear demonstration of statistical significance for the adenocarcinomas.

In summary, the majority of these studies of different populations, in different locations, exposure settings, and using different study designs reported increased risks of sinonasal cancer

[29]For Andjelkovich et al. (1995), assuming a rate of SNC for U.S. workers of 0.6 per 100,000 person-years (Curado et al., 2007), the expected number of cases would have been 0.33 and the ~SMR = 0 (95% CI 0, 5.99).

associated with formaldehyde exposure that was unlikely to have been confounded by coexposure to wood dust.

Strength of the observed association

While reported relative effect estimates were largely elevated above the null value of unity (1.0) across the sets of results that detected cases of sinonasal cancer, the magnitude of the relative effect estimates varied with the quality of the exposure assessment and stratification by histological cell type. The adenocarcinoma results classified with *medium* confidence reported three-fold (and higher) increased risks of sinonasal cancer that appeared to be associated with higher exposure to formaldehyde after controlling for wood dust (Olsen and Asnaes, 1986; Luce et al., 2002; Hansen and Olsen, 1995). Olsen and Asnaes (1986) reported results among men for adenocarcinoma adjusted for wood dust and among those never exposed to wood dust: for "ever" vs "never" exposed to formaldehyde, the RR adjusted for ever being exposed to wood dust was 2.2 (95% CI 0.7, 7.2; 17 exposed cases) while the RR for formaldehyde among men never exposed to wood dust was 7.0 (95% CI: 1.1, 43.9; one exposed case after excluded men ever exposed to wood dust). Further restricting formaldehyde exposures to those first exposed more than 10 years prior to cancer incidence, the RR was 9.5 (95% CI 1.6, 57.8; one exposed case). Luce et al. (2002) reported increased risks for men with the highest cumulative formaldehyde exposure adjusted for wood dusts (OR = 3.0; 95% CI 1.5, 5.7; 91 cases) and for women (OR = 5.8; 95% CI 1.7, 19.4; five cases). Hansen and Olsen (1995), a low confidence study, reported that for formaldehyde exposures more than 10 years prior to cancer incidence, the Standardized Proportional Incidence Ratio was 3.0 (95% CI 1.4, 5.7; nine cases). One adenocarcinoma study that was classified with *low* confidence and was not able to report results by level of formaldehyde exposure, found a decreased risk of sinonasal cancer among woodworkers ever exposed to formaldehyde [Pesch et al. (2008): OR = 0.46; 95% CI 0.14, 1.54]. Pesch et al. (2008) was the only case-control study of sinonasal cancer that relied on prevalent cases and included cases accrued over a 10-year period. Since the controls in Pesch et al. (2008) were accident victims who were frequency matched on age (<60 vs. 60+ years), it is possible that the prevalent cases available at the time of the study could have been selected for survival, which may have resulted in a downward bias and may explain the inverse findings for this study.

The squamous cell carcinoma study results classified with *medium* confidence reported 1.5-to 2-fold increased risks of sinonasal cancer that appeared to be associated with higher exposure to formaldehyde after controlling for wood dust (Olsen and Asnaes, 1986; Luce et al., 2002), although one study result classified with *low* confidence found no association between sinonasal cancer in the 5% of cases "ever" exposed to formaldehyde (Siew et al. (2012): OR = 0.97; 95% CI 0.47, 2.00).

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants started prior to their diagnoses of sinonasal cancer. Three studies provided analyses of the temporal relationship showing some evidence of the effect of TSFE on the risk of dying from sinonasal cancer (Roush et al., 1987b; Olsen and Asnaes, 1986; Luce et al., 2002). Lagging formaldehyde exposures by 10 or 20 years to account for cancer latency increased the observed effects only slightly for adenocarcinoma results (Olsen and Asnaes, 1986; Luce et al., 2002) and for mixed cell type cancers (Roush et al., 1987b); but not for squamous cell carcinomas (Olsen and Asnaes, 1986). It is notable that for nasopharyngeal cancer in the tissue adjacent to the sinonasal tissues, the effect of latency on the temporal relationship between formaldehyde exposure and cancer mortality was generally longer than 25 years. Only one study of sinonasal cancer examined a lag of 20 years (Luce et al., 2002), and none examined the effect of an even longer latency. If the effect of exposure on the occurrence of sinonasal cancer took longer than the 20 years, then differences in results between lagged and unlagged exposure analyses would be consistent with the available epidemiological data.

Exposure-response relationship

Exposure-response relationships were not typically examined in these studies, most likely due to the rarity of cases in all of the studies except in the large, pooled study of information from 12 publications (Luce et al., 2002); see Table 3-33 for details). No results showing associations with duration of exposure were reported, but Luce et al. (2002) did state that even though their studies reported primarily on cumulative exposure, "All exposure variables (probability, maximum level, and duration) were associated with the risk of adenocarcinoma." The majority of studies reported only comparisons of exposed versus unexposed subjects. Hansen and Olsen (1995) did report an increase in risk among formaldehyde-exposed blue-collar worker (OR = 3.0; 95% CI 1.4, 5.7) compared to exposed white-collar workers whose likely formaldehyde exposures were considered to have been lower (OR = 0.8; 95% CI 0.02, 4.4). Luce et al. (2002) pooled 196 cases of sinonasal adenocarcinoma and 432 cases of squamous cell carcinoma and was able to contrast risks in three levels of exposure probability with the risk in the unexposed. An exposure-response relationship for adenocarcinoma, controlling for coexposure to wood dust, was observed for both men and women (see Table 3-33) with the highest risks among those with the highest probability of exposure. The OR among men with the highest cumulative exposure was 3.0 (95% CI 1.5, 5.7), while it was 5.8 (95% CI 1.7, 19.4) among women. Among men with adenocarcinoma, the odds ratios adjusted for wood dust increased from OR = 0.7 (95% CI: 0.3, 1.9; six cases) among those with 'low' cumulative exposure, to OR = 2.4 (95% CI: 1.3, 4.5; 31 cases) among those with 'medium' cumulative exposure, to OR = 3.0 (95% CI: 1.5, 5.7; 91 cases) among those with 'high' cumulative exposure.

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias is an unlikely bias in the epidemiological studies of sinonasal cancer as the case-control studies evaluated exposure status without regard to outcome status and most had participation levels of 85–100%, although one case-control study of prevalent cases accrued over long periods of time had lower participation levels (67% in Pesch et al. (2008)). The cohort study (Hansen and Olsen, 1995) included 72% of eligible participants. Selection biases could obscure a truly larger effect of formaldehyde exposure in analyses based on "external" comparisons with mortality in the general population (Hansen and Olsen, 1995), but would not influence analyses using "internal" or matched comparison groups (Roush et al., 1987b; Pesch et al., 2008; Olsen and Asnaes, 1986; Luce et al., 2002). Information bias from the use of indirect exposure measures is unlikely to have resulted in bias away from the null, however random measurement error or nondifferential misclassification is almost certain to have resulted in some bias toward the null among these studies of sinonasal cancer.

Confounding is a potential bias that could arise if another cause of sinonasal cancer were also associated with formaldehyde exposure. Chemicals and other coexposures that have not been independently associated with sinonasal cancer are not expected to confound results. Other known risk factors for sinonasal cancer include wood dust (Olsen and Asnaes, 1986; Hansen and Olsen, 1995), smoking, and alcohol consumption (Vaughan, 1989). While smoking and alcohol may be independent risk factors for sinonasal cancer they are unlikely to be related to formaldehyde exposure and therefore unlikely to be across-the-board confounders. Wood dust, however, is a potential confounder as many wood-related jobs also have exposures to formaldehyde and the association between wood dust exposure and sinonasal cancer is extremely strong, with relative risks greater than 30-fold (Olsen and Asnaes, 1986).

Wood dust may be an independent risk factor for sinonasal cancer; however, the majority of investigators presented analytic results for formaldehyde among workers who were either not exposed to wood dusts (Olsen and Asnaes, 1986; Hansen and Olsen, 1995), or else controlled for the potential confounding of the effects of wood dust on the risk of sinonasal cancer and did not find wood dust to be a confounder (Luce et al., 2002).

Consistency across multiple studies is demonstrated by a pattern of increased risk in different populations, exposure scenarios, and time periods. Such consistency makes unmeasured confounding an unlikely alternative explanation for the observed associations. This consistency also reduces the likelihood of chance as an alternative explanation by increasing confidence in the statistical strength of the findings through the accumulation of a larger body of similar evidence. The observations of multiple instances of very strong associations in different settings reduce the likelihood that chance, confounding, or other biases can explain the observed associations.

Summary of Human Evidence Synthesis Judgments, Causal Evaluation, and Conclusion

Summary of human evidence synthesis judgments

The following factors were most influential to the causal evaluation and synthesis conclusion:

- *Consistency and Study Confidence:* Consistent increases in risk across studies (particularly for adenocarcinoma)—including four sets of results classified with *medium* confidence—one of which represents a large, pooled analysis of 12 case-control studies with considerably more cases and with greater detail on formaldehyde exposures.

- *Strength and Precision:* The magnitude of the relative effect estimates varied with the quality of the exposure assessment and by histological cell type. Two studies classified with *medium* confidence reported at least a 3-fold increase in risk for adenocarcinoma with lower associations for squamous cell carcinoma.

- *Coherence:* Biologically coherent temporal relationship consistent with a pattern of exposure to formaldehyde and subsequent death from sinonasal cancer, allowing time for cancer induction, latency, and mortality - although the rarity of this cancer limited the available data on a specific latency period.

- *Dose-Response:* Reported exposure-response relationship in a large, pooled analysis of 12 case-control studies showed increased exposure to formaldehyde was associated with increased risk of sinonasal cancer among people with little, or no exposure to wood dust or in analyses that controlled for wood dust.

Causal evaluation

The human evidence synthesis judgments sufficiently support a causal conclusion and are further supported by a judgment of reasonable confidence that alternative explanations are ruled out, including chance, bias, and confounding within individual studies or across studies. Although the cancer incidence and mortality data alone are sufficient for the causal conclusion supported by the human evidence synthesis judgments described above, consistent observations of genotoxicity in exfoliated buccal cells or nasal mucosal cells across several occupational studies involving diverse exposure settings (discussed under MOA below) strengthens *biological plausibility*, providing further support.

This evidence was judged to be near the borderline of *robust* evidence and *moderate* evidence, but one additional consideration increased confidence that the evidence was *robust*. The large, pooled analysis using a case-control study design especially suited to identify associations for this extremely rare cancer (Luce et al., 2002) was considered to be especially informative in identifying the effects of formaldehyde on the risks of sinonasal cancer and provided clear evidence

of an association of increased risks of sinonasal cancer with formaldehyde exposure – especially for adenocarcinoma.

Conclusion

- The available epidemiological studies provide *robust* evidence of an association consistent with causation between formaldehyde exposure and increased risk of sinonasal cancer.

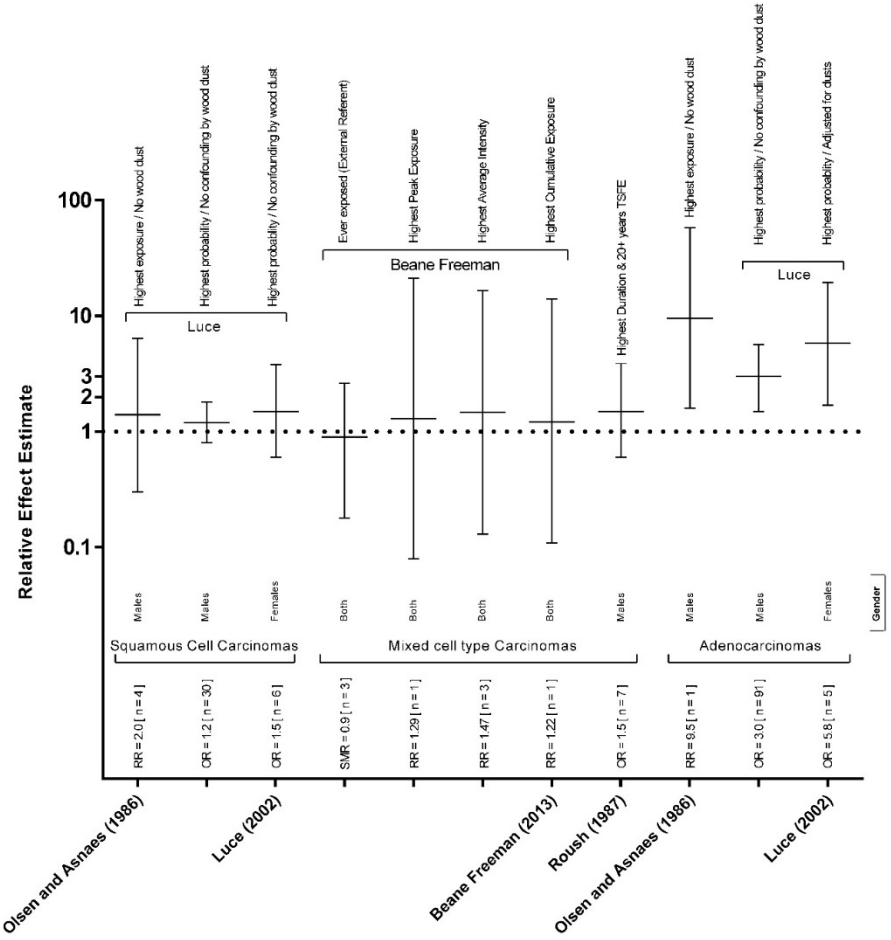


Figure 3-20. Highest (medium) confidence epidemiological studies reporting sinonasal cancer risk estimates.

Results are grouped by histological type as squamous cell carcinomas, mixed cell types, or adenocarcinoma. Details of the reported results of these studies are provided in the evidence table for sinonasal cancer (see Table 3-33). SMR: standardized mortality ratio. RR: relative risk. OR: odds ratio. TSFE: time since first exposure. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 4]). For studies reporting results on multiple metrics of exposure, only the highest category of each exposure metric is presented in the figure. Note that two studies (Olsen and Asnaes, 1986; Luce et al., 2002) reported separate results for squamous cell carcinoma and adenocarcinoma and appear twice in the figure. Also note that the pooled analysis by Luce et al. (2002) includes data from 12 publications and thus represents substantially more information than a single set of results (see Table 3-33 for details).

Table 3-33. Epidemiological studies of formaldehyde exposure and risk of sinonasal cancers

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Beane Freeman et al. (2013) **Population:** 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the United States followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. 676 workers (3%) were lost to follow-up. Vital status was 97.4% complete and only 2.6% lost to follow-up. **Outcome definition:** Death certificates used to determine underlying cause of death from nasal cancer (ICD-8: 160). Histological typing not reported. **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. Results were presented for 15-year lag. SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Blair et al. (1986) Hauptmann et al. (2004) Marsh et al. (2007a) Beane Freeman et al. (2009) **Confidence in effect estimates:**[a] **MEDIUM** (No appreciable bias) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A) Low sensitivity (few cases)	**Exposure assessment:** Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists who took 2,000 air samples from representative job, and monitoring data from 1960 through 1980. Median TWA (over 8 hours) = 0.3 ppm (range 0.01–4.3). Median cumulative exposure = 0.6 ppm-years (range 0–107.4). Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1946 to 1980. Median length of follow-up: 42 years. Median length of employment was 2.6 years (range 1 day–47.7 years). Duration and timing since first exposure were not evaluated. **Variation in exposure:** Peak exposure: Level 1 (>0 to <2.0 ppm) Level 2 (2.0 to <4.0 ppm) Level 3 (≥4.0 ppm) Average intensity: Level 1 (>0 to <0.5 ppm) Level 2 (0.5 to <1.0 ppm) Level 3 (≥1.0 ppm) Cumulative exposure: Level 1 (>0 to <1.5 ppm-years) Level 2 (1.5 to <5.5 ppm-years) Level 3 (≥5.5 ppm-years) Duration of exposure: Level 1 (0 years) Level 2 (>0 to <5 years) Level 3 (5 to <15 years) Level 4 (≥15 years) **Coexposures:** Exposures to 11 other compounds were identified and evaluated as potential confounders and found not be confounders. [As noted in Appendix B.3.9: There was no information on smoking, however, according to Blair et al.	**Internal comparisons:** Peak exposure Unexposed RR = 5.67 (0.41–78.89) [2] Level 1 RR = 1.00 (Ref. value) [1] Level 2 RR = 1.53 (0.09–24.68) [1] Level 3 RR = 1.29 (0.08–21.23) [1] *p*-trend (exposed) > 0.5; *p*-trend (all) = 0.37 Average intensity Unexposed RR = 4.31 (0.48–38.67) [2] Level 1 RR = 1.00 (Ref. value) [2] Level 2 RR = 1.47 (0.13–16.50) [1] Level 3 RR = N/A [0] *p*-trend (exposed) > 0.50; *p*-trend (all) = 0.23 Cumulative exposure Unexposed RR = 3.90 (0.41–37.06) [2] Level 1 RR = 1.00 (Ref. value) [2] Level 2 RR = 1.22 (0.11–14.11) [1] Level 3 RR = N/A [0] *p*-trend (exposed) > 0.50; *p*-trend (all) = 0.28 **External comparisons:** $SMR_{Unexposed}$ = 1.93 (0.23–6.98) [2] $SMR_{Exposed}$ = 0.90 (0.18–2.62) [3]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	(1986), "The lack of a consistent elevation for tobacco-related causes of death, however, suggests that the smoking habits among this cohort did not differ substantially from those of the general population."]	
Reference: Luce et al. (2002) **Population:** Males and females from seven different countries diagnosed with sinonasal cancer during 1968–1990. **Outcome definition:** Diagnoses originally assessed in 12 studies. 195 cases were adenocarcinomas (169 men and 26 women) and 432 were squamous cell carcinomas (330 men and 102 women). **Design:** Pooled analysis of 12 case-control studies that included 627 total cases of sinonasal cancer and 3,136 controls (2,349 men and 787 women). **Analysis:** ORs calculated by unconditional logistic regression. Adenocarcinoma results in men adjusted for age, study, and cumulative exposure to wood and leather dust. All other results adjusted for age and study. **Related studies:** Zheng et al. (1992) Luce et al. (1992) Luce et al. (1993) Leclerc et al. (1994) Bolm-Audorff et al. (1990) Comba et al. (1992a); Comba et al. (1992b) Magnani et al. (1993) Merler et al. (1986) Hayes et al. (1986b); Hayes et al. (1986a) Hardell et al. (1982) Vaughan et al. (1986a, 1986b) Vaughan and Davis (1991) Vaughan (1989) Mack and Preston-Martin (unpub. data) Brinton et al. (1984); Brinton et al. (1985)	**Exposure assessment:** Detailed occupational history information gathered from interview questionnaires provided the basis for developing an individual's index of exposure to formaldehyde. Standard occupational classification codes and standard industrial classification codes were used to develop a job-exposure matrix in conjunction with available industrial hygiene data. With the given occupational history information of the subjects and the job-exposure matrix, a semiquantitative index of cumulative exposure was determined for each individual calculated as the sum of the job-specific products of probability, level, and duration of exposure over the total work history. Subjects fell into one of four categories of probable exposure (unexposed, low exposure, medium exposure, or high exposure) based upon the job-exposure matrix. **Duration and timing:** Latency was evaluated with 10 and 20-year lags in exposure with somewhat higher effects. Results here are without lagged exposures. **Variation in exposure:** Cumulative exposure: Level 1 (unexposed) Level 2 (low) Level 3 (medium) Level 4 (high) **Coexposures:** Exposures to other compounds were identified and evaluated as potential confounders. Other occupational exposures potentially affecting the risk estimates were controlled for including wood dust, leather dust, textile dust, flour dust, coal dust, crystalline silica, asbestos, and man-made vitreous fibers.	**Internal comparisons:** **Adenocarcinoma** Men (Adjusted for wood dust) Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 0.7 (0.3–1.9) [6] Level 3 OR = 2.4 (1.3–4.5) [31] Level 4 OR = 3.0 (1.5–5.7) [91] Women (Not adjusted for wood dust) Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 0.9 (0.2–4.1) [2] Level 3 no cases Level 4 OR = 6.2 (2.0–19.7) [5] Women (Adjusted for wood dust) Level 1 OR = 1.0 (Ref. value) [# not given] Level 4 OR = 5.8 (1.7–19.4) [5] **Squamous cell carcinoma** Men (Adjusted for wood dust) Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.2 (0.8–1.8) [43] Level 3 OR = 1.1 (0.8–1.6) [40] Level 4 OR = 1.2 (0.8–1.8) [30] Women (Not adjusted for wood dust) Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 0.6 (0.2–1.4) [6] Level 3 OR = 1.3 (0.6–3.2) [7] Level 4 OR = 1.5 (0.6–3.8) [6] **Additional:** Authors reported that as an additional check for potential residual confounding, the formaldehyde adenocarcinoma results for men were further adjusted for wood dust and that the results were not markedly changed. Among women the result for high probability of formaldehyde exposure was slightly diminished (OR = 5.8; 95% CI: 1.7–19.4).

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Confidence in effect estimates:[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) with attenuation of association.		
Reference: Roush et al. (1987b) **Population:** Males identified from the Connecticut Tumor Registry who died of any cause during 1935−1975. **Outcome definition:** Diagnosis of sinonasal cancer based on case registration by the Connecticut Tumor Registry. Clinical records reviewed for >75% of cases. Histological typing not reported. **Design:** Population-based case-control study of 198 male cases of sinonasal cancer. Controls were 605 males dying in Connecticut during the same time period, randomly selected from state death certificates. **Analysis:** ORs calculated by logistic regression and adjusted for age at death, year at death, and availability of occupational information. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) with attenuation of association.	**Exposure assessment:** Occupational history obtained by city directories and death certificates, which yielded information on job, industry, employer, and year of employment. Exposure classification scheme based on potential for formaldehyde exposure, probability of exposure for each participant and each job-industry pair, and level of exposure. Probability of exposure defined as unexposed, possibly exposed, probably exposed, or definitely exposed. Level of exposure estimated as zero, low (<1 ppm), and high (≥1 ppm). Among those probably exposed to some level of formaldehyde for most of their working lifetime, the extent and level of exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure level and timing of exposure: Level 1 (unexposed) Level 2 (probably exposed most of working life) Level 3 (probably exposed most of working life and probably exposed 20+ years before death) High exposure level and timing of exposure: Level 1 (unexposed) Level 2 (probably exposed most of working life and probably to high level in some year)	**Internal comparisons:** Exposure level and timing of exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 0.8 (0.5−1.8) [21] Level 3 OR = 1.0 (0.5−1.8) [16] High exposure level and timing of exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.0 (0.5−2.2) [9] Level 3 OR = 1.5 (0.6−3.9) [7]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	Level 3 (probably exposed most of working life and probably exposed to high level 20+ years before death) **Coexposures:** Not evaluated. **[**As noted in Appendix B.3.9: Exposure to wood dust was not found to be a risk factor for all nasal cancers (NPC + SNC). This suggests a lower potential for confounding by wood dust.]	
Reference: Olsen and Asnaes (1986) **Population:** Identified from the Danish Cancer Registry between 1970 and 1982. Exposures to formaldehyde and wood dust were identified too rarely to allow for risk estimation. **Outcome definition:** Diagnosis of cancer of the nasal cavity (ICD-7 160.0) or sinuses (ICD-7 160.2–160.9) was histologically confirmed. Of all male cases for cancer of the nasal cavity and paranasal sinuses (*n* = 310), 69% were squamous cell carcinoma and lymphoepithelioma, 13% were adenocarcinoma, 6% were sarcoma, 5% were malignant melanoma, and 7% were of other histological type. **Design:** Case-control study of 254 men with sinonasal cavity and paranasal cancers (215 with squamous cell carcinoma/lymphoepithelioma and 39 with adenocarcinomas). 2,465 controls with other cancers matched for gender, age, and year of diagnosis. **Analysis:** The Mantel-Haenszel summary estimates of the relative risk were used to account for possible confounding since the subjects were stratified according to several variables. **Related studies:** Olsen and Jensen (1984) **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment	**Exposure assessment:** Employment histories from 1964 maintained by Danish Cancer Registry estimated by industrial hygienists. Occupational exposures estimated by industrial hygienists based on industry or occupations considered to have certain or probably exposure. Authors reported that 4.2% of control males exposed to formaldehyde. Multiple exposure metrics including known exposure and duration since first exposure were evaluated. **Duration and timing:** Exposure period starting at 1964. **Variation in exposure:** Exposure to formaldehyde: Level 1 (Unexposed) Level 2 (Exposed) Exposure to formaldehyde and wood dust: Level 1 (unexposed to either) Level 2 (exposed to formaldehyde and unexposed to wood dust) Level 3 (unexposed to formaldehyde and exposed to wood dust) Level 4 (exposed to both) ≥10 years since 1st exposure to formaldehyde and wood dust: Level 1 (unexposed to either) Level 2 (exposed to formaldehyde and unexposed to wood dust)	**Internal comparisons:** **Adenocarcinoma** Exposure to formaldehyde controlling for wood dust: Level 1 RR = 1.0 (Ref. value) [10] Level 2 RR = 2.2 (0.7–7.2) [17] Exposure to formaldehyde and wood dust: Level 1 RR = 1.0 (Ref. value) [8] Level 2 RR = 7.0 (1.1–43.9) [1] Level 3 RR = 24.0 (7.6–75.6) [2] Level 4 RR = 39.5 (22.0–70.8) [16] ≥10 years since 1st exposure to formaldehyde and wood dust: Level 1 RR = 1.0 (Ref. value) [6] Level 2 RR = 9.5 (1.6–57.8) [1] Level 3 RR = 36.8 (13.5–96.0) [3] Level 4 RR = 44.1 (22.2–87.8) [11] **Squamous cell carcinoma and lymphoepithelioma** Exposure to formaldehyde controlling for wood dust: Level 1 RR = 1.0 (Ref. value) [113] Level 2 RR = 2.3 (0.9–5.8) [13] Exposure to formaldehyde and wood dust: Level 1 RR = 1.0 (Ref. value) [113] Level 2 RR = 2.0 (0.7–5.9) [4] Level 3 no cases Level 4 RR = 1.6 (0.8–3.3) [9] ≥10 years since 1st exposure to formaldehyde and wood dust: Level 1 RR = 1.0 (Ref. value) [81] Level 2 RR = 1.4 (0.3–6.4) [2] Level 3 no cases Level 4 RR = 1.8 (0.7–4.4) [6]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
(Exposure Group C) with attenuation of association.	Level 3 (unexposed to formaldehyde and exposed to wood dust) Level 4 (exposed to both) **Coexposures:** Exposure to wood dust was identified and evaluated as a potential confounder and as an effect modifier.	
Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories which produced formaldehyde. Cohort mortality followed from 1941 through 2012. Cause of deaths was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378 deaths through 2012. Vital status was 98.9% complete through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from nasal cancer. Histological typing not reported. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941–1982. Duration was evaluated as "more," or "less," than one year only among the 'High' exposure group. Timing since first exposure was not evaluated. **Variation in exposure:** Highest exposure level attained Level 1 (Background) Level 2 (low/moderate) Level 3 (High) **Coexposures:** Not evaluated. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. [As noted in Appendix B.3.9: Styrene is associated with LHP cancers but not URT cancers. Asbestos is associated with URT cancers, but not this outcome. Other coexposures are not known risk factors for this outcome.]	**External comparisons:** Overall: SMR = 0.71 (0.09–2.55) [2] Exposed: Level 1 SMR = 1.08 (0.03–6.01) [1] Level 2 SMR = 1.01 (0.03–5.62) [1] Level 3 SMR = 0 (0–4.03) [0]
Reference: Meyers et al. (2013)	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and	**External comparisons:** SMR = 0 (0–3.89) [0]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Population: 11,043 workers in 3 U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion **Outcome definition:** Death certificates used to determine both the underlying cause of death from nasal cancer (ICD-code in use at time of death). Histological typing not provided. **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Pinkerton et al. (2004) Stayner et al. (1985) Stayner et al. (1988) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	1984 with 12−73 within each department. Formaldehyde levels across all departments and facilities were similar. Geometric TWA8 exposures ranged from 0.09 to 0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm, (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 to 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were not evaluated for this cancer. **Variation in exposure:** Not evaluated. **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings. [As noted in Appendix B.3.9: There was no information on smoking in this analysis, however, according to Leclerc et al. (1997), "the overall prevalence of cigarette smokers was … similar to those reported in a 1980 survey of adult Americans, in which 29.2% of females and 38.3% of males over the age of 20 were current cigarette smokers." Therefore, confounding was considered to be unlikely.	
Reference: Siew et al. (2012) **Population:** All Finnish men born during 1906−1945 who participated in census and were employed in 1970 (*n* = 1.2 million). Vital status was "virtually complete." **Outcome definition:** Diagnosis of nasal squamous cell cancer reported to the Finnish Cancer Registry.	**Exposure assessment:** Individual-level exposure estimates based on matching occupations listed in the census to the Finnish job-exposure matrix which covers major occupational exposures and provided exposure estimates for formaldehyde. **Duration and timing:** Duration and timing since first exposure were not evaluated.	**Internal comparisons:** Exposure to formaldehyde: Level 1 RR = 1.00 (Ref. value) [158] Level 2 RR = 0.97 (0.47−2.00) [9]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Design: Prospective national cohort incidence study with internal comparison groups. **Analysis:** RRs calculated controlling for sex, age, socioeconomic status, period of follow-up, and smoking. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association. Low sensitivity (low background rate of cancer).	**Variation in exposure:** Exposure to formaldehyde: Level 1 (none) Level 2 (any) **Coexposures:** Wood dust exposures were controlled for in formaldehyde analyses.	
Reference: Pesch et al. (2008) **Population:** Male workers insured by a liability insurance association for the German wood-working industries with an occupational disease during 1994–2003. Of 129 cases of sinonasal adenocarcinoma identified, 86 cases (67%) agreed to participate (including 29 next of kin). 204 controls (75%) participated (including 69 next of kin). **Outcome definition:** Cases were ever employed in German wood industries and diagnosed with histopathologically confirmed sinonasal adenocarcinoma. **Design:** Insurer-based case-control study of 86 cases of sinonasal adenocarcinoma. Controls were 204 workers with accidents between home and work or falls during working shifts. Controls were frequency matched on age with 60 years as the stratification point. **Analysis:** ORs calculated using logistic regressions controlling for age (<60 vs. 60+), region, interviewee, and average wood dust exposure. All temporal exposure variables were lagged by 5 years. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null)	**Exposure assessment:** Occupational history information gathered from structured questionnaires. Because next of kin information on exposure to wood additives was considered poor, the probability of exposure to formaldehyde was rated by an expert team as none, low, medium, or high. In Germany, legislation or new formulations altered potential formaldehyde exposure in 1985 (likely lowering them). Final analyses classified exposure as unexposed, any probability of exposure before 1985, or any probability of exposure in 1985 or afterwards. **Duration and timing:** Duration of formaldehyde exposure was not evaluated. **Variation in exposure:** Exposure level: Level 1 (unexposed) Level 2 (any exposure <1985) Level 3 (any exposure ≥1985) **Coexposures:** Wood dust exposures were controlled for in formaldehyde analyses.	**Internal comparisons:** Exposure level: Level 1 OR = 1.0 (Ref. value) [39] Level 2 OR = 0.46 (0.14–1.54) [8] Level 3 OR = 0.94 (0.47–1.9) [39]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Selection bias possible. High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and weak latency analysis with attenuation of association.		
Reference: Jakobsson et al. (1997) **Population:** 727 male employees of two plants producing stainless steel sinks and saucepans employed at least one year during 1927–1981 with minimum 15-year follow-up. **Outcome definition:** Incidence of sinonasal cancer from the Swedish Tumor Registry (ICD-7:160). **Design:** Cohort incidence study with external comparison group. **Analysis:** SIRs calculated using sex, age, and calendar-year-expected number of cases from the national population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias with attenuation of association (Exposure Group D). Confounding possible. Low sensitivity (few cases).	**Exposure assessment:** Workers grind stainless steel with grinding plates made of formaldehyde resins which may release formaldehyde when heated during grinding operations. **Duration and timing:** Occupational exposure preceding death during 1927–1981. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Coexposures may have included chromium, nickel, and abrasive dusts including silicon carbide, aluminum oxide, silicon dioxide, and clay. [As noted in Appendix B.3.9: Nickel and chromium are associated with URT cancers and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect. Other coexposures are not known risk factors for these outcomes. No mention of exposure to wood dust.]	**External comparisons:** Observed: 0 Expected: 0.5 SIR = 0 (0–8.0) [0]
Reference: Teschke et al. (1997) **Population:** 48 incident cases of nasal cancers (31% female) older than 19 years and registered by the British Columbia Cancer Agency during 1990–1992. Controls were randomly selected from age and sex strata of voter lists of the same time period (frequency matched).	**Exposure assessment:** Detailed occupational history information gathered from interview questionnaires. 57 Occupational groups assessed. Investigators discussed that textile workers, pulp and paper mill workers, and chemical and biological laboratory personnel may have formaldehyde exposures.	**External comparisons:** All histological types: Textile workers (all) Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 7.6 (1.4–56.6) [6] Textile workers (most recent 20 years removed) Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 5.0 (0.8–43.0) [4]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
6 of original 54 cases (11%) were excluded for lack of interview as were 36 of 195 eligible controls (18%). **Outcome definition:** Incidence of sinonasal cancer from the British Columbia Cancer Agency (ICD-O:160.0, 160.2, 160.9). Histological types: 23 squamous cell carcinomas (48%), seven melanomas, seven lymphomas, two adenocarcinomas (4%), two adenoid cystic carcinomas, and seven other histologies with one case each. **Design:** Population-based case-control study of nasal cancer. **Analysis:** ORs controlled for sex, age, and smoking. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) with attenuation of association. Potential confounding. Low sensitivity (rare exposure).	**Duration and timing:** Duration of exposure was not evaluated. Timing of exposure was evaluated for nasal cancer with results for 20-year latency presented. **Variation in exposure:** Ever employed in occupational group: Level 1 (never) Level 2 (ever) **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Potential confounders for these outcomes include chlorophenols, acid mists, dioxin, and perchloroethylene and would likely be positively correlated with formaldehyde exposure. However, on acids mists are associated with URT cancers. Potential for confounding is unknown but could have inflated the observed effect.]	Pulp and paper mill workers (all) Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 3.1 (0.4–25.4) [3] Pulp and paper mill workers (20-year lag) Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 3.1 (0.4–25.4) [3] Chemical and biological lab workers (all) Level 1 OR = 1.0 (Ref. value) [8] Level 2 OR = 0.7 (0.1–4.0) [2] Chemical and biological lab workers (20-year lag) Level 1 OR = 1.0 (Ref. value) [7] Level 2 OR = 0.9 (0.1–5.3) [2] Squamous cell carcinoma: Textile workers (all) Level 1 OR = 1.0 (Ref. value) [not given] Level 2 OR = 5.3 (0.2–5.3) [not given]
Reference: Hansen and Olsen (1995) **Population:** 2,041 men with cancer who were diagnosed during 1970–1984 and whose longest work experience occurred at least 10 years before cancer diagnosis. Identified from the Danish Cancer Registry and matched with the Danish Supplementary Pension Fund. Ascertainment considered complete. Pension record available for 72% of cancer cases. **Outcome definition:** Nasal cavity cancer (ICD-7: 160) listed on Danish Cancer Registry file. Of all male cases (*n* = 13), histological types of nasal cavity tumors included four squamous cell carcinomas, three adenocarcinomas, one adenoid cystic carcinoma, one melanoma, and one unknown type. Tumors of the maxillary sinus included two squamous cell carcinomas and one	**Exposure assessment:** Individual occupational histories including industry and job title established through company tax records to the national Danish Product Register. Subject were considered to be exposed to formaldehyde if: (1) they had worked in an industry known to use more than 1 kg formaldehyde per employee per year; and (2) subjects longest single work experience (job) in that industry since 1964 was ≥10 years prior to cancer diagnosis. All subjects were stratified based on job title as either low exposure (white collar worker), above background exposure (blue collar worker), or unknown (job title unavailable). **Duration and timing:** Exposure period not stated. Based on date of diagnosis during 1970–1984, and the requirement of exposure more than	**External comparisons:** Overall (exposure to formaldehyde ≥10 years prior to cancer diagnosis) SPIR = 2.3 (1.3–4.0) [13] Exposure to formaldehyde: Level 1 SPIR = 1.0 (0.03–6.1) [1] Level 2 SPIR = 0.8 (0.02–4.4) [1] Level 3 SPIR = 3.0 (1.4–5.7) [9] Level 4 SPIR = 5.0 (0.5–13.4) [2]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
anaplastic carcinoma. Overall, there were six squamous cell carcinomas (46%) and two adenocarcinomas (15%). **Design:** Proportionate incidence study with external comparison group. **Analysis:** Standardized proportionate incidence ratio calculated as the proportion of cases for a given cancer in formaldehyde-associated companies relative to the proportion of cases for the same cancer among all employees in Denmark. Adjusted for age and calendar time. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association. Low sensitivity for NPC (few cases).	10 years prior to diagnosis, the approximate period was 1960–1974. **Variation in exposure:** Exposure to formaldehyde: Level 1 (unknown) Level 2 (low formaldehyde exposure) Level 3 (formaldehyde exposure, no wood dust) Level 4 (formaldehyde and wood dust exposure) **Coexposures:** Exposure to wood dust was evaluated as a potential confounder of sinonasal cancer. Authors excluded wood dust exposed Cases from Level 3 analyses.	
Reference: Hayes et al. (1990) **Population:** 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975–1985. Death certificates obtained for 79% of potential study subjects (*n* = 6,651) with vital status unknown for 21%. **Outcome definition:** Death certificates and licensing boards used to determine cause of death from sinonasal cancer (ICD-8: 160). **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a]	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. Exposure based on occupation which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to 3.99 ppm (low ventilation) with peaks up to 20 ppm. Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975–1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60–74 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated.	**External comparisons:** Observed: 0 cases Expected: 1.7 cases PMR = 0 (0–1.76) † [0] **Additional:** By Race White PMR = 0 (0–2.00) † [0] Non-White PMR = 0 (0–14.98) † [0] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979)).

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
LOW ↓ (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	[As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.]	
Reference: Bertazzi et al. (1986) **Population:** 1,332 male workers ever employed in the plant between 1959 and 1980. Deaths were identified from vital statistics offices. Vital status was 98.6% complete. **Outcome definition:** Nasal cancer listed as cause of death on death certificates. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, age, and calendar-year-expected number of deaths from the local population. **Confidence in effect estimates:**[a] **SNC: LOW ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group B) with attenuation of association. Low sensitivity (few cases).	**Exposure assessment:** Individual-level exposure estimates based on occupational histories. Over the whole cohort, approximately 28% of person time was estimated to be exposed to formaldehyde. **Duration and timing:** Occupational exposure preceding death during 1959–1980. Duration and timing since first exposure were not evaluated for nasal cancer. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Other exposures included styrene, xylene, toluene, and methyl isobutyl ketone. Styrene is associated with LHP cancers but not URT cancers. Other coexposures are not known risk factors for this outcome.]	**External comparisons:** Observed: 0 Expected: 0.0327 SMR = 0 (0–91.61) † [0] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))
Reference: Stroup et al. (1986) **Population:** 2,239 white male members of the American Association of Anatomists from 1888 to 1969 who died during 1925–1979. Death certificates obtained for 91 with 9% lost to follow-up.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure during 1925–1979. Median birth year was 1912. By 1979, 33% of anatomists had died. Duration and	**External comparisons:** SMR = 0 (0–7.2) [0]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Outcome definition: Cancer of the nasal cavity and sinuses listed as cause of death on death certificates. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for selection bias. Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Confounding possible for ML. Low sensitivity (few cases).	timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. [Benzene is not associated with URT cancer.]	
Reference: Levine et al. (1984a) **Population:** 1,477 male undertakers first licensed during 1928–1977 with mortality follow-up from 1950 to 1977. Vital status was 96% complete with cause of death available for 94%. **Outcome definition:** Cancer of the nasal cavity and sinuses listed as underlying cause of death on death certificates (ICD-8: 160). **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, age, and calendar-year-expected number of deaths from the Canadian population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null)	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure during 1928–1977. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.]	Observed: 0 Expected: 0.2 PMR = 0 (0–14.98)† [0] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).		
Reference: Walrath and Fraumeni (1984) **Population:** 1,007 deceased white male embalmers from the California Bureau of Funeral Directing and Embalming who died during 1925–1980. Death certificates obtained for all. **Outcome definition:** Nasal cancer listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1916–1978. Birth year ranged from 1847–1959. Median age of death was 62 years. Most deaths were among embalmers with active licenses. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.]	**External comparisons:** Observed: 0 Expected: 0.6 PMR = 0 (0–4.99)† [0] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))
Reference: Walrath and Fraumeni (1983) **Population:** 1,132 deceased white male embalmers licensed to practice during 1902–1980 in New York who died during 1925–1980 identified from registration files. Death certificates obtained for 75% of potential study subjects (*n* = 1,678). **Outcome definition:** Nasal cancer listed as cause of death on death certificates.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1902–1980. Median year of birth was 1901. Median year of initial license was 1931. Median age at death was 1968. Expected median duration of exposure was 37 years. Duration and timing since first exposure were not evaluated.	**External comparisons:** Observed: 0 Expected: 0.5 PMR = 0 (0–5.99)† [0] †**Note:** EPA derived CIs using the Mid-P Method (see (Rothman and Boice, 1979))

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Design: Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.]	

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Oropharyngeal/Hypopharyngeal cancer

Epidemiological evidence

Oropharyngeal and hypopharyngeal cancer is commonly reported across the epidemiological literature based on the Seventh, Eighth, or Ninth Revision of the ICD code (ICD-7/8/9: 146 and ICD-7/8/9: 148, respectively). Two studies reported specifically on hypopharyngeal cancer risks (Marsh et al., 2007a; Laforest et al., 2000), and one study reported specifically on oropharyngeal cancer risks (Marsh et al., 2007a). The results from five other studies (of three populations) allowed for grouping these two adjacent tissue sites for analyses to examine the risks of pharyngeal cancers below the nasopharynx (Vaughan et al., 1986a, b; Vaughan, 1989; Marsh et al., 2002; Gustavsson et al., 1998).

Overall, evidence describing an association between formaldehyde exposure and the risk of developing or dying from oropharyngeal/hypopharyngeal cancer was available from nine reports on six distinct study populations—four reports on three cohort studies (Meyers et al., 2013; Marsh et al., 2002; Marsh et al., 2007a; Coggon et al., 2014) and five reports on three case-control studies (Vaughan et al., 1986a, b; Vaughan, 1989; Laforest et al., 2000; Gustavsson et al., 1998). No studies with data specific to these pharyngeal cancer sites were excluded. The outcome-specific evaluations of confidence in the precise effect estimate of an association from each study are provided in Appendix B.3.9). Details of the reported results of *high*, *medium*, and *low* confidence are provided in

the evidence table for oropharyngeal/hypopharyngeal cancer (see Table 1-34) following the causal evaluation.

Consistency of the observed association

The nine papers describing six populations reported the risks of oropharyngeal/hypopharyngeal cancer among study subjects who had a high likelihood of formaldehyde exposure (e.g., based on occupational history). The study results presented in Table 1-34 (by confidence level and publication date) detail all of the reported associations. Results are plotted in Figure 3-21 with results grouped by cancer site as "Oropharyngeal only," "Undifferentiated oropharyngeal/hypopharyngeal," or "Hypopharyngeal only."

Based on results for overall SMRs for all workers (both exposed and unexposed) compared to external referent populations in three cohort studies (all classified with *medium* confidence), the effect estimates were generally elevated and ranged in magnitude between 1.1 and 2.01, but none had sufficient statistical power to exclude the null. The effect estimate for oropharyngeal cancer alone was 1.95 (Marsh et al., 2007a); 95% CI 0.63, 4.56); for the combination of oropharyngeal and hypopharyngeal cancer, the effect estimates were 1.1 (Meyers et al., 2013); 95% CI 0.40, 2.39) and 1.29 (Coggon et al., 2014); 95% CI 0.76, 2.05), respectively; and for hypopharyngeal cancer alone the effect estimate was 2.01 (Marsh et al., 2007a); 95% CI 0.87, 3.96). The only case-control study results classified with *medium* confidence (Laforest et al., 2000) reported effect estimates by the probability of exposure with an OR = 1.35 for "Ever" exposure to formaldehyde associated with hypopharyngeal cancer (95% CI 0.86, 2.14), but for cases with >50% probability of formaldehyde exposure the OR was 3.78 (95% CI 1.50, 9.49). The results from the two case-control studies classified with *low* confidence (Gustavsson et al., 1998), and the three Vaughan reports (Vaughan et al., 1986a, b; Vaughan, 1989) were largely surrounding the null.

Subgroup analyses provide some indication of increased risk when a latency period was accounted for. Increased risks of oropharyngeal/hypopharyngeal cancer were also reported by Marsh et al. (2002) among workers with at least 10 years of formaldehyde exposure (SMR = 2.48; 95% CI 0.63, 6.75)—especially for those with at least 10 years of exposures greater than 0.2 ppm (SMR = 4.94; 95% CI 1.25, 13.38). After excluding those with <10% probability of being exposed to formaldehyde, Laforest et al. (2000) found that for those with at least 20 years of exposure, the OR was 2.70 (95% CI 1.08, 6.73).

Overall, the findings were heterogeneous. Results from the two case-control studies classified with *low* confidence Gustavsson et al. (1998) and the Vaughan papers (Vaughan et al., 1986a, b; Vaughan, 1989) did not show increased risks, although Gustavsson et al. (1998) did not assess differences by exposure concentration or duration. The Vaughan analyses (Vaughan et al., 1986a, b; Vaughan, 1989) did examine differences in exposures but did not observe consistently increased risks. As with the Gustavsson et al. (1998) study, the Meyers et al. (2013) cohort study did not assess differences in exposure concentration or duration and found only a minimally increased risk. Coggon et al. (2014) did report results for duration greater than 1 year but did not

observe consistently increased risks, and Vaughan et al. (1986b) did not observe an increased risk of oropharyngeal/hypopharyngeal cancer for living more than 10 years in a mobile home (although the corresponding OR for NPC was 5.5). Two other results from Marsh et al. (2002) and Laforest et al. (2000) did observe increased risks associated with >10 and >20 years of exposure duration.

Strength of the observed association

Summary effect estimates (SMR or RR) ranged from 1.01 (Gustavsson et al., 1998) to slightly more than a doubling of the relative effect estimates (Marsh et al., 2007a). Only one study (Marsh et al., 2007a) reported a summary effect estimate (for cancers of the oropharynx, hypopharynx and unspecified pharynx) that excluded the null (OR = 1.98; 95% CI 1.17, 3.15). The magnitude of the relative effect estimates varied but did not appear to depend on the specific non-nasopharyngeal cancer site. Marsh et al. (2002) provided specific SMRs for oropharyngeal (ICD-9: 146), hypopharyngeal (ICD-9: 148), and "pharyngeal cancer, unspecified" (ICD-9: 149), which were very similar at 1.95, 2.01, and 2.11 respectively. Exposure level-specific estimated risks ranged from 0.8 for the highest residential duration of exposure to particleboard (Vaughan et al., 1986b) up to 4.94 for workers exposed to concentrations of formaldehyde greater than 200 ppb for more than 10 years.

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants started before their diagnoses of oropharyngeal/hypopharyngeal cancer. Only one study (Vaughan et al., 1986a) reported results for formaldehyde exposure lagged by 15 years to account for latency and did not find higher risks. It is notable that for nasopharyngeal cancer in the tissue neighboring the oropharynx, the latency between formaldehyde exposure and cancer mortality was generally longer than 25 years (see Section 3.2.5 Nasopharyngeal cancer); thus, studies without similar follow-up time and appropriately lagged exposure may be insufficiently sensitive.

Marsh et al. (2002) reported on the effect of time since first employment in a formaldehyde-related occupation as a proxy for latency. Those data (see Table 3-34) indicate that the risk of workers with 20–29 years at a chemical plant producing or using formaldehyde had an SMR = 1.50 (95% CI 0.48, 3.61), while workers with more than 30 years' tenure had a higher risk (SMR = 2.69; 95% CI 1.31, 4.94). Extended duration of exposure can also be a reasonable proxy for latency. Compared to unexposed workers, Laforest et al. (2000) reported increasing risks with increasing duration of exposure for all workers (regardless of their probability of exposure) reaching an OR = 1.51 (95% CI 0.78, 2.92) for those with more than 20 years' exposure to formaldehyde with an even more pronounced effect of extended duration among those workers with the higher probabilities of exposure (OR = 2.70; 95% CI 1.08, 6.73).

Exposure-response relationship

Only three study populations were available for evaluating exposure-response relationships between formaldehyde and increased risk of oropharyngeal/hypopharyngeal cancer. The paired studies by Vaughan et al. (1986a, b) did not show evidence of an exposure-response relationship with the same exposure metrics as they did for nasopharyngeal cancer. Conversely, Laforest et al. (2000) reported a clear exposure-response trend for increasing probability of formaldehyde exposure ($p < 0.005$) and for increasing duration of formaldehyde exposure among subjects with at least 10% probability of exposure ($p < 0.04$), with some indication of a trend with increasing cumulative exposure ($p < 0.14$). Marsh et al. (2002) also found higher risks at higher durations of exposure.

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias is an unlikely bias in the epidemiological studies of oropharyngeal/hypopharyngeal cancer as the cohort study followed by (Marsh et al., 2002; Marsh et al., 2007a) included 98% of eligible participants and lost relatively few participants over the course of mortality follow-up, and the case-control study by Laforest et al. (2000) evaluated exposure status without regard to outcome status and had participation levels of 80% for cases and 86% for controls. Information bias is unlikely to have resulted in bias away from the null; however, random measurement error or nondifferential misclassification is almost certain to have resulted in some bias toward the null among these studies of oropharyngeal/hypopharyngeal cancer. For example, regarding one particular analysis from Marsh et al. (2002), the authors reported risks for exposure greater than 700 ppb of formaldehyde that might have been useful for comparison with the risk for exposure of greater than 200 ppb; however, by comparing risk above 700 ppb to risk among "unexposed" workers (with exposures ranging from 0 to 699 ppb), information bias was likely induced, which may have attenuated that risk and made the inclusion of this result unsuitable for exposure-response evaluation.

Confounding is a potential bias that could arise if another cause of oropharyngeal/hypopharyngeal cancer is also associated with formaldehyde exposure. There does not appear to be any evidence of confounding that would provide an alternative explanation for the observed association of formaldehyde exposure with increased risk of oropharyngeal/hypopharyngeal cancer seen across these studies. Chemical and other coexposures that have not been independently associated with oropharyngeal/hypopharyngeal cancer are not expected to confound results. Other known risk factors for oropharyngeal/hypopharyngeal cancer include smoking and alcohol consumption (Vaughan, 1996). While these other exposures may be independent risk factors for oropharyngeal/hypopharyngeal cancer, smoking and alcohol consumption are unlikely to be generally related to occupational and residential formaldehyde exposures and are therefore unlikely to be across-the-board confounders. This is especially true for studies comparing risks within a cohort of workers who may be more similar to each other in

smoking status than they are compared to an external population. This is relevant to the NCI cohort which Beane Freeman (2013) noted had a high prevalence of current or former smokers across all levels of formaldehyde exposure (i.e., smoking prevalence was likely independent of formaldehyde exposure and not a confounder). However, the Marsh reports on one plant in this cohort (Marsh et al., 2002; Marsh et al., 2007a) compared the risk of those workers to an external population which might have had lower prevalences of smoking allow for a greater potential for confounding by smoking in those reports.

Overall, the findings were heterogeneous with no association observed in study results of *low* confidence and a mix of positive associations and null findings in study results of *medium* confidence. For oropharyngeal/hypopharyngeal cancer, the lack of consistency weakens the etiologic conclusion. However, the observations of increased risks across multiple *medium* confidence results, as well as two identified exposure-response relationships with increased duration of formaldehyde exposure is suggestive of an association.

Summary of Human Evidence Synthesis Judgments, Causal Evaluation, and Conclusion

Summary of human evidence synthesis judgments

The following factors were most influential to the causal evaluation and synthesis conclusion:

- *Consistency and Study Confidence:* Results were heterogeneous with five study reporting results near the null—but three medium confidence studies with more specific exposure metrics showing some significantly increase risks.

- *Strength and Precision:* Variable strength of the association across studies and metrics with two medium confidence studies reporting 3-fold to 5-fold increases in risk among groups with the highest exposure probability or duration and several studies reporting results near the null.

- *Coherence:* Biologically coherent temporal relationship consistent with a pattern of exposure to formaldehyde and subsequent death from oropharyngeal/hypopharyngeal cancer, allowing time for cancer induction, latency, and mortality—although the rarity of this cancer limited the available data on a specific latency period.

- *Dose-Response:* Reported exposure-response relationships using multiple metrics of exposure from one study showed that increased exposure to formaldehyde was associated with increased risk of developing oropharyngeal/hypopharyngeal cancer.

Causal evaluation

The human evidence synthesis judgment is suggestive of an association, but does not sufficiently support a causal conclusion. Although consistent observations of genotoxicity in exfoliated buccal cells or nasal mucosal cells have been observed across several occupational studies, these data were not interpreted as sufficient to provide additional biological plausibility for these associations or strengthen the judgment on the human evidence of cancers of the oropharynx and, more indirectly, the hypopharynx.

Conclusion

- The available epidemiological studies provide *slight* evidence of an association between formaldehyde exposure and increased risk of oropharyngeal/hypopharyngeal cancer.

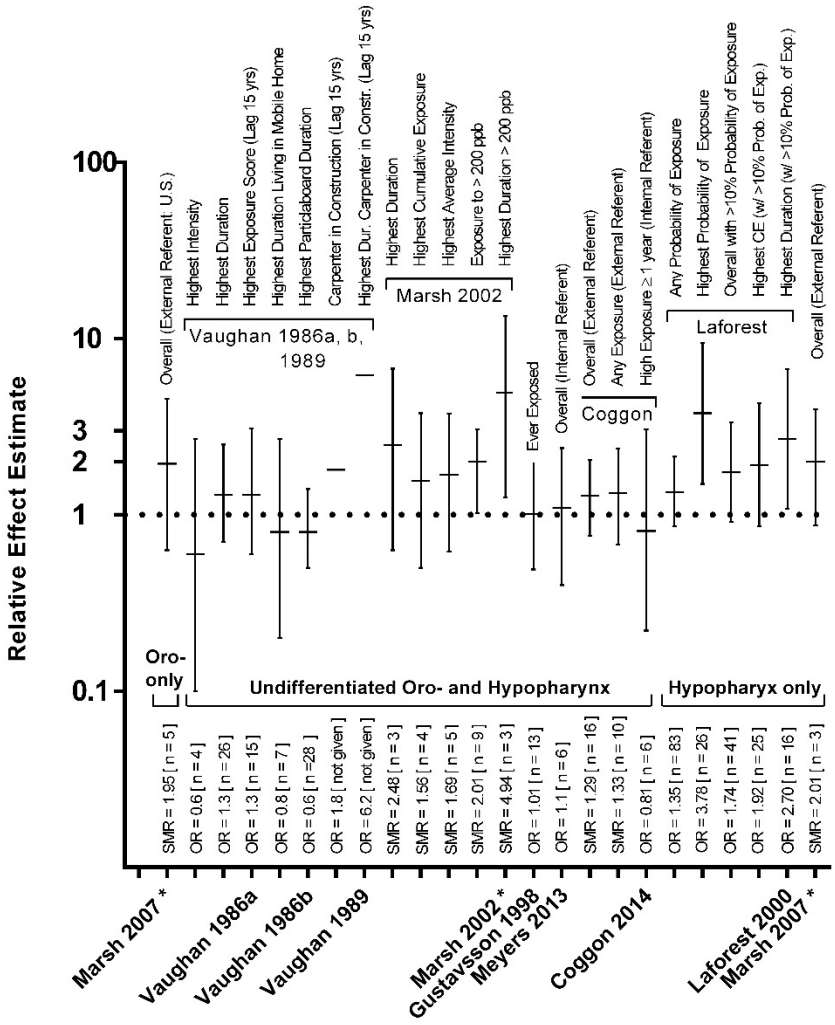


Figure 3-21. Epidemiological studies reporting oropharyngeal or hypopharyngeal cancer risk estimates.

Results are grouped by cancer site as oropharyngeal only, oropharyngeal grouped with hypopharyngeal and unspecified pharyngeal, or hypopharyngeal only. Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for oropharyngeal/hypopharyngeal cancer (see Table 3-34). SMR: standardized mortality ratio. RR: relative risk. OR: odds ratio. CE: cumulative exposure. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 6]). For studies reporting results on multiple metrics of exposure, only the highest category of each exposure metric is presented in the figure. Data from (Marsh et al., 2002; Marsh et al., 2007a) are based on the same study subjects; however, exposure-response data were only included in the 2002 study, and the 2007 study had more recent comparisons with external referents.

Table 3-34. Studies of formaldehyde exposure and risk of cancer of oropharynx/hypopharynx

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories which produced formaldehyde. Cohort mortality followed from 1941 through 2012. From Coggon et al. (2003), cause of death was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378 deaths through 2012. Vital status was 98.9% complete and only 1.1% lost to follow-up through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from pharyngeal cancer minus deaths from nasopharyngeal cancer. **Design:** Cohort mortality study with external comparison group with a nested case-control study. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941–1982. Duration was evaluated as more, or less, than one year only among the "High" exposure group. Timing since first exposure was not evaluated. **Variation in exposure:** Duration of "High" exposures Level 1 (Background) Level 2 (<1 year) Level 3 (1 year or more) **Coexposures:** Not evaluated. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. [As noted in Appendix B.3.9: Styrene is associated with LHP cancers but not URT cancers. Asbestos is associated with URT cancers, but not this outcome. Other coexposures are not known risk factors for this outcome.]	**External comparisons:** For NPC (p. 1,307 in Coggon et al.): 1 observed case with exposure above background vs. 1.7 expected. For all pharyngeal cancers (see Table 3 in Coggon et al.): 17 cases observed in all subjects vs. 14.1 expected. 11 cases with exposures above background v. 9.2 expected. Therefore, for OHPC: 10 observed cases with exposure above background vs. 7.5 expected. 16 observed cases in all subjects vs. 12.4 expected. $SMR_{All\ Subjects}$ = 1.29 (0.76–2.05)† [16] $SMR_{Exposed}$ = 1.33 (0.68–2.38)† [10] **Internal comparisons:** Since the 1 NPC case had "low/Moderate exposure," the all-pharyngeal-cancer results in Table 6 in Coggon et al. (2014) for "High exposure" are OHPC. Duration of 'High' exposures Level 1 OR = 1.00 (Ref. value) [10] Level 2 OR = 0.63 (0.13–3.03) [3] Level 3 OR = 0.81 (0.22–3.05) [6] †**Note:** EPA derived CIs using the Mid-P Method (see (Rothman and Boice, 1979))
Reference: Meyers et al. (2013) **Population:** 11,043 workers in 3 U.S. garment plants exposed for at least 3 months. Women comprised 82% of	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984. Geometric TWA8 exposures ranged from 0.09–0.20 ppm. Overall	**External comparisons:** SMR = 1.1 (0.40–2.39) [6]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
the cohort. Vital status was followed through 2008 with 99.7% completion. **Outcome definition:** Death certificates used to determine the underlying cause of death from other/unspecified pharymgeal cancer (ICD code in use at time of death). Histological typing not provided. **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Pinkerton et al. (2004) Stayner et al. (1985) Stayner et al. (1988) **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due lack of latency analysis with attenuation of association.	geometric mean concentration of formaldehyde was 0.15 ppm, (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 to 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were not evaluated for this cancer. **Variation in exposure:** Not evaluated. **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	
Reference: Marsh et al. (2007a); Marsh et al. (2002) **Population:** 7,328 workers employed at formaldehyde-using plant in the United States followed from 1945 through 2003. Vital status was identified from the National Death Index, private businesses, or state and local agencies, and was 98% complete and 1.4% lost to follow-up. Among the deceased, the cause of death was available for 95.2%. This population was from one plant from Beane Freeman et al. (2009). **Outcome definition:** Death certificates used to determine underlying cause of death from oropharyngeal/hypopharyngeal cancer according to the ICD-9 codes (146, 148).	**Exposure assessment:** Worker-specific exposure from job-exposure matrix based on available sporadic sampling data from 1965 to 1987, job descriptions, and verbal job descriptions by plant personnel and industrial hygienists. Exposures ranked on a 7-point scale with exposure range assigned to each rank. 17% of jobs validated with company monitoring data; remaining 83% based on professional judgment. Assumed pre-1965 exposure levels same as post-1965 levels. Exposure assessment did not include the same industrial hygiene sampling conducted by Stewart et al. (1986) used in the (Beane Freeman et al., 2009; Beane Freeman et al., 2013) analyses which included this plant. Exposure estimates generated by this method were 10 times lower on	**External comparisons:** Oropharyngeal cancer U.S. referent SMR = 1.95 (0.63–4.56) [5] County referent SMR = 1.71 (0.56–4.00) [5] Hypopharyngeal cancer U.S. referent SMR = 2.01 (0.87–3.96) [3] County referent SMR = 1.88 (0.81–3.70) [3] Pharyngeal cancer excluding nasopharyngeal U.S. referent SMR = 1.98 (1.17–3.15) [16] County referent SMR = 1.71 (1.01–2.72) [16]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Design: Cohort mortality study with external comparison groups. **Analysis:** SMRs calculated by dividing the number of observed deaths by the number of expected deaths. Expected deaths were the product of death rate (at national, state, or local level) and person-years accumulated by all the members of the cohort. SMRs made age, race, gender, and period specific to reduce bias and to generate tabular information by these variables. Mortality was compared with death rates in two Connecticut counties and the United States. These results are shown in Table 2 in Marsh et al. (2007a). **Related studies:** (Beane Freeman et al., 2009) Hauptmann et al. (2004) (Marsh et al., 1994; Marsh et al., 1996; Marsh et al., 2002) **Confidence in effect estimates:**[a] **OHPC together:** **MEDIUM ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency analysis with attenuation of association.	average than those estimated by the NCI. Multiple exposure metrics including, known exposure, average intensity and cumulative exposures were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** None. **Coexposures:** Coexposures previously identified in Marsh et al. (1996) included product and nonproduct particulates and airborne pigments. [As noted in Appendix B.3.9: Marsh et al. (2002) attempted to evaluate smoking but data were incomplete. No other potential confounders were evaluated. (Beane Freeman et al., 2009; Beane Freeman et al., 2013) evaluated 11 potential confounders among a set of 10 plants that included this one and did not find any confounding.]	
Reference: Marsh et al. (2002) **Population:** 7,328 workers employed at formaldehyde-using plant in the United States followed from 1945 through 1998. Vital status was identified from the National Death Index, private businesses, or state and local agencies, and was 98.4% complete and 1.6% lost to follow-up. This population was from one plant from (Beane Freeman et al., 2009; Beane Freeman et al., 2013). **Outcome definition:** Death certificates used to determine underlying cause of death from oropharyngeal/hypopharyngeal	**Exposure assessment:** Worker-specific exposure from job-exposure matrix based on available sporadic sampling data from 1965 to 1987, job descriptions, and verbal job descriptions by plant personnel and industrial hygienists. Exposures ranked on a 7-point scale with exposure range assigned to each rank. 17% of jobs validated with company monitoring data; remaining 83% based on professional judgment. Assumed pre-1965 exposure levels same as post-1965 levels. Exposure assessment did not include the same industrial hygiene sampling conducted by Stewart et al. (1986) used in the (Beane Freeman et al.,	**External comparisons:** Oropharyngeal cancer U.S. referent SMR = 2.17 (0.71–5.07) [5] County referent SMR = 1.80 (0.58–4.19) [5] Hypopharyngeal cancer U.S. referent SMR = 2.25 (0.46–6.58) [3] County referent SMR = 1.52 (0.31–4.43) [3] Pharyngeal cancer, unspecified U.S. referent SMR = 2.11 (0.85–4.35) [7] County referent SMR = 1.89 (0.76–3.89) [7] Oropharyngeal/Hypopharyngeal cancer Exposure to formaldehyde: Level 1 SMR = 1.24‡ (0.21–4.10)† [2] Level 2 SMR = 1.83‡ (1.02–3.05)† [13] Duration of formaldehyde exposure: Level 1 SMR = 1.24‡ (0.21–4.10)† [2]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
cancer according to the ICD-9 codes (146, 148). **Design:** Cohort mortality study with external comparison groups. **Analysis:** SMRs calculated by dividing the number of observed deaths by the number of expected deaths. Expected deaths were the product of death rate (at national, state, or local level) and person-years accumulated by all the members of the cohort. SMRs made age, race, sex, and period specific to reduce bias and to generate tabular information by these variables. Mortality was compared with death rates in two Connecticut counties and the United States. These results are shown in Table 2 in Marsh et al. (2002). **Related studies:** (Beane Freeman et al., 2009; Beane Freeman et al., 2013) (Marsh et al., 1994; Marsh et al., 1996; Marsh et al., 2007a) **Confidence in effect estimates:**[a] **Oro- alone & Hypo- alone:** **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency analysis with attenuation of association. Low sensitivity (few cases).	2009; Beane Freeman et al., 2013) analyses which included this plant, Exposure estimates generated by this method were 10 times lower on average than those estimated by the NCI. Multiple exposure metrics including, known exposure, average intensity and cumulative exposures were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure** (*from Table 3 in Marsh et al. (2002)*)**:** For all variations in exposure: Level 1 (unexposed) Exposure to formaldehyde: Level 2 (exposed) Duration of exposure to formaldehyde: Level 2 (0 to <1 years) Level 3 (1 to 9 years) Level 4 (>10 years) Cumulative exposure to formaldehyde: Level 2 (0 to <0.004 ppm-years) Level 3 (0.004 to 0.219 ppm-years) Level 4 (>0.22 ppm-years) Average intensity exposure: Level 2 (0 to <0.03 ppm) Level 3 (0.03 to 0.159 ppm) Level 4 (>0.16 ppm) Exposure to formaldehyde >0.2 ppm: Level 2 (exposed) Duration of exposure to >0.2 ppm: Level 2 (0 to <1 years) Level 3 (1 to 9 years) Level 4 (>10 years) **Coexposures:** Coexposures previously identified in Marsh et al. (1996) included product and nonproduct particulates and airborne pigments.	Level 2 SMR = 1.75‡ (0.77–3.46)† [7] Level 3 SMR = 1.58‡ (0.40–4.32)† [3] Level 4 SMR = 2.48‡ (0.63–6.75)† [3] Cumulative exposure to formaldehyde: Level 1 SMR = 1.24‡ (0.21–4.10)† [2] Level 2 SMR = 3.20‡ (1.17–7.10)† [5] Level 3 SMR = 1.28‡ (0.40–3.07)† [4] Level 4 SMR = 1.56‡ (0.50–3.77)† [4] Average intensity exposure: Level 1 SMR = 1.24‡ (0.15–4.49)† [2] Level 2 SMR = 1.96‡ (0.72–4.33)† [5] Level 3 SMR = 1.91‡ (0.49–5.20)† [3] Level 4 SMR = 1.69‡ (0.62–3.74)† [5] Exposure to formaldehyde >0.2 ppm: Level 1 SMR = 1.51‡ (0.21–4.10)† [6] Level 2 SMR = 2.01‡ (1.02–3.05)† [9] Duration of exposure to >0.2 ppm: Level 1 SMR = 1.51‡ (0.21–4.10)† [6] Level 2 SMR = 1.72‡ (0.47–4.16)† [4] Level 3 SMR = 1.30‡ (0.22–4.29)† [2] Level 4 SMR = 4.94‡ (1.25–13.38)† [3] ‡**Note:** EPA derived SMRs for the combination of oropharyngeal, hypopharyngeal and unspecified pharyngeal cancer by subtracting the number of observed and expected nasopharyngeal cancer from the same counts for all pharyngeal cancers. †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))
Reference: Marsh et al. (2002)	**Exposure assessment:** Worker-specific exposure from job-exposure matrix based on available sporadic sampling data from 1965 to 1987, job descriptions, and verbal job descriptions by plant personnel and industrial hygienists. Exposures ranked on a 7-point scale with exposure range assigned to each rank. 17% of jobs	**External comparisons:** Exposure to formaldehyde >0.7 ppm: Level 1 SMR = 1.86‡ (1.01–3.16)† [12] Level 2 SMR = 1.46‡ (0.37–3.98)† [3] Duration of exposure to >0.7 ppm: Level 1 SMR = 1.86‡ (1.01–3.16)† [12] Level 2 SMR = 1.49‡ (0.25–4.93)† [2] Level 3 SMR = 1.41‡ (0.07–6.95)† [1]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	validated with company monitoring data; remaining 83% based on professional judgment. Assumed pre-1965 exposure levels same as post-1965 levels. Exposure estimates generated by this method were 10 times lower on average than those estimated by the NCI. Multiple exposure metrics including, known exposure, average intensity, and cumulative exposures were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in work *history*** *(from Table 3 in* Marsh et al. (2002)*)*: For all variations in exposure: Level 1 (unexposed) Exposure to formaldehyde: Level 2 (exposed) Work history: Level 1 (short-term workers: <1 year) Level 2 (long-term workers: 1+ year) Year of hire: Level 1 (1941–1946) Level 2 (1947–1956) Level 3 (1957+) Duration of employment: Level 1 (unexposed) Level 2 (<1 year) Level 3 (1+ years) Time since first employment: Level 1 (<20 year) Level 2 (20–29 years) Level 3 (30+ years)	Work history: Level 1 SMR = 2.82‡ (1.31–5.37)† [8] Level 2 SMR = 1.70‡ (0.74–3.37)† [7] Year of hire: Level 1 SMR = 0.46‡ (0.11–10.73)† [1] Level 2 SMR = 2.49‡ (1.35–4.23)† [12] Level 3 SMR = 1.14‡ (0.19–3.78)† [2] Duration of employment: Level 1 SMR = 1.83‡ (0.85–3.47)† [8] Level 2 SMR = 1.77‡ (0.56–4.27)† [4] Level 3 SMR = 1.62‡ (0.41–4.41)† [3] Time since first employment: Level 1 SMR = 0.82‡ (0.14–2.71)† [2] Level 2 SMR = 1.50‡ (0.48–3.61)† [4] Level 3 SMR = 2.69‡ (1.31–4.94)† [9] ‡**Note:** EPA derived SMRs for the combination of oropharyngeal, hypopharyngeal and, unspecified pharyngeal cancer by subtracting the number of observed and expected nasopharyngeal cancer from the same counts for all pharyngeal cancers. †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))
Reference: Laforest et al. (2000) **Population:** Males diagnosed with primary hypopharyngeal squamous cell cancers between January 1989 and May 1991 and identified through 15 French hospitals. Interviews	**Exposure assessment:** Occupational history obtained by interview. Exposure assessment based on job-exposure matrix that included level and probability of exposure, duration, and cumulative exposure to formaldehyde.	**Internal comparisons:** All subjects Exposure to formaldehyde: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 1.35 (0.86–2.14) [83]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
completed for 79.5% of eligible cases and 86% of eligible controls. **Outcome definition:** Diagnosis of laryngeal and hypopharyngeal cancers was histologically confirmed. **Design:** Hospital-based case-control study of 201 hypopharyngeal cancers. 296 hospital controls frequency matched on age. **Analysis:** ORs were calculated by unconditional logistic regression and adjusted for age, alcohol, and smoking. Induction periods of 5, 10, and 15 years was also utilized to account for latency in evaluating risk. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) and lack of latency analysis with attenuation of association	Multiple exposure metrics including known exposure, probability of exposure, and cumulative exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** All subjects Exposure to formaldehyde: Level 1 (never exposed) Level 2 (ever exposed) Probability of exposure: Level 1 (never exposed) Level 2 (<10%) Level 3 (10 to 50%) Level 4 (>50%) Duration of exposure: Level 1 (never exposed) Level 2 (<7 years) Level 3 (7 to 20 years) Level 4 (>20 years) Cumulative exposure: Level 1 (never exposed) Level 2 (low, <0.02) Level 3 (medium, 0.02 to 0.09) Level 4 (high, >0.09) Subjects with a probability of exposure >10% Exposure to formaldehyde: Level 1 (never exposed) Level 2 (ever exposed) Duration of exposure: Level 1 (never exposed) Level 2 (≤7 years) Level 3 (7 to 20 years) Level 4 (>20 years) Cumulative exposure: Level 1 (never exposed) Level 2 (low) Level 3 (medium) Level 4 (high) **Other exposures:** asbestos, coal dust, leather dust, wood dust, flour dust, silica, and textile dust. [As noted in Appendix B.3.9: Of these, only coal dust significantly increased the risk of hypopharyngeal cancer in this study but coal dust and asbestos	Probability of exposure: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 1.08 (0.62−1.88) [42] Level 3 OR = 1.01 (0.44−2.31) [15] Level 4 OR = 3.78 (1.50−9.49) [26] *p*-trend (all) < 0.005 Cumulative exposure: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 1.03 (0.51−2.07) [23] Level 3 OR = 1.57 (0.81−3.06) [32] Level 4 OR = 1.51 (0.74−3.10) [28] Duration of exposure: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 1.09 (0.50−2.38) [18] Level 3 OR = 1.39 (0.74−2.62) [37] Level 4 OR = 1.51 (0.78−2.92) [28] Subjects with a probability of exposure >10% Exposure to formaldehyde: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 1.74 (0.91−3.34) [41] Cumulative exposure: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 0.78 (0.11−5.45) [3] Level 3 OR = 1.77 (0.65−4.78) [13] Level 4 OR = 1.92 (0.86−4.32) [25] *p*-trend (all) < 0.14 Duration of exposure: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 0.74 (0.20−2.68) [6] Level 3 OR = 1.65 (0.67−4.08) [19] Level 4 OR = 2.70 (1.08−6.73) [16] *p*-trend (all) < 0.04 Introduction of induction times as described did not substantially change the results.

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	were controlled for in the OHPC analysis.]	
Reference: Gustavsson et al. (1998) **Population:** Males between the ages of 40 and 79 years residing in Sweden identified by hospitals reports or regional cancer registries during 1988−1990. Interviews completed for 90% of cases and 85% of controls. **Outcome definition:** Diagnosis of cancer of the pharyngeal cancer based on ICD-9 codes 146 (oropharynx) and 148 (hypopharynx) but not including code 147 (nasopharynx) on weekly reports from departments of otorhinolaryngology, oncology, and surgery and from regional cancer registries. **Design:** Community-based, case-control study of 138 cases of squamous cell carcinoma of the oropharynx/hypopharynx. 641 controls were randomly identified from population registers and frequency matched by region and age. **Analysis:** RRs were calculated by unconditional logistic regression and adjusted for region, age, drinking, and smoking. **Confidence in effect estimates:**[a] **SUMMARY:** **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) and lack of latency analysis with attenuation of association. Confounding possible. Low sensitivity (exposure was rare).	**Exposure assessment:** Occupational history obtained by interview and yielded information on all jobs held >1 year, starting and stopping times, job title, tasks, and company. Histories reviewed by industrial hygienist who coded jobs based on intensity and probability of exposure to 17 occupational factors. Exposure assessments estimated intensity on a 4-point scale and probability of exposure as point estimates. Cumulative exposure calculated as the product of exposure intensity, probability of exposure, and duration of exposure, and by adding contributions over entire work history. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (never) Level 2 (ever) **Other exposures:** polycyclic aromatic hydrocarbons, asbestos, general dust, wood dust, quartz, metal dust, oil mist, welding fumes, manmade mineral fibers, paper dust, textile dust, hexavalent chromium, phenoxy acids, nickel, acid mist, and leather dust. [As noted in Appendix B.3.9: Of these, only leather dust was a risk factor but only five cases were exposed.]	**Internal comparisons:** Exposure to formaldehyde: Level 1 OR = 1.00 (Ref. value) [# not given] Level 2 OR = 1.01 (0.49−2.07) [13]
Reference: Vaughan (1989) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System during	**Exposure assessment:** Presumed exposure to formaldehyde. Interview-based information on lifetime occupational history by job type and industry.	**Internal comparisons:** Carpenter (lagged 15 years) All Industries: OR = 1.3 (0.5−3.4) [11] All Industries by Duration: Level 1 OR = 1.0 (Ref. value)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
1980–1983. Participation for all cases was 68.7 and 80.0% for controls. **Outcome definition:** Diagnosis of pharyngeal cancer based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates. Nonsquamous cell cancers were excluded from the study. **Design:** Population-based, case-control study of 183 cases with oro pharyngeal/hypopharyngeal cancer. 552 controls were identified by random digit dialing in same geographic area. **Analysis:** ORs were calculated by logistic regression and adjusted for gender, cigarette smoking, and alcohol. Induction periods were evaluated. **Related studies:** Vaughan et al. (1986a, 1986b) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association.	Occupations evaluated for both no lag and 15-year lag time between recent exposure and diagnosis. **Duration and timing:** Duration and timing of exposure were evaluated. **Variation in exposure:** Occupation and industry Duration: Level 1 (unexposed) Level 2 (1 to 9 years) Level 3 (>10 years) **Other exposures:** Not evaluated. [As noted in Appendix B.3.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. However, as this is a case-control study the correlation between formaldehyde and wood dust is expected to be small and thus wood dust would not be expected to be a confounder.]	Level 2 OR = 0.6 (not given) Level 3 OR = 2.2 (not given) Carpenter (lagged 15 years) Construction industry: OR = 1.8 (0.7–4.8) [10] Construction by Duration: Level 1 OR = 1.0 (Ref. value) Level 2 OR = 0.7 (not given) Level 3 OR = 6.2 (not given)
Reference: Vaughan et al. (1986a) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System between 1980 and 1983. Participation for all cases was 69 and 80% for controls. Interviews completed for 71% of cases and 83% of controls. **Outcome definition:** Diagnosis of oropharynx/hypopharynx cancer (ICD codes 146 and 148) based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates.	**Exposure assessment:** Interview-based information on lifetime occupational exposure to formaldehyde with cases, next of kin, and controls. Exposure from available hygiene data, NIOSH and other data, and NCI job-exposure linkage system. Multiple exposure metrics including intensity, # of years exposed, and exposure score based on the sum of # years spent per job weighted by estimated formaldehyde level were evaluated. Exposure score calculated for both no lag and 15-year lag time between recent exposure and diagnosis.	**Internal comparisons:** Intensity: Level 1 OR = 1.0 (Ref. value) [147] Level 2 OR = 0.8 (0.5–1.4) [41] Level 3 OR = 0.8 (0.4–1.7) [13] Level 4 OR = 0.6 (0.1–2.7) [4] Number of years exposed: Level 1 OR = 1.0 (Ref. value) [147] Level 2 OR = 0.6 (0.3–1.0) [32] Level 3 OR = 1.3 (0.7–2.5) [26] Exposure score (no lag): Level 1 OR = 1.0 (Ref. value) [170] Level 2 OR = 0.6 (0.3–1.2) [14]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Design: Population-based, case-control study of 205 incident cases with cancer of the oropharynx/hypopharynx including unspecified pharyngeal sites. 552 controls were identified by random digit dialing in same geographic area. **Analysis:** ORs were calculated by logistic regression and adjusted for cigarette smoking, alcohol consumption, sex, and age. An induction period of 15 years was also utilized to account for latency in evaluating exposure score. **Related studies:** Vaughan et al. (1986b) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association.	**Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Intensity: Level 1 (background) Level 2 (low) Level 3 (medium) Level 4 (high) Number of years exposed: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years) Exposure score (no lag): Level 1 (0 to 4) Level 2 (5 to 19) Level 3 (≥20) Exposure score (15-year lag): Level 1 (0 to 4) Level 2 (5 to 19) Level 3 (≥20) **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. However, as this is a case-control study the correlation between formaldehyde and wood dust is expected to be small and thus wood dust would not be expected to be a confounder.]	Level 3 OR = 1.5 (0.7–3.0) [21] Exposure score (15-year lag): Level 1 OR = 1.0 (Ref. value) [174] Level 2 OR = 0.9 (0.4–1.8) [16] Level 3 OR = 1.3 (0.6–3.1) [15]
Reference: Vaughan et al. (1986b) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System between 1980 and 1983. Participation for all cases was 68.7 and 80.0% for controls. Interviews completed for 71% of cases and 83% of controls. **Outcome definition:** Diagnosis of oropharynx/hypopharynx cancer (ICD codes 146 and 148) based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates.	**Exposure assessment:** Interview-based information on lifetime occupational history and residential history from cases, controls, and next of kin for deceased cases. Multiple exposure metrics including type of dwelling (i.e., mobile home) and use of particleboard or plywood were evaluated. **Duration and timing:** Exposure period since 1950. Duration of exposure was evaluated. **Variation in exposure:** Residence in mobile home: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years)	**Internal comparisons:** Residence in mobile home: Level 1 OR = 1.0 (Ref. value) [177] Level 2 OR = 0.9 (0.5–1.8) [21] Level 3 OR = 0.8 (0.2–2.7) [7] Years of exposure to particleboard: Level 1 OR = 1.0 (Ref. value) [137] Level 2 OR = 1.1 (0.7–1.9) [40] Level 3 OR = 0.8 (0.5–1.4) [28]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Design: Population-based, case-control study of 205 incident cases with cancer of the oropharynx/hypopharynx including unspecified pharyngeal sites. 552 controls were identified by random digit dialing in same geographic area with one control per case randomly selected from all the eligible persons in the household and frequency matched for gender and age. **Analysis:** ORs were calculated by multiple logistic regression and adjusted for cigarette smoking, alcohol consumption, sex, and age. **Related studies:** Vaughan et al. (1986a) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association.	Years of exposure to particleboard or plywood: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years) **Coexposures:** Not evaluated. Information of occupational exposures provided in Vaughan et al. (1986a) [As noted in Appendix B.3.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. However, as this is a case-control study the correlation between formaldehyde and wood dust is expected to be small and thus wood dust would not be expected to be a confounder.]	

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Laryngeal cancer

Epidemiological evidence

Evidence describing an association between formaldehyde exposure and the risk of developing or dying from laryngeal cancer was available from 18 studies—13 cohort studies (Walrath and Fraumeni, 1983, 1984; Stroup et al., 1986; Meyers et al., 2013; Levine et al., 1984a; Jakobsson et al., 1997; Hayes et al., 1990; Hansen et al., 1994; Hansen and Olsen, 1995; Coggon et al., 2014; Beane Freeman et al., 2013; Band et al., 1997; Andjelkovich et al., 1995) and five case-control studies (Wortley et al., 1992; Shangina et al., 2006; Laforest et al., 2000; Gustavsson et al., 1998; Berrino et al., 2003). Two reported results were classified as *not informative*. Berrino et al. (2003) was classified as *not informative* due to likely confounding by highly correlated coexposures, one of which was a stronger risk factor for laryngeal cancer in that study than was formaldehyde (i.e., solvents). Hansen et al. (1994) was classified as *not informative* due to likely information bias

stemming from the rarity of exposure among cases in that cohort. The outcome-specific evaluations of confidence in the precise effect estimate of an association from each study are provided in Appendix B.3.9. Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for laryngeal cancer (see Table 3-35) following the causal evaluation.

Consistency of the observed association

The results of the 16 informative studies were not consistent. The study results presented in Table 3-35 (by confidence level and publication date) detail all of the reported associations. Only one set of results was classified with *high* confidence (Beane Freeman et al., 2013), and those results surrounded the null with a modest increase in risk overall with SMR = 1.23 (95% CI 0.91, 1.67), and at the highest level of average intensity of exposure a RR = 1.73 (95% CI 0.83, 3.60), and conversely, a modest decrease in risk at the highest level of peak exposure with RR = 0.72 (95% CI 0.32, 1.65), and a stronger decreased risk at the highest level of duration of exposure with RR = 0.33 (95% CI 0.10, 1.11). Of the five sets of results classified with *medium* confidence (Wortley et al., 1992; Shangina et al., 2006; Laforest et al., 2000; Hayes et al., 1990; Coggon et al., 2014), only two reported clearly increased risks; Shangina et al. (2006) showed an association with the highest level of cumulative exposure (OR = 3.12, 95% CI 1.23, 7.91) and Wortley et al. (1992) showed an association among those with at least 10 years of exposure and the highest peak exposures (OR = 4.3, 95% CI 1.0, 18.7). Coggon et al. (2014) found modestly increased risk for the cohort as a whole (SMR = 1.22, 95% CI 0.76, 1.84) and higher risks among those workers who had ever been "highly" exposed (SMR = 1.96, 95% CI 0.98, 3.50). They did not find greater risk among those who had been "highly" exposed for more than 1 year (SMR = 1.30, 95% CI 0.39, 4.38). The results from Laforest et al. (2000) and Hayes et al. (1990) did not show consistently increased risks. The study results classified with *low* confidence were consistently around the null. Results are plotted in Figure 3-22.

Strength of the observed association

Summary effect estimates for the association between formaldehyde exposure and the relative effect estimates of developing or dying from laryngeal cancer ranged from 0.33 to 4.3 and generally clustered around the null. The study results classified with *low* confidence were all limited to summary estimates without examination of exposures levels within the exposed study subjects. The results classified with *medium* confidence differentiated the risks by levels of exposure, and these results showed somewhat higher effect estimates among the most highly exposed groups, but these effect estimates were largely less than a doubling of risk. There were two results of *medium* confidence that reported more than a tripling of risk (Wortley et al., 1992; Shangina et al., 2006). However, the one set of results classified with *high* confidence (Beane Freeman et al., 2013) did not report a consistent pattern of increased risk.

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants started prior to their diagnoses of laryngeal cancer and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and done in a blinded fashion with respect to outcome status. While several of the studies did report results with lagged exposures to account for potential latency effects, none of the 16 studies provided details of analyses of a temporal relationship between the timing of exposure using different lags and the diagnoses of laryngeal cancer or deaths from laryngeal cancer. However, Shangina et al. (2006) did state that a 20-year lag in exposure was assessed but did not report those details for formaldehyde; and Wortley et al. (1992) reported that a 10-year lag in exposure 'only slightly' increased the estimated effects.

Exposure-response relationship

The strongest evidence of an exposure-response was reported by Shangina et al. (2006), who found that among cases of "Ever" exposed to formaldehyde, the OR = 1.68 (95% CI 0.85, 3.31), those cases with the highest tertile of cumulative exposure had an OR = 3.12 (95% CI 1.23, 7.91). Shangina et al. (2006) also reported suggestions of trends for increased risk with increasing tertiles of duration of exposure ($p < 0.06$) and with increasing tertile of cumulative exposure ($p < 0.07$). Wortley et al. (1992) also found higher risks among the most highly exposed with an OR = 4.3 (95% CI 1.0, 18.7). However, Beane Freeman et al. (2013) did not find consistent evidence of an exposure-response relationship for increasing peak exposure ($p > 0.5$), for increasing average intensity ($p = 0.44$), but did find a significant trend ($p = 0.02$) with cumulative exposure that may have been decreasing in nature with lower risks at higher exposures.

Potential impact of selection bias, information bias, confounding bias, and chance

For laryngeal cancer, the reliance of cohort studies on death certificates to detect cancers with relatively high survival underestimated the actual incidence of those cancers. Five-year survival rates are about 60% (see Appendix B.3.9). This may have resulted in undercounting of incident cases and underestimates of effect estimates in cohort studies compared to general populations. Selection bias could have somewhat obscured a truly larger effect of formaldehyde exposure on the risk of death from laryngeal cancer and may explain the preponderance of effect estimates near the null. The case-control studies Shangina et al. (2006), Laforest et al. (2000), Gustavsson et al. (1998), and Wortley et al. (1992), because they recruited incident cases, were less prone to such a bias. Information bias may distort findings when subjects' true personal exposures are inaccurately assigned. Random measurement error typically results in a bias toward the null, thereby obscuring any real effect by underestimating the effect's magnitude. Confounding is another potential bias that could arise if another cause of laryngeal cancer was statistically associated with formaldehyde exposure. However, there does not appear to be any evidence of negative confounding that could have obscured a real but unobserved effect. Overall, bias is

considered to be an unlikely alternative cause for the isolated reports of increased risks of laryngeal cancer associated with formaldehyde exposures.

Summary of Human Evidence Synthesis Judgments, Causal Evaluation, and Conclusion

Summary of human evidence synthesis judgments

The following factors were most influential to the causal evaluation and synthesis conclusion:

- *Consistency and Study Confidence*: The results of the 16 informative studies were not consistent – although there were suggestive associations reported for two medium confidence studies.

- *Strength and Precision*: Variable strength of the association across studies and metrics with two medium confidence studies reporting 3-fold increases in risk among groups with the highest exposure probability or duration and several studies reporting results near the null.

- *Coherence*: Where associations were observed, there were biologically coherent temporal relationship consistent with a pattern of exposure to formaldehyde and subsequent death from laryngeal cancer, allowing time for cancer induction, latency, and mortality - although the rarity of this cancer limited the available data on a specific latency period.

- *Dose-Response*: Suggestive exposure-response relationships of increased risk with increased formaldehyde exposure in one study, but lack of support for exposure-response from other studies including the single set of results classified with high confidence which found a significant downward trend in risks with increasing exposure.

Causal evaluation

The human evidence synthesis judgments is inconsistent. The moderate survival rate for laryngeal cancer (60%) may indicate that mortality data are not as good a proxy for incidence data for this cancer type.

Conclusion

- The available epidemiological studies provide *indeterminate* evidence of an association between formaldehyde exposure and increased risk of oropharyngeal/hypopharyngeal cancer.

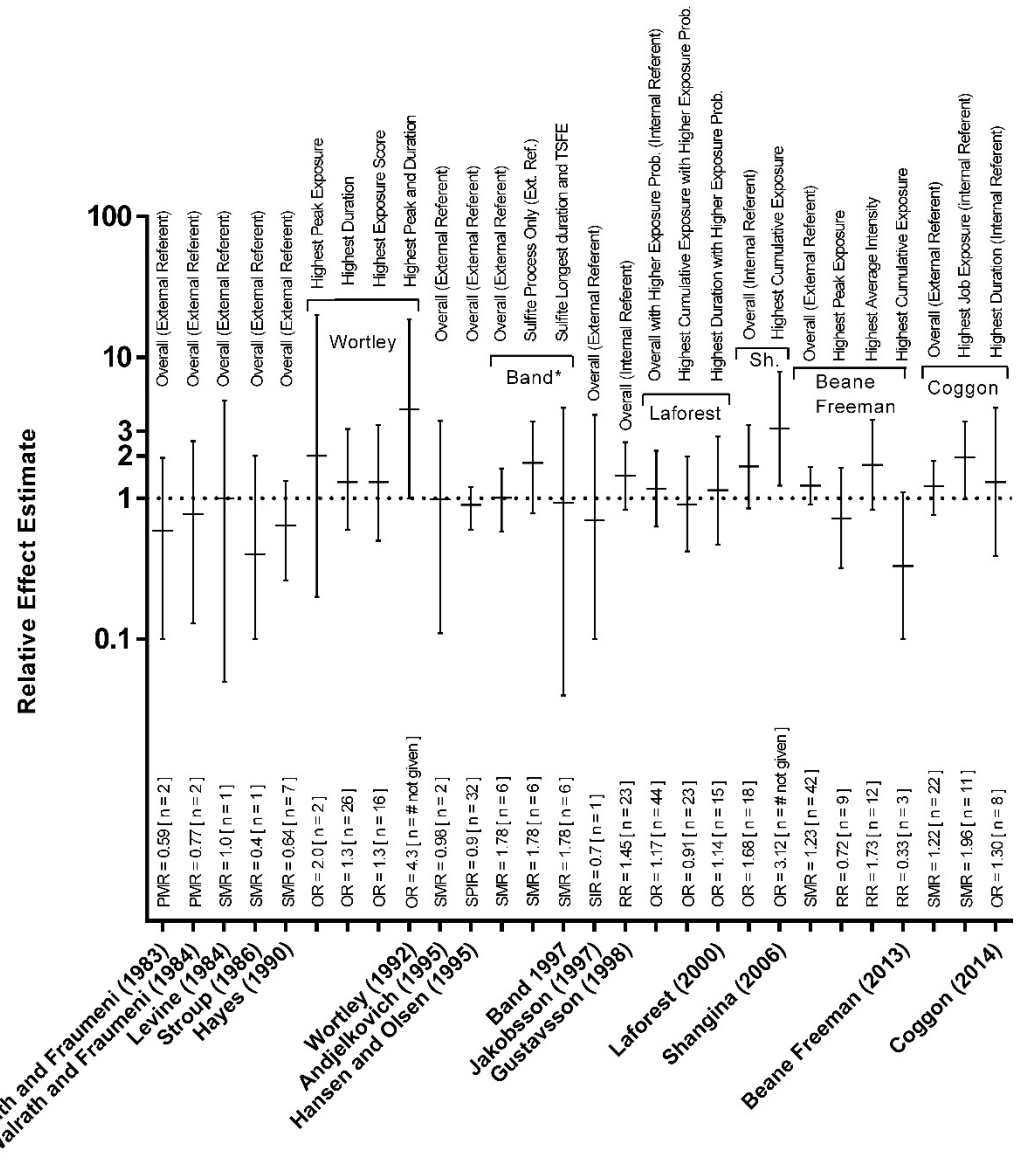


Figure 3-22. Epidemiological studies reporting laryngeal cancer risk estimates.

Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for laryngeal cancer (see Table 3-35). For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 1]). For studies reporting results on multiple metrics of exposure, only the highest category of each exposure metric is presented in the figure. Note that the confidence intervals for Band et al. (1997) are 90%, not 95%. Abbreviations: SMR = standardized mortality ratio; RR = relative risk; OR = odds ratio; SPIR = standardized proportional incidence ratio.

Table 3-35. Epidemiological studies of formaldehyde exposure and risk of laryngeal cancer

Study	Exposures	Results: effect estimate (95% CI) [# of cases]

Reference: Beane Freeman et al. (2013)
 	
Population: 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the United States followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. 676 workers (3%) were lost to follow-up. Vital status was 97.4% complete and only 2.6% lost to follow-up.
 	
Outcome definition: Death certificates used to determine underlying cause of death from laryngeal cancer (ICD-8: 161). Histological typing not reported.
 	
Design: Prospective cohort mortality study with external and internal comparison groups.
 	
Analysis: RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. Results were presented for 15-year lag.
 	
SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates.
 	
Related studies:
Hauptmann et al. (2004); Beane Freeman et al. (2009)
 	
Confidence in effect estimates:[a]
HIGH (No appreciable bias)
	Exposure assessment: Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists who took 2,000 air samples from representative job, and monitoring data from 1960 through 1980.
	
	Median TWA (over 8 hours) = 0.3 ppm (range 0.01−4.3). Median cumulative exposure = 0.6 ppm-years (range 0−107.4).
	
	Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data.
	
	Duration and timing: Exposure period from <1946 to 1980. Median length of follow-up: 42 years. Median length of employment was 2.6 years (range 1 day−47.7 years). Duration and timing since first exposure were not evaluated.
	
	Variation in exposure:
	Peak exposure:
	Level 1 (>0 to <2.0 ppm)
	Level 2 (2.0 to <4.0 ppm)
	Level 3 (≥4.0 ppm)
	Average intensity:
	Level 1 (>0 to <0.5 ppm)
	Level 2 (0.5 to <1.0 ppm)
	Level 3 (≥1.0 ppm)
	Cumulative exposure:
	Level 1 (>0 to <1.5 ppm-years)
	Level 2 (1.5 to <5.5 ppm-years)
	Level 3 (≥5.5 ppm-years)
	
	Coexposures: Exposures to 11 other compounds were identified and evaluated as potential confounders.
		Internal comparisons:
		Peak exposure
		Unexposed RR = 0.79 (0.25−2.48) [6]
		Level 1 RR = 1.00 (Ref. value) [17]
		Level 2 RR = 1.52 (0.76−3.05) [16]
		Level 3 RR = 0.72 (0.32−1.65) [9]
		p-trend (exposed) > 0.50;
		p-trend (all) > 0.50
		
		Average intensity
		Unexposed RR = 0.89 (0.29−2.75) [6]
		Level 1 RR = 1.00 (Ref. value) [21]
		Level 2 RR = 1.25 (0.57−2.76) [9]
		Level 3 RR = 1.73 (0.83−3.6) [12]
		p-trend (exposed) = 0.44;
		p-trend (all) = 0.39
		
		Cumulative exposure
		Unexposed RR = 0.67 (0.22−2.00) [6]
		Level 1 RR = 1.00 (Ref. value) [29]
		Level 2 RR = 1.01 (0.49−2.11) [10]
		Level 3 RR = 0.33 (0.10−1.11) [3]
		p-trend (exposed) = 0.02;
		p-trend (all) = 0.03
		
		External comparisons:
		$SMR_{Unexposed}$ = 0.93 (0.42−2.08) [6]
		$SMR_{Exposed}$ = 1.23 (0.91−1.67) [42]

Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories that produced formaldehyde. Cohort mortality followed from 1941 through 2012. Cause of deaths was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941−1982. Duration was evaluated as more, or less, than one year only among the "High"	**External comparisons:** SMR = 1.22 (0.76−1.84) [22] Highest exposure level attained Level 1 SMR = 0.33 (0.04−1.20) [2] Level 2 SMR = 1.40 (0.64−2.66) [9] Level 3 SMR = 1.96 (0.98−3.50) [11] **Internal comparisons:** Highest exposure level attained

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
deaths through 2012. Vital status was 98.9% complete through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from laryngeal cancer. **Design:** Cohort mortality study with external comparison group with a nested case-control study. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a] **MEDIUM ↓** High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency analysis with attenuation of association.	exposure group. Timing since first exposure was not evaluated. **Variation in exposure:** Highest exposure level attained Level 1 (Background) Level 2 (low/moderate) Level 3 (High) Duration of "High" exposures Level 1 (Background) Level 2 (<1 year) Level 3 (1 year or more) **Coexposures:** Not evaluated. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. [As noted in Appendix B.3.9: Styrene is associated with LHP cancers but not URT cancers. Asbestos is associated with URT cancers, including laryngeal cancer. Authors stated that the extent of coexposures was expected to be low. Potential for confounding may be mitigated by low coexposures. Other coexposures are not known risk factors for this outcome.]	Level 1 OR = 1.00 (Ref. value) [14] Level 2 OR = 1.20 (0.53–2.73) [17] Level 3 OR = not given [22] Duration of "High" exposures Level 1 OR = 1.00 (Ref. value) [14] Level 1 OR = 2.02 (0.65–6.27) [14] Level 2 OR = 1.30 (0.39–4.38) [8]
Reference: Shangina et al. (2006) **Population:** Males between the ages of 15 and 79 years residing in four European countries that were diagnosed with laryngeal cancer during 1999–2002 and identified by study centers in Romania, Poland, Russia, and Slovakia. **Outcome definition:** Diagnosis of laryngeal cancer was histologically or cytologically confirmed and included topographic subcategories from ICD-O code C32 (glottis, supraglottis, subglottis, laryngeal cartilage, overlapping lesion of the larynx, and larynx, unspecified). **Design:** Multicenter case-control study of 316 laryngeal cancer cases. 728	**Exposure assessment:** Occupational histories obtained by interview and yielded information on all jobs held >1 year. A general questionnaire obtained information of job titles, tasks, industries, starting and stopping times, full-time/part-time status, working environments, and specific exposures. A specific questionnaire was completed for employment in defined jobs or industries. Exposure assessment based on expert judgment of reported task descriptions. Exposure scored according to intensity, frequency, and confidence. Multiple exposure metrics including known exposure and cumulative exposure were evaluated.	**Internal comparisons:** Exposure to formaldehyde: Level 1 OR = 1.00 (Ref. value) [298] Level 2 OR = 1.68 (0.85–3.31) [18] Duration of exposure: *p*-trend (all) = 0.06 Cumulative exposure: Level 1 Unspecified Level 2 Unspecified Level 3 OR = 3.12 (1.23–7.91) *p*-trend (all) = 0.07 Duration of exposure: Level 1 Unspecified Level 2 Unspecified Level 3 Unspecified *p*-trend (all) = 0.06

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
hospital controls were frequency matched by age. **Analysis:** ORs were calculated by unconditional logistic regression and adjusted for age, country, tobacco smoking, and alcohol consumption. An induction period of 20 years was also utilized to account for latency in evaluating risk. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) with attenuation of association. Low sensitivity (exposure was rare).	**Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (never) Level 2 (ever) Cumulative exposure (tertiles): Level 1 (Tertile 1 unspecified) Level 2 (Tertile 2 unspecified) Level 3 (≥22,700 mg/m^3-hrs) Duration of exposure (tertiles): Level 1 (Tertile 1 unspecified) Level 2 (Tertile 2 unspecified) Level 3 (Tertile 3 unspecified) Definitions for levels of exposure for duration of exposure to formaldehyde and cumulative exposure not provided by authors except for the lower bound of Tertile 3 for cumulative exposure. **Other exposures:** Not evaluated as confounders. [As noted in Appendix B.3.9: Other exposures that were found to be risk factors included dusts of "hard alloys" (16 cases) and chlorinated solvents (15 cases). Hard-alloy dust and chlorinated solvents were each found in fewer than 6% of cases, the correlation between them is considered to be small enough to make confounding unlikely.]	No notable findings were reported between formaldehyde exposure and the risk of laryngeal cancer when considering an induction period of 20 years.
Reference: Laforest et al. (2000) **Population:** Males diagnosed with primary laryngeal squamous cell cancers between January 1989 and May 1991 and identified through 15 French hospitals. Interviews completed for 79.5% of eligible cases and 86% of eligible controls. **Outcome definition:** Diagnosis of laryngeal was histologically confirmed. **Design:** Hospital-based case-control study of 296 laryngeal cancers. 296 hospital controls frequency matched on age. **Analysis:** ORs were calculated by unconditional logistic regression and	**Exposure assessment:** Occupational history obtained by interview. Exposure assessment based on job-exposure matrix that included level and probability of exposure, duration, and cumulative exposure to formaldehyde. Multiple exposure metrics including known exposure, probability of exposure, and cumulative exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** All subjects Exposure to formaldehyde: Level 1 (never exposed) Level 2 (ever exposed)	**Internal comparisons:** All subjects Exposure to formaldehyde: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 1.14 (0.76–1.70) [102] Probability of exposure: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 1.16 (0.73–1.86) [58] Level 3 OR = 1.12 (0.55–2.30) [23] Level 4 OR = 1.04 (0.44–2.47) [21] Cumulative exposure: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 1.12 (0.62–2.01) [35] Level 3 OR = 1.44 (0.79–2.63) [38] Level 4 OR = 0.87 (0.45–1.67) [29] Duration of exposure: Level 1 OR = 1.00 (Ref. value) [194]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
adjusted for age, alcohol, and smoking. Induction periods of 5, 10, and 15 years was also utilized to account for latency in evaluating risk. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) and lack of latency analysis with attenuation of association.	Probability of exposure: Level 1 (never exposed) Level 2 (<10%) Level 3 (10 to 50%) Level 4 (>50%) Duration of exposure: Level 1 (never exposed) Level 2 (<7 years) Level 3 (7 to 20 years) Level 4 (>20 years) Cumulative exposure: Level 1 (never exposed) Level 2 (low, <0.02) Level 3 (medium, 0.02 to 0.09) Level 4 (high, >0.09) Subjects with a probability of exposure >10% Exposure to formaldehyde: Level 1 (never exposed) Level 2 (ever exposed) Duration of exposure: Level 1 (never exposed) Level 2 (≤7 years) Level 3 (7 to 20 years) Level 4 (>20 years) Cumulative exposure: Level 1 (never exposed) Level 2 (low) Level 3 (medium) Level 4 (high) **Other exposures:** asbestos, coal dust, leather dust, wood dust, flour dust, silica, and textile dust. [As noted in Appendix B.3.9: Of these, none significantly increased the risk of laryngeal cancer in this study but coal dust was controlled for in the laryngeal cancer analysis.]	Level 2 OR = 1.42 (0.75–2.68) [35] Level 3 OR = 1.09 (0.62–1.96) [37] Level 4 OR = 0.96 (0.52–1.76) [30] Subjects with a probability of exposure >10% Exposure to formaldehyde: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 1.17 (0.63–2.17) [44] Cumulative exposure: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 0.68 (0.12–3.90) [4] Level 3 OR = 1.86 (0.76–4.55) [17] Level 4 OR = 0.91 (0.42–1.99) [23] Duration of exposure: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 1.68 (0.60–4.72) [15] Level 3 OR = 0.86 (0.33–2.24) [14] Level 4 OR = 1.14 (0.47–2.74) [15] Introduction of induction times as described did not substantially change the results.
Reference: Wortley et al. (1992) **Population:** Males and females between the ages of 20 and 74 years residing in western Washington who were diagnosed with laryngeal cancer between September 1983 and February 1987 and identified through the cancer surveillance system of the Fred Hutchinson Cancer Research Center. Interviews completed for 80.8% of eligible cases and 80% of eligible controls.	**Exposure assessment:** Occupational history obtained by interview for all jobs held for ≥6 months and included job titles, description of tasks performed, and industry. Job titles analyzed by duration of exposure (≤9 year and ≥10 years). Exposures assessment based on job-exposure matrix. Industrial hygienists classified jobs into four levels of exposure to formaldehyde based on judgment of both likelihood and degree of exposure.	**Internal comparisons:** Peak exposure: Level 1 OR = 1.0 (Ref. value) [177] Level 2 OR = 1.0 (0.6–1.7) [42] Level 3 OR = 1.0 (0.4–2.1) [14] Level 4 OR = 2.0 (0.2–20) [2] Duration: Level 1 OR = 1.0 (Ref. value) [182] Level 2 OR = 0.8 (0.4–1.3) [27] Level 3 OR = 1.3 (0.6–3.1) [26] Exposure scores: Level 1 OR = 1.0 (Ref. value) [201] Level 2 OR = 1.0 (0.5–2.0) [18]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Outcome definition: Diagnosis of cancer of the larynx based on ICD codes 161.0−161.9 from cancer registry data. **Design:** Population-based case-control study of 235 cases of laryngeal cancer. 547 controls identified from random digit dialing and were selected for the same distributions of age and sex to the cases. **Analysis:** ORs were calculated by multiple logistic regression and adjusted for smoking, drinking, age, and education. An induction period of 10 years was also utilized to account for latency in evaluating duration and exposure score. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) with attenuation of association.	Exposure score calculated as the weighted sum of years with exposure, with weight based on level of exposure code. Exposure codes defined as: 0 = no, 1 = low, 2 = medium, and 3 = high. Multiple exposure metrics including peak exposure (subject's highest exposure code) and exposure score were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Peak exposure: Level 1 (none) Level 2 (low) Level 3 (medium) Level 4 (high) Duration: Level 1 (<1 years) Level 2 (1 to 9 years) Level 3 (≥10 years) Exposure scores: Level 1 (<5) Level 2 (5 to 19) Level 3 (≥20) Peak and Duration: Level 1 (none) Level 2 (med/high and ≥10 years) Level 3 (high and ≥10 years) **Other exposures:** asbestos, chromium, nickel, cutting oils, and diesel fumes. High-risk occupations (e.g., mechanics, carpenters, painters, textile machine operators) likely had coexposures to unidentified substances. [As noted in Appendix B.3.9: This is a case-control study the correlation between formaldehyde and those potential confounders is expected to be small, and thus, wood dust would not be expected to be a confounder.]	Level 3 OR = 1.3 (0.5−3.3) [16] Peak and Duration Level 1 OR = 1.0 (Ref. value) [177] Level 2 OR = 4.2 (0.9−19.4) [not given] Peak and Duration Level 1 OR = 1.0 (Ref. value) [177] Level 2 OR = 4.2 (0.9−19.4) [not given] Level 3 OR = 4.3 (1.0−18.7) [not given] No notable findings were reported between formaldehyde exposure and the risk of laryngeal cancer when considering an induction period of 10 years.
Reference: Hayes et al. (1990) **Population:** 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975−1985. Death certificates obtained for 79% of	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. Exposure based on occupation which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to 3.99 ppm (low ventilation) with peaks up to 20 ppm.	**External comparisons:** PMR = 0.64 (0.26−1.33) [7]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
potential study subjects (*n* = 6,651) with vital status unknown for 21%. **Outcome definition:** Death certificates and licensing boards used to determine cause of death from laryngeal cancer (ICD-8: 161). **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association.	Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975–1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60–74 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.]	
Reference: Meyers et al. (2013) **Population:** 11,043 workers in 3 U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion. **Outcome definition:** Death certificates used to determine the underlying cause of death from laryngeal cancer (ICD code in use at time of death). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Pinkerton et al. (2004) Stayner et al. (1985)	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984. Geometric TWA8 exposures ranged from 0.09 to 0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm, (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 to 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were not evaluated for this cancer. **Variation in exposure:** Not evaluated.	**External comparisons:** SMR = 0.77 (0.21–1.97) [4]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Stayner et al. (1988) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	
Reference: Gustavsson et al. (1998) **Population:** Males between the ages of 40 and 79 years residing in Sweden identified by hospitals reports or regional cancer registries during 1988–1990. Interviews completed for 90% of cases and 85% of controls. **Outcome definition:** Diagnosis of laryngeal cancer based on ICD-9 codes on weekly reports from departments of otorhinolaryngology, oncology, and surgery and from regional cancer registries. **Design:** Community-based, case-control study of 157 cases of squamous cell carcinoma of the larynx. 641 controls were randomly identified from population registers and frequency matched by region and age. **Analysis:** RRs were calculated by unconditional logistic regression and adjusted for region, age, drinking, and smoking. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) and lack of latency analysis with attenuation of association. Confounding possible. Low sensitivity (exposure was rare).	**Exposure assessment:** Occupational history obtained by interview and yielded information on all jobs held >1 year, starting and stopping times, job title, tasks, and company. Histories reviewed by industrial hygienist who coded jobs based on intensity and probability of exposure to 17 occupational factors. Exposure assessments estimated intensity on a 4-point scale and probability of exposure as point estimates. Cumulative exposure calculated as the product of exposure intensity, probability of exposure, and duration of exposure, and by adding contributions over entire work history. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (never) Level 2 (ever) **Other exposures:** polycyclic aromatic hydrocarbons, asbestos, general dust, wood dust, quartz, metal dust, oil mist, welding fumes, manmade mineral fibers, paper dust, textile dust, hexavalent chromium, phenoxy acids, nickel, acid mist, and leather dust. [As noted in Appendix B.3.9: Asbestos and metal dust were both stronger risk factors for laryngeal cancer so there is a potential for confounding.]	**Internal comparisons:** Exposure to formaldehyde: Level 1 RR = 1.00 (Ref. value) [# not given] Level 2 RR = 1.45 (0.83–2.51) [23]
Reference: Band et al. (1997) **Population:** 30,157 male workers in the pulp and paper industry with at least 1-year employment accrued by January 1950. Followed through December 1982. Loss to follow-up was	**Exposure assessment:** Occupational data limited to hire and termination dates for all workers and type of chemical process of pulping (sulfate vs. sulfite). No job-specific data available. Presumed exposure to formaldehyde known to be used in the plant.	**External comparisons:** All workers SMR = 1.01 (90% CI 0.58–1.63) [12] **Workers only in sulfite process** All workers SMR = 1.78 (90% CI 0.78–3.52) [8]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
less than 6.5% for workers exposed to the sulfate process (67% of original cohort of 30,157) and less than 20% for workers exposed to the sulfite process. **Outcome definition**: Cause of death obtained from the National Mortality Database based on ICD version in effect at time of death and standardize to ICD-9 version. Larynx: ICD-9 161. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the Canadian population. **Confidence in effect estimates:**[a] ↓ (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) with attenuation of association. Confounding possible.	Formaldehyde is known to be an exposure risk for pulp and paper mill workers: job-specific median exposures ranging from 0.04 to 0.4 ppm with peaks as high as 50 ppm (Korhonen et al., 2004). **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** No variation in formaldehyde exposure was reported. Results presented by pulping process (sulfate vs. sulfite) but neither process uses formaldehyde which is used in paper making. **Coexposures:** Not evaluated as confounders. [As noted in Appendix B.3.9: Potential confounders for these outcomes include chlorophenols, **acid mists**, dioxin, and perchloroethylene and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	Work duration <15 years TSFE <15 years SMR = 2.46 (90% CI 0.10–11.63) [1] TSFE ≥15 years SMR = 2.13 (90% CI 0.72–4.87) [4] Work duration ≥15 years TSFE ≥15 years SMR = 0.93(90% CI 0.04–4.38) [1]
Reference: Jakobsson et al. (1997) **Population:** 727 male employees of two plants producing stainless steel sinks and saucepans employed at least 1 year during 1927–1981 with minimum 15-year follow-up. **Outcome definition:** Incidence of laryngeal cancer from the Swedish Tumor Registry (ICD-7:161). **Design:** Cohort incidence study with external comparison group. **Analysis:** SIRs calculated using sex, age, and calendar-year-expected number of cases from the national population. **Confidence in effect estimates:**[a] **LOW** ↓ (Potential bias toward the null)	**Exposure assessment:** Workers grind stainless steel with grinding plates made of formaldehyde resins, which may release formaldehyde when heated during grinding operations. **Duration and timing:** Occupational exposure preceding death during 1927–1981. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated as confounders. [As noted in Appendix B.3.9: Nickel and chromium are associated with URT cancers and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.	**External comparisons:** SIR = 0.7 (0–3.9) [1]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
High potential for information bias with attenuation of association (Exposure Group D). Confounding possible. Low sensitivity (few cases).	Other coexposures are not known risk factors for these outcomes.]	
Reference: Andjelkovich et al. (1995) **Population:** 3,929 automotive industry iron foundry workers exposed from 1960 to 1987 and followed through 1989. **Outcome definition**: Underlying cause of death obtained from Social Security Administration, Pension Benefit Informations, and National Death Index) Larynx: ICD 161 **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex-, age-, race-, and calendar-year-specific U.S. mortality rates. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency analysis with attenuation of association. Confounding possible for URT cancers. Low sensitivity (few cases).	**Exposure assessment:** Individual-level exposure status (Yes/No, Quartile) based on review of work histories by an industrial hygienist. Exposure assessment blinded to outcome. Independent testing of iron foundries by NIOSH reported a range from 0.02 ppm to 18.3 ppm (cited in IPCS (1989) Env. Health Criteria 89: Formaldehyde). **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Nickel and chromium are associated with URT cancers and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect. Other coexposures are not known risk factors for these outcomes.]	**External comparisons:** $SMR_{Unexposed}$ = 0.70 (0.01−3.91) [1] $SMR_{Exposed}$ = 0.98 (0.11−3.53) [2]
Reference: Hansen and Olsen (1995) **Population:** 2,041 men with cancer who were diagnosed during 1970−1984 and whose longest work experience occurred at least 10 years before cancer diagnosis. Identified from the Danish Cancer Registry and matched with the Danish Supplementary Pension Fund. **Outcome definition:** Cancer of the larynx (ICD-7: 161) listed on Danish Cancer Registry file. **Design:** Proportionate incidence study with external comparison group.	**Exposure assessment:** Individual occupational histories including industry and job title established through company tax records to the national Danish Product Register. Subjects whose longest work experience was ≥10 years prior to cancer diagnosis were considered potentially exposed to formaldehyde. All subjects were stratified based on job title as either low exposure (white collar worker), above background exposure (blue collar worker), or unknown (job title unavailable). **Duration and timing:** Exposure period since 1964.	Overall (exposure to formaldehyde ≥10 years prior to cancer diagnosis) SPIR = 0.9 (0.6−1.2) [32]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Analysis: Standardized proportionate incidence ratio calculated as the proportion of cases for a given cancer in formaldehyde-associated companies relative to the proportion of cases for the same cancer among all employees in Denmark. Adjusted for age and calendar time. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association. Low sensitivity for NPC (few cases).	**Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: While other coexposures were not evaluated, the overall correlation between coexposures in multiple occupational industries is likely to be low.]	
Reference: Stroup et al. (1986) **Population:** 2,239 white male members of the American Association of Anatomists from 1888 to 1969 who died during 1925−1979. Death certificates obtained for 91% with 9% lost to follow-up. **Outcome definition:** Laryngeal cancer (ICD-8: 161) listed as cause of death on death certificates. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for selection bias. Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Confounding possible for ML. Low sensitivity (few cases).	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1925−1979. Median birth year was 1912. By 1979, 33% of anatomists had died. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.]	**External comparisons:** SMR = 0.4 (0−2.0) [1]
Reference: Levine et al. (1984a)	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative.	**External comparisons:** Observed: 1 Expected: 1.0

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Population: 1,477 male undertakers licensed with the Ontario Board of Funeral Services from 1928 to 1957 who died during 1950–1977. Vital status was followed through 1977 with 96% completion and only 4% lost to follow-up. **Outcome definition:** Death certificates used to determine cause of death from cancer of the larynx (ICD-8: 161). **Design:** Retrospective cohort mortality study with external comparison group. **Analysis:** Ontario mortality rates for <1950 not available for SMR calculations. Expected deaths were determined by applying age- and calendar year-specific mortality rates of Ontario men to the 1950 through 1977 experience of the cohort. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Duration and timing:** Occupational exposure preceding death during 1950–1977. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.]	SMR = 1.00 (0.05–4.93)† [1] †EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))
Reference: Walrath and Fraumeni (1984) **Population:** 1,007 deceased white male embalmers from the California Bureau of Funeral Directing and Embalming who died during 1925–1980. Death certificates obtained for all. **Outcome definition:** Laryngeal cancer listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a]	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1916–1978. Birth year ranged from 1847 to 1959. Median age of death was 62 years. Most deaths were among embalmers with active licenses. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation.	**External comparisons:** Observed: 2 Expected: 2.6 PMR = 0.77 (0.13–2.54)† [2] †EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
LOW ↓ (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	Anatomists may also be coexposed to stains, benzene, toluene, xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.]	
Reference: Walrath and Fraumeni (1983) **Population:** 1,132 deceased white male embalmers licensed to practice during 1902–1980 in New York who died during 1925–1980 identified from registration files. Death certificates obtained for 75% of potential study subjects (*n* = 1,678). **Outcome definition:** Laryngeal cancer listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1902–1980. Median year of birth was 1901. Median year of initial license was 1931. Median age at death was 1968. Expected median duration of exposure was 37 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.]	**External comparisons:** Observed: 2 Expected: 3.4 PMR = 0.50 (0.10–1.94)† [2] †EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Respiratory Tract Cancers in Animal Studies

This section describes histopathological evidence reporting the induction of carcinomas, other neoplasms, and dysplasia in the respiratory tract of experimental animals after formaldehyde

exposure. The discussion emphasizes observations of malignant tumors (e.g., adenocarcinomas and carcinomas and squamous cell carcinomas (SCCs), which were those most commonly observed) as representing the most advanced stage of rodent tumor malignancy. Other neoplasms were reported in the database, including adenomas and papillomas. While these neoplasms also represent abnormal changes to the respiratory tissue, the use of benign lesions to characterize potential human cancer risk is more straightforward when chemical-specific data are available to associate such lesions with the development of more malignant lesions along relevant progression pathways. For example, while squamous cell papillomas are benign lesions that could progress to become malignant SCCs in various rodent tissues, this progression through a benign papillomatous stage may not occur in rat nasal passages, whereas SCCs may arise directly from hyperplastic or dysplastic tissue (McConnell et al., 1986). Conversely, nasal polypoid adenomas (representing a different cellular lineage from those developing into SCCs) may progress to adenocarcinomas, which represent the more advanced stage in this cancer continuum. While benign and malignant rodent tumors are considered neoplasms, dysplasia is an example of a dedicated, preneoplastic lesion which may progress to neoplasia, and is therefore informative to the potential for human carcinogenesis. However, dysplasia itself is not cancer per se, but simply one possible stage along the presumed continuum of progressive changes characteristic of epithelial carcinogenesis. Thus, this section prioritizes discussion of incidence data for malignant tumors, representing the most advanced and rare lesions relevant to informing human cancer hazard; discussion of other neoplasms or dysplasia is presented separately, as supporting evidence.

This section describes the incidence, location, and severity of these lesions. Although, generally, the study authors cited in this section did not provide statistical comparisons for the reported lesions data, given the rarity of these neoplasms in unexposed animals (SCCs in particular), any observations of malignant tumors in the respiratory tract are considered to be biologically relevant, abnormal changes. Potential relationships between lesions or the potential for progression of benign lesions to malignant tumors are presented in the MOA discussion that follows. Other respiratory tract lesions that may be relevant to cancer development include hyperplasia and squamous metaplasia, which were discussed in Section 3.2.4.

Considering the long duration necessary for the development of these cancers, the evidence tables of the experimental animal studies are organized by study duration, specifically focusing on chronic exposure (≥1 year) and subchronic exposure (≥3 months) with long-term follow-up (typically assessed after ≥1 year). These studies are further organized by study confidence and species in Table 3-36. This section focuses on studies of *high* and *medium* confidence. Studies interpreted with *low* confidence for these endpoints are briefly summarized but excluded from the evidence tables. This includes all *low* confidence subchronic exposure studies that did not include a follow-up period to allow for the development of respiratory tract cancers, as described above (Zwart et al., 1988; Woutersen et al., 1987; Wilmer et al., 1989; Rusch et al., 1983; Maronpot et al., 1986; Andersen et al., 2010). The studies classified as *not informative* are not discussed (Horton et

al., 1963; Coon et al., 1970; Casanova et al., 1994; Arican et al., 2009). A single, *low* confidence shorter-term (8 week) exposure study with less follow-up (32 week) is also discussed, as it was conducted in potentially sensitive mice (Morgan et al., 2017).

Animal studies investigating formaldehyde-induced respiratory carcinogenesis were carried out primarily in rats and to a lesser extent in mice, hamsters, and nonhuman primates. While the most consistent evidence of formaldehyde-induced respiratory cancers in animals is restricted to the nasal cavity and consists primarily of squamous cell carcinomas (SCCs), other neoplasms that have been observed include carcinomas other than SCCs, sarcomas, papillomas, and adenomas (Sellakumar et al., 1985; Morgan et al., 1986b; Monticello et al., 1996; Kerns et al., 1983; Kamata et al., 1997). Nasal tumors are rare in both mice and rats (Brown, 1990), thus any consistent increase in incidence is notable. Although dysplastic lesions, as well as hyperplasia and squamous metaplasia (see Section 3.2.4), have been observed posterior to the nasal cavity, respiratory tract tumors in these regions have not been reported to be significantly increased by formaldehyde treatment. In chronic studies in rats, carcinogenic effects generally first occur around 12 months in high exposure groups, with increased tumor incidence and decreased latency correlating with increasing exposure concentrations. Two *medium* confidence subchronic studies in rats with an extended period of observation also reported an increase in tumor incidence (Woutersen et al., 1989; Feron et al., 1988).

Although the bioassays in mice, hamsters, and rats represent similar exposure concentrations and duration of exposure, clear species differences in the severity of lesions are present. Hamsters display little histopathological change whereas rats exhibit gross toxicity and even increased mortality. Mice exhibit a range of effects on the respiratory epithelium, but not to the severity observed in rats. There are significant species differences in the anatomical structure of the airways, and in oral/nasal breathing patterns, including reflex bradypnea (see Appendix C.2 for discussion), all of which may influence areas of formaldehyde absorption or flux into the tissue. The differential toxicity of formaldehyde on the URT in animals may also be due to localized differences in mucus flow and production, as well as differences in the expression or distribution of enzymes involved in formaldehyde detoxification. Overall, as discussed below, inhalation exposure to formaldehyde in experimental animals induces nasal cancer and dysplasia with increasing incidence as a function of exposure duration and concentration at the POE.

Squamous cell carcinomas

Squamous cell carcinomas (SCCs) are the most consistently observed respiratory tract cancer in mice and rats exposed to formaldehyde. These malignant tumors likely arise from squamous cells, a type of differentiated epithelial cell that also comprises the majority of the epidermis ("skin" cells). Formaldehyde-induced SCCs are restricted to the nasal cavity and have not been observed in any other region of the respiratory tract. The most useful and abundant SCC data (i.e., the large majority of studies interpreted with *medium* or *high* confidence) are from studies of exposed rats. Following exposure of rats to formaldehyde for 2 years, an increase in SCCs was

observed in 5 of 6 studies (see Table 3-36 and Figure 3-23). These tumors were detected in exposed male and female Fischer 344 (F344) and Sprague Dawley rats, but findings in Wistar rats were less clear (see discussion below). Overall, SCCs were not reproducibly detected below 6 mg/m^3 formaldehyde in rats; however, none of the available rat studies tested exposure between 3 and 6 mg/m^3, introducing uncertainty. Reflecting the rarity of these tumors [rat background incidence averages <0.3% (Brown et al., 1991)], the incidence in control groups across the chronic formaldehyde exposure studies in rats was 0%. Generally, the incidence increased to around 1% at approximately 7 mg/m^3 formaldehyde, and further increased to around 40% as formaldehyde concentrations neared 18 mg/m^3 (Note that for purpose of comparison across studies, Table 3-36 reports incidence rates unadjusted for mortality; see Section 5.2.1 for mortality-adjusted rates. Unadjusted rates are generally underestimates; for example, the adjusted cumulative incidence rate in female rats exposed for 24 months at 17.6 mg/m^3 by Kerns et al. (1983) was reported at 87%).

The data as reported in Kerns et al. (1983) and Monticello et al. (1996) were corrected in a memorandum issued by the CIIT Centers for Health Research, which had sponsored or conducted these studies (Bermudez, 2004). The corrected data are noted in separate rows in Table 3-36. The correction for Kerns et al. (1983) in the CIIT memo (2004) indicates the number of animals examined instead of the number of animals in the experiment. The corrections for Monticello et al. (1996) issued in the CIIT memo (2004) arise from an examination by CIIT scientists of tissues for an additional group of 94 rats from the study that had not been previously examined (as explained in(Conolly et al., 2003)).[30] These tissues were from the 12-, 18-, and 24-month time points and were distributed approximately evenly across the six exposure concentrations. The CIIT memo (Bermudez, 2004) is reproduced in the Appendix D.2.2.

[30]Conolly et al. (2003) modeled the dose-response for squamous cell carcinoma (SCC) data by combining the data from Kerns et al. (1983) and Monticello et al. (1996) and the data from these 94 rats. The individual animal data pertaining to the combined data are reported in the Appendix in Conolly et al. (2003). EPA's dose-response analysis used the combined data.

Table 3-36. Squamous cell carcinoma (SCC) incidence in rats[a] exposed to formaldehyde for ≥2 years

	Strain	Sex	Formaldehyde concentration range[b] (specific mg/m^3 examined)						
			0	0 < × < 3	3 < × < 6	6 < × < 9	9 < × < 12	12 < × < 15	15 > × > 18.5
High confidence									
Kerns et al. (1983)	F344	M	0/118	0/118 (2.5[c])	—	1/119 (6.9)	—	—	51/117 (17.6)
		F	0/114	0/118 (2.5)	—	1/116 (6.9)	—	—	52/115 (17.6)
Corrected Bermudez (2004)		M and F	0/237	0/239	—	2/235	—	—	83/225
Monticello et al. (1996)	F344	M	0/90	0/90 (0.9); 0/90 (2.5)	—	1/90 (7.4)	—	20/90 (12.2)	69/147 (18.4)
Corrected Bermudez (2004)		M and F	0/104	0/221	—	1/108		22/103	79/161
Woutersen et al. (1989)	Wistar	M	0/26	1/26 (0.1); 1/28 (1.2)	—	—	—	1/26 (12.1)	—
Medium confidence									
Holmstrom et al. (1989b)	Sprague Dawley	F	0/15	—	—	—	—	—	1/16 (15.3)
Kamata et al. (1997)	F344	M	0/32	0/32 (0.4); 0/32 (2.7)	—	—	—	—	13/32 (18.3)
Sellakumar et al. (1985)	Sprague Dawley	M	0/99	—	—	—	—	—	38/100 (18.2)
Formaldehyde range (mg/m^3)			0	0 < × < 3	3 < × < 6	6 < × < 9	9 < × < 12	12 < × < 15	15 > × > 18.5
Total rats examined Range of percentage incidence[d]/study			494 0–0%	534 0–3.8% [e]	0 —	325 0.8–1.1%	0 —	116 3.8–22.2%	527 6.3–46.9%

F344: Fischer 344; M: Male; F: Female; — Concentrations in this range were not examined.

[a]This table is restricted to experimental studies in rats, given toxicokinetic differences across species. A mouse (Kerns et al., 1983) and hamster (Dalbey, 1982) study also meet confidence and exposure duration criteria.

[b]These ranges were arbitrarily chosen to cover the available data and do not have a biological basis.

[c]The specific concentration(s) of formaldehyde tested in the study is in parentheses.

[d]Incidence rates are unadjusted for mortality.

[e]Both SCCs in this concentration range are from Woutersen et al. (1989), which did not observe any increases in SCCs at much higher formaldehyde concentrations in Wistar rats, reducing confidence in these findings.

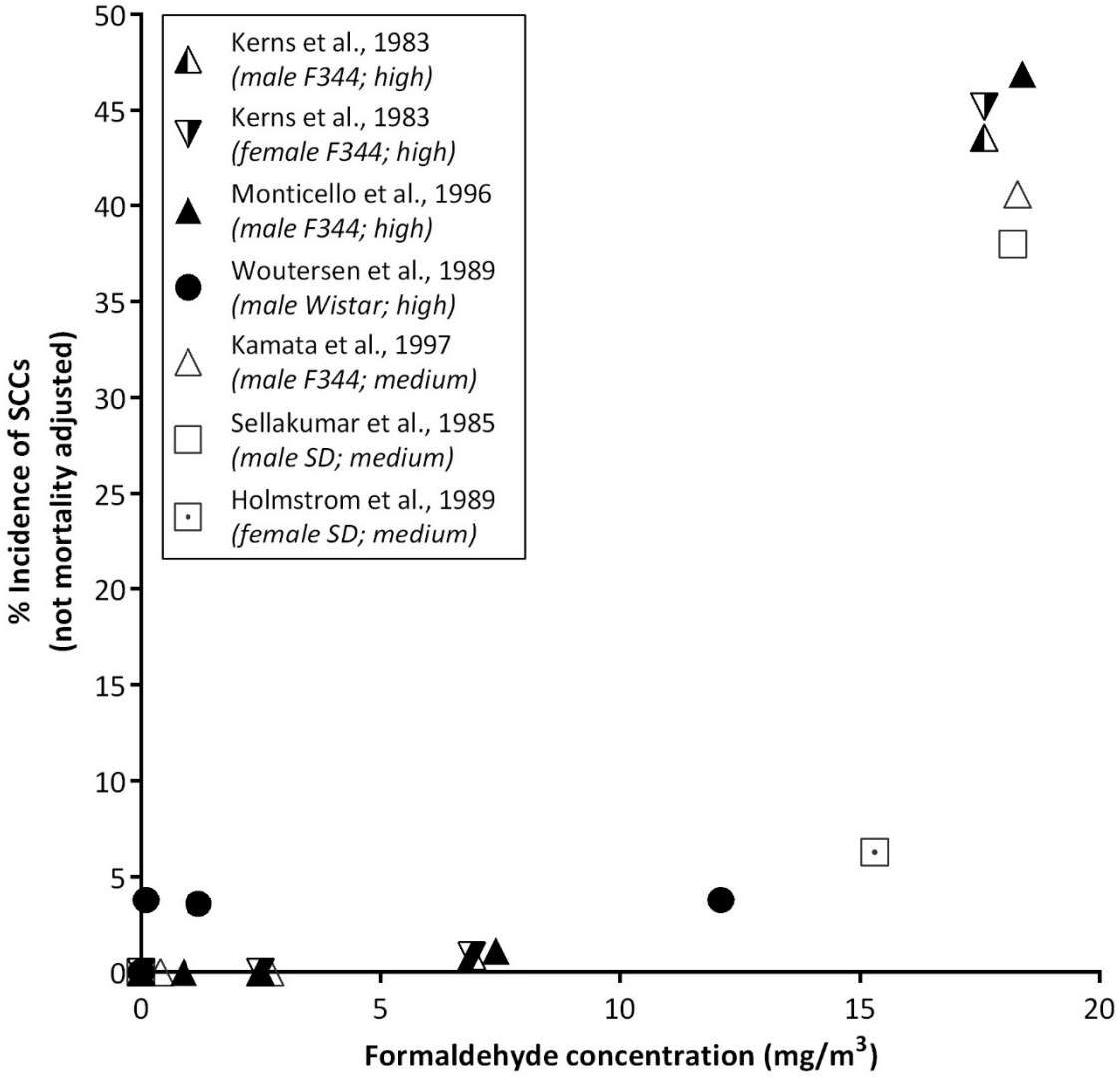


Figure 3-23. Nasal SCCs in rats exposed to formaldehyde for at least 2 years.

Incidence data for squamous cell carcinomas from the *high* and *medium* (unfilled shapes) confidence studies evaluating formaldehyde exposures of at least 2 years.

The data suggest that rats of different strains may vary in their sensitivity to formaldehyde-induced SCCs. The only rat study with 2 years of formaldehyde exposure that did not observe an association of SCCs with increasing formaldehyde exposure was conducted in Wistar rats (Woutersen et al., 1989). Although the authors reported a single SCC in each of the treatment groups (no SCCs were observed in controls), these tumors may not have been related to formaldehyde exposure as the incidence did not change at higher formaldehyde levels and observations of SCCs occurred at far lower concentrations than in any other rat studies. Consistent with this potential resistance of Wistar rats to formaldehyde-induced SCCs observed by Woutersen et al. (1989), an earlier study from the same laboratory examining Wistar rats at identical

formaldehyde concentrations did not detect any SCCs (Appelman et al., 1988); however, the earlier study only exposed and observed animals for 12 months, substantially reducing its ability to detect cancers. Two additional experiments from the same laboratory examined whether subchronic formaldehyde exposure with follow-up for more than 2 years resulted in SCCs in Wistar rats (Woutersen et al., 1989; Feron et al., 1988). Both of these studies observed a single SCC induced in response to formaldehyde exposure at approximately 11 mg/m^3, with an increased incidence of formaldehyde-induced SCCs to 3 of 44 in the study that tested a higher exposure of 24.4 mg/m^3 (Feron et al., 1988). The <4% incidence in Wistar rats exposed to approximately 11 mg/m^3 in these studies contrasts with the 22% incidence observed at this level in F344 rats by Monticello et al. (1996). Taken together, although some of the data with a sufficient duration of observation suggest that formaldehyde exposure can induce a low incidence of SCCs in Wistar rats (Woutersen et al., 1989; Feron et al., 1988), these findings indicate that this strain may be resistant to formaldehyde-induced nasal SCCs, as compared to F344 and Sprague Dawley rats.

The effects of long-term formaldehyde exposure in species other than rats are less well studied, but the available data suggest that rats may be the most sensitive laboratory rodents. The only mouse study testing exposure of at least 2 years (Kerns et al., 1983) provided support for the consistent observations of SCCs in formaldehyde-exposed rats. In this well-conducted (i.e., *high* confidence) study, SCCs were observed at 17.6 mg/m^3, but not at 6.9 or 2.5 mg/m^3 (incidence in controls was 0%). The incidence at 17.6 mg/m^3 was <2% (2/120), in contrast with the >40% incidence detected in F344 rats exposed to similar formaldehyde concentrations by the same study authors (Kerns et al., 1983). The authors also reported that the SCCs in rats were more invasive and severe than those observed in mice. These differences could reflect the use of a mouse strain that might be insensitive to these effects, similar to the above discussion of Wistar rats, but the differences more likely reflect a decreased response due to a lower inhaled dose of formaldehyde resulting from differences in breathing patterns and irritant responses across species (see Appendices A2 and A3). In contrast, no respiratory tract tumors were observed in Syrian golden hamsters exposed to 12.3 mg/m^3 of formaldehyde for a lifetime (Dalbey, 1982), although no other exposure levels were tested to inform whether this species or strain may also be less sensitive than exposed F344 and Sprague Dawley rats, and exposed mice.

In rats and mice, SCC formation appears to be dependent on both the formaldehyde concentration and the duration of exposure and observation. Specifically, higher formaldehyde exposure levels tend to be associated with both an increased incidence and an earlier onset of tumor formation. An example of this was demonstrated in a follow-up to the Kerns et al. (1983) study by Monticello et al. (1996). Monticello et al. (1996) reported that the incidence of SCCs in rats exposed to 18.4 mg/m^3 formaldehyde was 47%, with the first tumor noted at 12 months. The incidence of SCCs in the 12.2 mg/m^3 exposure group was lower, at 22%, and the tumor latency was longer, with the first SCC observed at 18 months. Of the 90 rats exposed at 7.4 mg/m^3 for 20 months, only one SCC was noted, and no SCCs were detected at 0, 0.85, or 2.52 mg/m^3 over

28 months (Monticello et al., 1996). Initial observations of SCCs varied across the available rat studies, and the study design sometimes prevented an accurate determination of the timing (e.g., microscopic examinations may have been conducted every 6 months, every year, or only after 2 years). However, the first tumor generally was not observed before 12 months of observation, and often took 16 months or longer to develop (see Table 3-37). Consistent with this long latency, SCCs observed in mice took 2 years to develop (Kerns et al., 1983), and no URT neoplasms were observed during 8 months of observation in a short-term, *low* confidence (i.e., due to its 8-week exposure duration and <1 year follow-up) study of potentially sensitive mice (Morgan et al., 2017). In light of these observations, subchronic and shorter-term exposure studies without a long duration of follow-up are not expected to be capable of detecting formaldehyde-induced SCCs[31]. In studies where interim sacrifices were performed and described, longer durations of exposure were generally associated with an increased incidence, severity, and sometimes more posterior location, of the induced SCCs (Monticello et al., 1996; Kerns et al., 1983). These data suggest that longer formaldehyde exposure duration is correlated with a greater incidence and severity of SCCs.[32]

The large bioassay of Kerns et al. (1983) in F344 rats showed no overt differences in the development of SCCs across sexes (i.e., 51/117 in males vs. 52/117 in females at 17.6 mg/m^3). There is some evidence to suggest that male rodents may be more sensitive to these effects. For example, only 1 of 16 female Sprague Dawley rats exposed to 15.3 mg/m^3 developed SCCs (Holmstrom et al., 1989b), whereas slightly higher levels (18.2 mg/m^3) of formaldehyde in another study of male Sprague Dawley rats (Sellakumar et al., 1985) induced more than six times as many SCCs (38/100). In addition, only male mice (2/120), but not female mice (0/120), developed SCCs in a chronic study (Kerns et al., 1983). However, these suggestions of differential sensitivity between sexes are not easily interpreted given the small sample sizes (Holmstrom et al., 1989b) and a low incidence of SCCs in exposed mice (Kerns et al., 1983).

The locations of the induced SCCs were consistent with both the distribution of inhaled formaldehyde and locations of other formaldehyde-induced nasal pathologies (see Section 3.2.4), with SCCs arising from the epithelium lining the airway and not from the underlying glandular epithelium. These tumors were most commonly observed in anterior regions of the nasal cavity, although higher exposure levels sometimes resulted in progression of SCCs to more posterior

[31]In fact, studies of subchronic formaldehyde exposure without follow-up consistently failed to observe dysplasia or neoplasms in the nose, trachea, larynx, or lungs across a range of formaldehyde concentrations in rats (Zwart et al., 1988; Woutersen et al., 1987; Wilmer et al., 1989; Rusch et al., 1983; Feron et al., 1988; Appelman et al., 1988) and mice (Maronpot et al., 1986), and at lower formaldehyde levels (<3.65 mg/m^3) in hamsters and cynomolgus monkeys (Rusch et al., 1983). Studies with a long observation period were not identified to inform the possibility of cancer development in nonhuman primates exposed to formaldehyde.

[32]While some data exist to suggest that SCCs can be induced following subchronic formaldehyde exposure when observations continue for more than 2 years (Woutersen et al., 1989; Feron et al., 1988), definitive experiments in rats that are sensitive to the development of SCCs have not been performed (e.g., comparing SCC incidence in Sprague Dawley or F344 rats exposed for shorter durations and followed up for >2 years versus rats exposed to the same concentrations for >2 years with no additional follow up).

locations. Morgan et al. (1986b) mapped the location of formaldehyde-induced SCCs from the Kerns et al. (1983) study. In F344 rats, the majority of animals had single tumors, with a little under 20% of each sex with tumors developing multiple neoplasms. More than half (57%) of the SCCs occurred on the lateral side of the nasoturbinate and adjacent lateral wall at the front of the nose (Levels I and II; see Table 3-37); approximately 25% were located on the midventral nasal septum (Levels II and III); and about 10% were on the dorsal septum and roof of the dorsal meatus (Levels I, II, and III). A small number (3%) were found on the maxilloturbinate (Levels II and III), which only involved the medial aspect. Similar observations were reported for other studies of F344 rats (Monticello et al., 1996) and B6C3F1 mice (Kerns et al., 1983). Locations of SCCs in Sprague Dawley and Wistar rats were not as specifically reported in the available studies, but were generally similar, primarily affecting the respiratory epithelium lining the septum and nasoturbinates (Woutersen et al., 1989; Sellakumar et al., 1985).

Other malignant neoplasms

Although the data on other neoplasms are far less robust than those related to SCCs, formaldehyde inhalation also appears to induce other types of malignant nasal tumors. The incidence of these other neoplasms was typically only one, or rarely two, animals in an exposed group (never in controls); however, it is considered highly unlikely that these are incidental, as these rare neoplasms only developed after exposure to the highest formaldehyde concentrations, typically those above 17 mg/m^3 (see Table 3-37). As with SCCs, these neoplasms were limited to the nasal cavity. Carcinomas, which derive from epithelial tissues, were reported in several studies with an observation period greater than 2 years, consistent with the pronounced effect of inhaled formaldehyde on the nasal epithelium. A single nasal carcinoma was observed in both male and female F344 rats (Kerns et al., 1983), a mixed carcinoma was observed in male Sprague Dawley rats (Sellakumar et al., 1985), and a carcinoma in situ was observed in male Wistar rats exposed to 24 mg/m^3 (Feron et al., 1988), but not ≤12.1 mg/m^3 (Woutersen et al., 1989; Feron et al., 1988; Appelman et al., 1988).

Nonmalignant neoplasms

Several other benign tumors of the respiratory tract have been reported following formaldehyde exposure in rats, but not in other species. These tumors parallel findings for the other observed tumors, in that they are restricted to the nasal cavity and generally take more than 12 months to develop. Overall, these tumors appear to represent an erratic growth of the nasal epithelial tissue (i.e., adenomas and papillomas), with the exception being an ameloblastoma observed at 24 mg/m^3 formaldehyde (Feron et al., 1988), a tumor that presumably secondarily infiltrated the nasal cavity. In male Sprague Dawley rats, 10% of animals (10/100) exposed to 18.2 mg/m^3 for their lifetime developed nasal polyps or papillomas (Sellakumar et al., 1985; Albert et al., 1982), while approximately the same percentage of male F344 rats (3/32) exposed to a near-identical formaldehyde concentration (18.3 mg/m^3) developed squamous cell papillomas (Kamata

et al., 1997). Polypoid adenomas have also been consistently observed in response to formaldehyde exposure. Similar to SCCs, and in contrast to the other malignant tumors discussed above, these neoplasms may be inducible at formaldehyde concentrations below 12 mg/m^3, and perhaps even below 7 mg/m^3, although the data are somewhat more variable as compared to the SCC data (see Table 3-37). Polypoid adenomas were increased compared to controls in male Wistar rats exposed to 11.3 mg/m^3 (Woutersen et al., 1989) or 24.2 mg/m^3 (Feron et al., 1988) for 3 months with follow-up to >2 years, and in chronically exposed F344 rats (Monticello et al., 1996; Kerns et al., 1983). The responses in F344 rats occurred primarily in males and were reported at concentrations as low as 2.5 mg/m^3 (Kerns et al., 1983), although interpretation of the incidence data across exposure levels is not straightforward. Taken together, the data indicate that benign epithelial tumors in the nasal cavity can be induced by formaldehyde exposure.

Dysplasia

Similar to observations of nasal tumors, the incidence of dysplasia in long-term formaldehyde inhalation studies in rats and mice (i.e., chronic or subchronic exposure with observation periods of >12 months) increased in severity and occurred in more distal portions of the nasal cavity with both formaldehyde concentration and duration. Whereas the rat nasal tumor data consistently demonstrated that tumors are restricted to the nasal cavity, one study reported that F344 rats (which appear to be sensitive to these effects) also exhibited mild dysplasia in the trachea (Kerns et al., 1983), although the tracheal lesions were not observed when rats exposed for 2 years were left unexposed for 3 months. The study authors did not observe any tracheal lesions in mice (Kerns et al., 1983). Epithelial dysplasia of the nasal cavity was first noted at 12 months in rats exposed to concentrations as low as 2.5 mg/m^3, and in a "few" mice after 18 or 24 months of exposure at concentrations as low as 6.9 mg/m^3 formaldehyde (Kerns et al., 1983). However, after 24 months of exposure to 17.6 mg/m^3 formaldehyde, the incidence of nasal dysplasia was significantly increased in rats and mice, with greater than 90% of mice exhibiting this lesion (Kerns et al., 1983). The study authors noted that the identification of dysplasia in this study may have been termed metaplasia or hyperplasia by other study authors (Kerns et al., 1983), suggesting that this may represent a sensitive estimate of dysplasia. In another study, a female Sprague Dawley rat exposed to 15.3 mg/m^3 formaldehyde for a lifetime also developed dysplasia of the nasal epithelium (Holmstrom et al., 1989b). In line with the nasal tumor data, studies of Wistar rats and hamsters did not identify dysplastic lesions (see Table 3-37).

Table 3-37. Respiratory tract cancer—chronic and subchronic (with long-term follow up) exposure in rats, mice, and hamsters

Reference and study design[a]	Results
Chronic exposure	
High confidence	

<table>
<tr><th>Reference and study design[a]</th><th>Results</th></tr>
<tr><td colspan="2">Rats</td></tr>
<tr><td>Monticello et al. (1996)
Rats: F344; male; 90–147/group
Test article: Paraformaldehyde
Exposure: 6 hr/d, 5 d/week for up to 24 months at 0, 0.85, 2.52, 7.40, 12.2, or 18.4 mg/m^3
Histopathology [b]: 6 sections of the nasal cavity</td><td>
<table>
<tr><td colspan="5">Malignant tumors in the nasal cavity[a]</td></tr>
<tr><td></td><td>0, 0.85, or 2.52 mg/m^3</td><td>7.4 mg/m^3</td><td>12.2 mg/m^3</td><td>18.4 mg/m^3</td></tr>
<tr><td>Squamous cell carcinoma[b]</td><td>0/90</td><td>1/90 (1%)</td><td>20/90 (22%)</td><td>69/147 (47%)</td></tr>
<tr><td>Adenocarcinoma</td><td>0/90</td><td>0/90</td><td>1/90</td><td>1/147</td></tr>
<tr><td>Rhabdomyosarcoma</td><td>0/90</td><td>0/90</td><td>1/90</td><td>1/147</td></tr>
<tr><td colspan="5">Other neoplasms</td></tr>
<tr><td>Polypoid adenoma</td><td>0/90</td><td>0/90</td><td>5/90 (6%)</td><td>14/147 (10%)</td></tr>
</table>
[a]Spontaneous buccal SCCs were observed at 0, 2.52, and 18.4 mg/m^3
[b]SCCs that could be localized were identified most often in the anterior or posterior lateral meatus 1/90, 12/90, 17/147 or 0/90, 12/90, 9/147 corresponding to 7.4, 12.2, and 18.4 mg/m^3); SCCs were also observed in the mid- and dorsal septum, as well as the maxilloturbinates, but only at 18.4 mg/m^3; however, most tumors were too large to localize and these often eroded through nasal bone and invaded the subcutis of the dermis. Tumors began appearing ~1 year at 18.4 mg/m^3 and ~1.5 year at 12.2 mg/m^3
No tumors observed beyond the respiratory tract
</td></tr>
<tr><td>Woutersen et al. (1989)
Rats: Wistar; male; 30/group
Test article: Paraformaldehyde
Exposure: 6 hr/d, 5 d/week for 28 months at 0, 0.1, 1.2, or 12.1 mg/m^3
Histopathology [b]: 6 nasal cross sections
Note: experiments with nasal damage prior to exposure are not presented here</td><td>
<table>
<tr><td colspan="5">Malignant tumors</td></tr>
<tr><td></td><td>0 mg/m^3</td><td>0.1 mg/m^3</td><td>1.2 mg/m^3</td><td>12.1 mg/m^3</td></tr>
<tr><td>Squamous cell carcinoma</td><td>0/26</td><td>1/26</td><td>1/28</td><td>1/26</td></tr>
<tr><td>Adenosquamous carcinoma</td><td>0/26</td><td>0/26</td><td>0/28</td><td>0/26</td></tr>
<tr><td>Adenocarcinoma</td><td>0/26</td><td>0/26</td><td>0/28</td><td>0/26</td></tr>
</table>
Note: the specific locations of these tumors was not described
</td></tr>
<tr><td>Sellakumar et al. (1985)
Rats: Sprague Dawley; male; 99–100/group
Test article: Paraformaldehyde (slurry in paraffin oil)
Exposure: 6 hr/d, 5 d/week for lifetime at 0 or 18.2 mg/m^3 [Note: prior reporting of levels during first 588 days at 17.5 mg/m^3 (Albert et al., 1982)]
Histopathology [b]: multiple (interpreted as ≥ 5 based on study description) sections of the head (from just behind the nostril to the eye orbits), lung, trachea, and larynx
Related study: Albert et al. (1982)</td><td>
<table>
<tr><td></td><td>Colony Control</td><td>Air sham</td><td>18.2 mg/m^3</td></tr>
<tr><td colspan="4">Malignant tumors in the nasal mucosa</td></tr>
<tr><td>Squamous cell carcinoma[a]</td><td>0/100</td><td>0/99[b]</td><td>38/100</td></tr>
<tr><td>Adenocarcinoma</td><td>0/100</td><td>0/99</td><td>0/100</td></tr>
<tr><td>Mixed carcinoma</td><td>0/100</td><td>0/99</td><td>1/100</td></tr>
<tr><td>Fibrosarcoma</td><td>0/100</td><td>0/99</td><td>1/100</td></tr>
<tr><td colspan="4">Other neoplasms in the nasal mucosa</td></tr>
<tr><td>Polyp or papillomas</td><td>0/100</td><td>0/99</td><td>10/100</td></tr>
</table>
[a]Predominantly moderate/well differentiated, keratin obstructed lumen; latency to tumor formation was approximately 603–645 days

No tumors observed in the trachea or lungs
</td></tr>
<tr><td>Kerns et al. (1983)
Rats: F344; males and females; 119 to 121/sex/group
Test article: Paraformaldehyde</td><td>
<table>
<tr><td colspan="5">Malignant tumors</td></tr>
<tr><td>mg/m^3</td><td>0</td><td>2.5</td><td>6.9</td><td>17.6</td></tr>
<tr><td colspan="5">Squamous cell carcinoma[a]</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Reference and study design[a]</th><th>Results</th></tr>
<tr><td>*Exposure*: 6 hr/d, 5 d/week for up to 2 year (recovery: 27 and 30 months) at 0, 2.5, 6.9, or 17.6 mg/m^3
Histopathology [b]: 5 sections of nasal turbinates (Levels I–V) for animals that died or at interval sacrifices (i.e., at months 6, 12, 18, 24, 27, and 30)
Related study/earlier reports: (Battelle, 1981, 1982); [interim findings presented in Swenberg et al. (1980b)]
Note: viral infection reported (sialodacryoadenitis) at approximately weeks 52–53 (Kerns et al., 1983); the authors attributed transient decreases in body weight to this infection. This infection was not interpreted to affect the reliability of the cancer incidence data, in part because dysplasia and other lesions were already present at 12 months (when the infection began)</td><td>
<table>
<tr><td>Male</td><td>0/118</td><td>0/118</td><td>1/119</td><td>51/117</td></tr>
<tr><td>Female</td><td>0/114</td><td>0/118</td><td>1/116</td><td>52/115</td></tr>
<tr><td colspan="5">*Nasal carcinoma*</td></tr>
<tr><td>Male</td><td>0/118</td><td>0/118</td><td>0/119</td><td>1/117[b]</td></tr>
<tr><td>Female</td><td>0/114</td><td>0/118</td><td>0/116</td><td>1/115</td></tr>
<tr><td colspan="5">*Carcinosarcoma*</td></tr>
<tr><td>Male</td><td>0/118</td><td>0/118</td><td>0/119</td><td>1/117</td></tr>
<tr><td>Female</td><td>0/114</td><td>0/118</td><td>0/116</td><td>0/115</td></tr>
<tr><td colspan="5">*Undifferentiated carcinoma or sarcoma*</td></tr>
<tr><td>Male</td><td>0/118</td><td>0/118</td><td>0/119</td><td>2/117[b]</td></tr>
<tr><td>Female</td><td>0/114</td><td>0/118</td><td>0/116</td><td>0/115</td></tr>
<tr><td colspan="5">*Other Neoplasms*</td></tr>
<tr><td colspan="5">*Polypoid adenoma*</td></tr>
<tr><td>Male</td><td>1/118</td><td>4/118</td><td>6/119</td><td>4/117</td></tr>
<tr><td>Female</td><td>0/114</td><td>4/118</td><td>0/116</td><td>1/115</td></tr>
<tr><td colspan="5">*Epithelial Dysplasia*</td></tr>
<tr><td>6 months</td><td>–[c]</td><td>–</td><td>–</td><td>–[d]</td></tr>
<tr><td>12 months</td><td>–[c]</td><td>Level I [e]</td><td rowspan="3">Level I–III[f]</td><td rowspan="3">Level I–V[f]</td></tr>
<tr><td>18 months</td><td>–[c]</td><td>NR</td></tr>
<tr><td>24 months</td><td>–[c]</td><td>Level I</td></tr>
</table>
[a]SCCs became clinically observable in females at ~12 months, and in males at ~14 months; most appeared to originate in the nasoturbinates
[b]A rat in this group also had SCC
[c]Lesion frequency (dysplasia or metaplasia) of <15% at 0 mg/m^3 (Level I)
[d] Although formaldehyde-induced lesions were identified in Level I–III, the authors did not specify them as dysplasia
[e]Squamoid epithelial lining several cells thick with polarity changed from vertical to horizontal was noted and termed dysplasia, but authors acknowledged related changes can be termed hyperplasia or metaplasia
[f]Dysplasia was most intense in Level I. Exposure-related effects were observed in Levels I–III and I–V at 6.9- and 17.6-mg/m^3, respectively, although the specific timing for these lesions was not provided; note: dysplasia was consistently detected earlier than squamous metaplasia
Trachea: at 17.6 mg/m^3, minimal-to-mild dysplasia at 18 months, with greater frequency ($p < 0.05$) in 24-month and unscheduled deaths groups; trachea lesions not observed in postexposure group or at lower levels</td></tr>
<tr><td colspan="2">***Mice***</td></tr>
<tr><td>Kerns et al. (1983)
Mice: B6C3F1; males and females; 119 to 121/sex/group
Exposure: 6 hr/d, 5 d/week for up to 24 months (recovery at 27 and 30 months) at 0, 2.5, 6.9, or 17.6 mg/m^3
Test article: Paraformaldehyde</td><td>
<table>
<tr><td colspan="5">*Malignant tumors*</td></tr>
<tr><td></td><td>0 mg/m^3</td><td>2.5 mg/m^3</td><td>6.9 mg/m^3</td><td>17.6 mg/m^3</td></tr>
<tr><td>SCCs at 24 months [a]</td><td>0/~120 (both sexes)</td><td>0/~120 (both sexes)</td><td>0/~120 (both sexes)</td><td>2/~120 male
0/~120 female</td></tr>
<tr><td colspan="5">*Dysplasia* [b]</td></tr>
<tr><td>12 months</td><td>–</td><td>–</td><td>–</td><td>–</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Reference and study design[a]</th><th>Results</th></tr>
<tr><td>Histopathology [b]: 3 sections of nasal turbinates, defined as Levels II, III, and V for all animals that died or were sacrificed at scheduled intervals (i.e., at month 6, 12, 18, 24, 27, and 30)
Earlier reports: Battelle (1981, 1982)

Main limitations: Lesion incidence NR for dysplasia; only 3 nasal sections examined</td><td>
<table>
<tr><td>18 months</td><td>–</td><td>–</td><td>Level II: “few”</td><td>Level II (~90%)</td></tr>
<tr><td>24 months</td><td>–</td><td>–</td><td>Level II: “few”</td><td>>90%</td></tr>
<tr><td>Recovery (27 months)</td><td>–</td><td>–</td><td>none</td><td>yes (incidence and level NR)</td></tr>
</table>
[a]SCCs were not observed prior to 24 months ($p > 0.05$); both SCCs originated from nasoturbinates; the number of mice evaluated was not specified, but assumed ~120 based on 119−121 mice/group
[b]Unless noted, exact frequency of lesion NR, and sex not specified

No tracheal lesions were observed
</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td colspan="2">Rats</td></tr>
<tr><td>Kamata et al. (1997)
Rats: F344; male; 32/group
Test article: Formalin (methanol control)
Exposure: nose-only 6 hr/d, 5 d/week for up to 28 months at 0, 0.40, 2.67, or 18.27 mg/m^3 (methanol—0, 18.27 mg/m^3 groups, estimated at 5.5 mg/m^3, presumed from percentage methanol in formalin)
Histopathology [b]: nasal region (sections from five anatomical levels) and trachea

Main limitations: small sample size; use of formalin (uncertainties, such as possible differences in tissue formaldehyde due to methanol, remain despite inclusion of a methanol control)</td><td>
<table>
<tr><td></td><td colspan="4">Months (interim sac.)</td><td rowspan="2">Dead</td><td rowspan="2">All</td></tr>
<tr><td></td><td>12</td><td>18</td><td>24</td><td>28</td></tr>
<tr><td colspan="7">Squamous cell carcinomas at 18.27 mg/m^3 [a]</td></tr>
<tr><td>SCCs</td><td>0/5</td><td>1/5</td><td>0/2</td><td>0/0</td><td>12/20</td><td>13/32[b]</td></tr>
<tr><td colspan="7">Other malignant tumors at 18.27 mg/m^3 [a]</td></tr>
<tr><td>Unclassified sarcoma</td><td>0/5</td><td>0/5</td><td>0/2</td><td>0/0</td><td>0/20</td><td>0/32</td></tr>
<tr><td>Sarcoma</td><td>0/5</td><td>0/5</td><td>0/2</td><td>0/0</td><td>1/20</td><td>1/32</td></tr>
<tr><td colspan="7">Other neoplasms at 18.27 mg/m^3[a]</td></tr>
<tr><td>Squamous cell papilloma</td><td>0/5</td><td>1/5</td><td>0/2</td><td>0/0</td><td>2/20</td><td>3/32</td></tr>
</table>
[a]No nasal tumors were observed at 0, 0.4, or 2.67 mg/m^3 (note: 1 unclassified sarcoma found in a dead room control group rat); average latency across groups varied from 603 and 645 days
[b]Significant at $p \leq 0.01$, compared with the 0 mg/m^3 group.
Note: Most tumors were located in levels B and C (see diagram in left column); large tumors invaded the subcutis through the nasal bones

No tumors were observed in the trachea
</td></tr>
<tr><td>Holmstrom et al. (1989b)
Rats: Sprague Dawley; female; 15−16/group
Test articles: Paraformaldehyde
Exposure: 6 hr/d, 5 d/week for 104 weeks at 0 or 15.3 mg/m^3
Histopathology [b]: 5 sections of the nose from the vestibulum to the posterior ethmoturbinatic region, and the lungs
Note: data on wood dust combined with formaldehyde exposure not evaluated

Main limitations: Limited reporting; some health issues noted</td><td>
<table>
<tr><td colspan="3">Malignant tumors</td></tr>
<tr><td></td><td>Air control</td><td>15.3 mg/m^3</td></tr>
<tr><td>Squamous Cell Carcinoma</td><td>0/15</td><td>1/16[a]</td></tr>
<tr><td colspan="3">Dysplasia</td></tr>
<tr><td></td><td>0/15</td><td>1/16[b]</td></tr>
</table>
[a]Observed after 21 months after exposure
[b]An addition two rats exhibited pronounced squamous metaplasia with keratinization (7 more exhibited squamous metaplasia)

Note: Mortality was similar in both groups
</td></tr>
</table>

<table>
<tr><th>Reference and study design[a]</th><th>Results</th></tr>
<tr><td>Appelman et al. (1988)
Rats: SPF Wistar; male; 10/group
Test article: Paraformaldehyde
Exposure: 6 hr/d, 5 d/week for 52 weeks at 0.12, 1.2, or 12.1 mg/m^3
Histopathology [b]: nose (6 standard cross levels), larynx, trachea, and lungs
Note: experiments with nasal damage prior to exposure are not presented here

Main limitations: 1-year short duration to allow for cancer development</td><td>*No dysplasia or nasal neoplasms were observed in nose, larynx, trachea, or lungs with exposure up to 12.1 mg/m^3 for up to 1 year (assumed, based on histopathological evaluation of these tissues, although the study authors did not specifically state these conclusions)*</td></tr>
<tr><td colspan="2">***Hamsters***</td></tr>
<tr><td>Dalbey (1982)
Hamsters: Syrian golden; male; 132 untreated controls and 88 exposed
Test article: Paraformaldehyde
Exposure: 5 hr/d, 5 d/week for a lifetime at 0 or 12.3 mg/m^3
Histopathology [b]: Two transverse sections of the nasal turbinates, and sections of the larynx, trachea, and lungs

Main limitations: minimal sampling, histological evaluation, and reporting
Note: mixture experiment not evaluated</td><td>*No tumors reported in the nose, larynx, lungs, or trachea with a lifetime of exposure to 12.3 mg/m^3*

Note: study authors indicated formaldehyde exposure at 36.9 mg/m^3 amplified diethylnitrosamine-induced respiratory tumors.</td></tr>
<tr><td colspan="2">***Subchronic exposure with long-term follow-up***</td></tr>
<tr><td colspan="2">*High confidence*</td></tr>
<tr><td colspan="2">**Rats**</td></tr>
<tr><td>Woutersen et al. (1989)
Rats: Wistar; male; 30/group
Test article: Paraformaldehyde
Exposure: 6 hr/d, 5 d/week for 3 months at 0, 0.1, 1.2, or 11.3 mg/m^3; sacrificed at 28 months
Histopathology [b]: 6 nasal cross sections
Note: short duration of exposure</td><td>
<table>
<tr><th></th><th>0 mg/m^3</th><th>0.1 mg/m^3</th><th>1.2 mg/m^3</th><th>11.3 mg/m^3</th></tr>
<tr><td colspan="5">*Malignant tumors*</td></tr>
<tr><td>*Squamous cell carcinoma*</td><td>0/26</td><td>0/30</td><td>0/29</td><td>1/26</td></tr>
<tr><td>*Carcinoma in situ*</td><td>0/26</td><td>0/30</td><td>0/29</td><td>0/26</td></tr>
<tr><td colspan="5">*Other neoplasms*</td></tr>
<tr><td>*Polypoid adenoma*</td><td>0/26</td><td>0/30</td><td>0/29</td><td>1/26</td></tr>
</table>
Note: cross-section locations not specified</td></tr>
<tr><td colspan="2">*Medium confidence*</td></tr>
<tr><td colspan="2">**Rats**</td></tr>
<tr><td>Feron et al. (1988)
Rats: Wistar; male; 45/group
Test article: Paraformaldehyde</td><td>
<table>
<tr><th></th><th>0 mg/m^3</th><th>~11.5 mg/m^3</th><th>~24 mg/m^3</th></tr>
<tr><td colspan="4">*Malignant tumors*</td></tr>
<tr><td colspan="4">*Squamous cell carcinoma:*</td></tr>
<tr><td>4-week exposure</td><td>0/44</td><td>0/44</td><td>1/45
(week 106)</td></tr>
</table>
</td></tr>
</table>

Reference and study design[a]	Results			
Exposure: 6 hr/d, 5 d/week for up to 13 weeks at 0, 11.3−11.9, or 24.2−24.4 mg/m^3; sacrificed at 130 weeks *Histopathology* [b]: 6 standard cross levels of the nose. **Main limitations**: Limited reporting; short duration of exposure	(week sacrificed indicated)			
	8-week exposure	2/45 (week 94, 130)	1/44 (week 130)	1/43 (week 121)
	13-week exposure	0/45	1/44 (week 82)	3 or 4/44[a] (week 63, 112, 114, NR)
	Other malignant tumors with 13 week exposure [b]:			
	Carcinoma in situ:	0/45	0/44	1/44 (week 81)
	Other neoplasms			
	Ameloblastoma:	0/45	0/44	1/44 (week 73)
	Polypoid adenoma:			
	4 week exposure	0/44	0/44	1/45 (week 110)
	8 week exposure	0/45	0/44	1/43 (week 100)
	13 week exposure	0/45	0/44	0/44
	[a]1 SCC was classified as a "cystic SCC," which may have been derived from the palate, and which the authors did not associate with exposure [b]carcinomas other than SCC were not observed with <13 week exposure			

Organized by study design, species, confidence, and then descending publication date.
Abbreviations: NR = not reported; F = Fischer; hr = hour(s); d = day(s); wk = week(s); yr = year(s).
[a]Analytical formaldehyde levels are presented and, unless otherwise noted, whole-body exposures were used.
[b]The studies used the same sectioning levels described for noncancer lesions in Section 3.2.4.

Summary of Animal Evidence Synthesis Judgments

The available animal studies on respiratory tract cancers provide *robust* evidence of formaldehyde exposure-induced nasal cancers. The locations of the observed cancers in animals are interpreted as most relevant to human NPC and sinonasal cancers. The following factors were most influential to the synthesis judgment.

- *Consistency and Study Confidence*: Tumors of the respiratory tract (predominantly nasal squamous cell carcinomas, SCCs, but including other epithelial and nonepithelial tumors) were consistently observed in mice and in several strains of rats in numerous *high* and *medium* confidence studies, but not in hamsters, generally at formaldehyde levels above 6 mg/m^3. These lesions were never observed in other respiratory tract regions, such as the larynx and lung, and they generally only developed in animals that were observed for longer than 12 months.

- *Dose-Response:* The lesion incidence, as well as the tumor invasiveness and latency, was demonstrated to worsen with increasing formaldehyde exposure level. In addition, the development of these lesions, particularly the SCCs, depended on the duration of observation and, based on an increasing incidence and severity of lesions in animals exposed for longer periods of time, the formaldehyde exposure duration. Likewise, the lesions progressed to more posterior locations with increasing duration and concentration of formaldehyde exposure.

- *Coherence*: Precancerous dysplastic lesions were induced in rats and mice, sometimes at lower formaldehyde concentrations.

- *Biological Plausibility:* Mechanistic changes consistent with cancer development in nasal tissues were observed across species, including rats, mice, and monkeys. In F344 rats chronically exposed to formaldehyde, a clear temporal, dose-responsive, and biological relationship was observed in the appearance of genotoxicity, sustained epithelial damage, cellular proliferation, and eventual tumor development (see MOA synthesis below). This provides strong plausibility for the observed effects.

Evidence on Mode of Action

As described above, formaldehyde exposure has been associated with elevated incidence of carcinomas in human URT tissues, with the strongest evidence for nasopharyngeal and sinonasal tumor formation. Formaldehyde inhalation reproducibly induces squamous cell carcinomas (SCC) in the nasal passages of F344, Sprague Dawley, and Wistar rats (obligate nose-breathers), as well as polypoid adenomas (PA); SCCs and PAs are both rare tumors in rats, with background frequencies of ≤0.3% and ≤0.04%, respectively (Poteracki and Walsh, 1998; Chandra et al., 1992; Brown et al., 1991). SCCs were also elevated in the anterior nasal passages of chronically exposed $B6C3F_1$ mice [background frequency of 0/2,818; (Brown et al., 1991)], but not in hamsters. Formaldehyde-associated SCCs and PAs originate in the nasoturbinates, maxilloturbinates, or lateral wall of the nasal cavity, and likely arise from the same target cell population (i.e., the nasal respiratory or transitional epithelium). The neoplastic response to formaldehyde exposure in rat nasal epithelium appears to be complex; SCC incidence is dramatically induced at exposure levels associated with other proliferative epithelial pathology, increasing from 1% at 7 mg/m^3 to 60% at 18 mg/m^3 in chronically exposed F344 rats. In contrast, relatively low frequencies of PAs are induced at concentrations ranging from 2.5 to18 mg/m^3, with PA incidence increasing moderately to a maximum of 10% at 18 mg/m^3 (see Table 3-37). SCCs and PAs are similarly induced in Sprague Dawley rats, and although nasal tumor incidence may be somewhat lower in Wistar rats, studies in the latter strain provide some evidence of tumor induction following subchronic exposure with lifetime follow-up.

Following inhalation exposure at analogous POE tissues in humans (nasal, buccal, and nasopharyngeal epithelium), nonhuman primates (nasal and extranasal respiratory and transitional epithelium, larynx, trachea, and carina), and rodents (nasal respiratory and transitional epithelium), evidence exists supporting the evaluation of a cancer mode of action (MOA). Among a variety of influential forces, two primary mechanistic considerations appear to contribute, both directly and indirectly, to tumorigenesis resulting from formaldehyde exposure at POE tissues: genotoxicity-associated mutagenicity, and cytotoxicity-induced regenerative proliferation. Furthermore, formaldehyde may stimulate nasal epithelial cell proliferation to some extent, even in the absence of frank tissue cytotoxicity. Instead of considering independent, sequential series of key events for each of these mechanistic considerations, evidence for genotoxicity and mutagenicity, cellular proliferation (independent from tissue pathology), and cytotoxicity-induced regenerative

tissue proliferation is evaluated in an integrated manner, whereby hypothesized mutagenesis and increased cellular turnover initiate and then augment URT carcinogenesis as a function of exposure duration, periodicity, and tissue dose. This approach is consistent with the observation that, while mitogenesis can drive rodent tumor prevalence, it may not supplant the contribution of mutagenicity to chemically induced carcinogenesis (Ames and Gold, 1990).

Much of the available evidence relevant to these mechanistic considerations is discussed in detail in the prior sections on URT cancer data in human and animal studies, as well as in Sections 3.2.3 and 3.2.4, and in Appendix C.3 (genotoxicity) and C.7 (MOA information for noncancer respiratory effects). Herein, these findings are summarized and integrated into a proposed cancer MOA network to serve as a framework for the evidence evaluation and MOA analysis (see Figures 3-24 to 3-26). The evidence is synthesized with an emphasis placed on observations from humans and experimental animals repeatedly exposed to formaldehyde via the inhalation route, evaluated following the Bradford Hill considerations (U.S. EPA, 2005a), and conclusions are discussed in the context of URT carcinogenesis proceeding via this hypothesized, integrated cancer MOA. While evidence from biochemical investigations or cells cultured in vitro is not exhaustively described, pertinent observations are presented when useful in providing a mechanistic interpretation to effects described in vivo, when the available in vivo evidence is limited or nonexistent, or does not inform the effect under consideration. Only results from studies reporting some quantitative estimate of formaldehyde exposure concentration were synthesized, due to a general abundance of information relevant to the mechanistic considerations, and relative paucity of studies failing to provide formaldehyde exposure estimates. Evidence informing other modulating or modifying effects such as immune dysfunction and oxidative stress, DNA repair inhibition, and epigenetic alterations are also discussed briefly (for more detail see Appendices C.3 and C.7), while evidence for systemic genotoxicity and immune system effects outside the URT as relevant to carcinogenesis are primarily discussed elsewhere (see Section 3.3.3, *Evidence on Mode of Action*). While these factors may contribute significantly at various stages of URT carcinogenesis to the mechanistic considerations described above, the limited available data preclude evaluating their independent contribution to the formaldehyde URT cancer MOA. Likewise, while various aspects of this analysis may be directly relevant to formaldehyde exposure by other routes, or cancer at other (i.e., distal) tissue locations, this discussion is focused on cancers at POE tissues (i.e., the URT) following inhalation exposure.

Summary of genotoxicity and mutagenicity

This overall summary is relevant to MOA interpretations for both URT cancers (this section) and lymphohematopoietic cancers (see Section 3.3.3). Formaldehyde is a direct-acting chemical that has been shown to be genotoxic or mutagenic in a variety of in silico and in vitro test systems; experimental animals including mice, rats, and monkeys; as well as in humans. Formaldehyde exposure typically induces genotoxicity, mutagenicity, or related endpoints in a concentration- and duration-dependent manner, including deletions and point mutations; DNA-protein and DNA-DNA

crosslinks (DPX and DDC, respectively) and DNA mono (hmDNA) adducts; clastogenic-related effects such as micronuclei (MN) and chromosomal aberration (CA) formation, as well as sister chromatid exchanges (SCEs), single-strand and double-strand breaks (SSBs, DSBs, respectively); and unscheduled DNA synthesis (UDS), DNA repair inhibition, and cellular transformation. For a comprehensive description of the evidence on formaldehyde genotoxicity, see Appendix C.3, which includes a summary table of genotoxicity endpoints investigated across the test systems most relevant to human inhalation exposure and, when possible, separates the results into respiratory- versus nonrespiratory-related tissues or systems.

This evaluation emphasizes the experiments interpreted to best inform the potential for genotoxicity in humans following inhalation exposure to formaldehyde, and therefore focuses on in vivo studies in mammalian species. In addition, the relative importance of the specific genotoxic endpoints was considered when prioritizing results in the synthesis of epidemiological evidence for genotoxicity. For example, it has been shown that increased frequency of CAs and MN are associated with increased cancer mortality, and these endpoints are considered by EPA to be highly relevant to the assessment of genotoxicity in humans (U.S. EPA, 2005a; Bonassi et al., 2004b; Bonassi et al., 2007; Bonassi et al., 2008). SSBs and DSBs in DNA indicate genetic instability and are also considered by EPA to be highly relevant to the assessment of genotoxicity for humans, while increased frequencies of sister chromatid exchange (SCE) are less strongly associated with cancer mortality (Bonassi et al., 2004a).

Inhaled formaldehyde primarily encounters cellular macromolecules at POE tissues, including both nasal and buccal epithelial cells in humans, while preferentially affecting the nasal epithelium in rodents, which are obligate nose-breathers. In these barrier tissues, formaldehyde can interact directly with DNA, resulting in DPX and DDC, DNA mono (hmDNA) adducts, SSBs, MN, and CAs. Furthermore, cells in the lower respiratory tract (LRT) and tissues distal to the initial point of exogenous formaldehyde exposure, such as peripheral blood lymphocytes (PBLs), are also potential targets of formaldehyde genotoxicity.

Neither DPX nor hmDNA adduct levels have been assessed specifically in nasal or buccal tissues from formaldehyde-exposed human workers, although occupational exposure to formaldehyde was associated with a significant exposure- and duration-related increase in DPX formation in PBLs. Formaldehyde-induced DPXs in the URT of rats and nonhuman primates in a dose-responsive manner across several studies. The predominant location of DPX formation varied due to anatomical differences in the nasal physiology and breathing patterns of primates versus rodents; however, the distribution of DPXs in rat nasal tissues corresponded to sites of tumor incidence, cell proliferation, and cytotoxicity. hmDNA monoadducts have been observed in the nasal epithelium of rats and the maxilloturbinate regions of rhesus monkeys following formaldehyde exposure, as well as in cell-free systems, and cultured cell lines including human nasal epithelial cells.

The majority of occupational studies have associated formaldehyde exposure with increased MN formation in human nasal or buccal epithelial cells, predominantly forming centromere-negative micronuclei suggesting clastogenic effects. Although no MN in nasal tissues were observed in one short-term, high-dose rodent inhalation study, MN were consistently induced in different mammalian cells in vitro. In addition, long-term occupational exposure was associated with significantly increased MN in PBLs, and aneugenicity appears to be the predominant effect in peripheral tissues (see Section 3.3.3). Exposure to formaldehyde also was associated with significantly increased CAs in PBLs of human workers, as well as in rodents from a short-term, high-dose study. Formaldehyde also induced CAs in rat pulmonary lavage cells, as well as hamster and primary human cells in vitro. Exposure-related increases in SSBs were observed in rat nasal tissues in one experimental study and in several studies of PBLs from exposed workers and rodents. Occupational exposure to formaldehyde caused increased mutant p53 protein expression in the serum of exposed workers, while cell lines derived from formaldehyde-induced rat nasal SCCs showed *p53* mutations. Across the available database, formaldehyde consistently induces various endpoints consistent with mutagenicity, such as base pair mutations, deletions, insertions and point mutations, SCEs, SSBs, UDS, and DNA repair inhibition in various cells in vitro, in experimental animal models in vivo, as well as in exposed humans.

Formaldehyde is genotoxic. This conclusion is supported by several streams of evidence including observations of CAs, MN, and SSBs in exposed humans across a range of studies, occupations, and exposure scenarios, with supporting, similar findings in exposed rodents and in vitro systems, and consistent observations of DPXs detected in multiple experimental systems, showing a pattern of concentration-dependent increases. Together, these multiple streams of evidence (from human, animal, in vitro and nonmammalian systems) converge to clearly indicate that formaldehyde is genotoxic in most systems tested, is mutagenic in systems specifically evaluating genetic or chromosomal mutations, and exhibits strong evidence for mutagenicity in the URT of rodents and humans following inhalation exposure.

Summary and integration of mechanistic pathways into a cancer mode of action

The evidence pertaining to URT carcinogenesis following formaldehyde exposure was assembled into a putative URT cancer MOA network highlighting the potential contributions of genotoxicity and cytotoxicity-induced regenerative proliferation (see Figure 3-24), as well as incorporating the influences of increased cell turnover independent of tissue pathology, underlying chronic inflammation and epigenetic activity as prime examples of other considerations that can interact with and further modify the primary mechanisms propelling formaldehyde-induced URT cancer, in addition to potentially contributing independently. Table 3-38 presents a concordance summary view of the available evidence (Meek et al., 2014), illustrating the exposure concentration and duration required to either elicit or amplify formaldehyde-associated effects in the URT of F344 rats (the model species most sensitive to SCC development with the most diverse and robust data set available). These rat data are informative of the mechanistic pathways of primary concern,

including genotoxicity endpoints as an indicator of mutagenic potential; reports of tissue pathology including hyperplasia, squamous metaplasia, dysplasia, and necrosis; cellular DNA synthesis as an indicator of epithelial proliferation rate (independent of cause); as well as formaldehyde-associated tumor induction (see Section 3.2.5, *Respiratory Tract Cancers in Animal Studies*). These interrelated streams of evidence are summarized separately (below) and then integrated into a composite MOA, which is evaluated in subsequent sections.

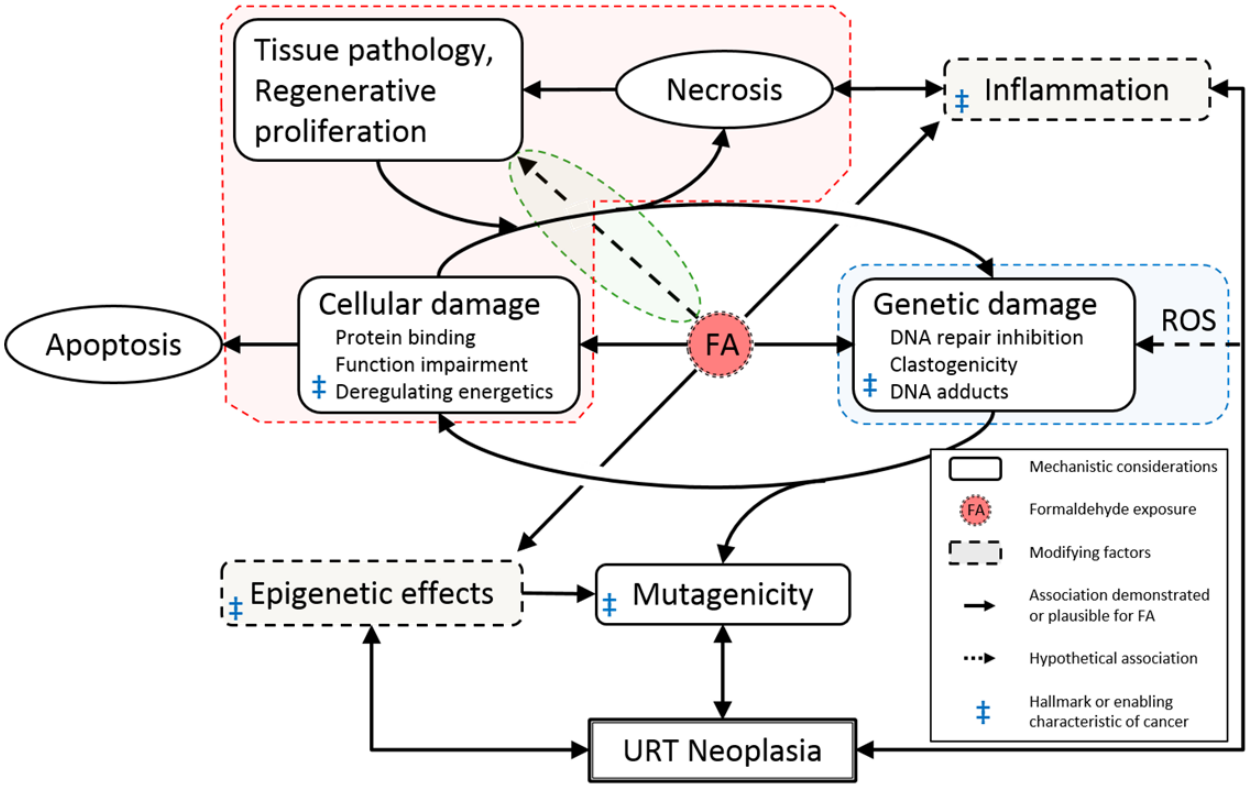


Figure 3-24. An integrated cancer mode-of-action (MOA) network for the URT.

Various effects occur in a manner dependent upon duration and magnitude of formaldehyde (FA) inhalation exposure. Primary mechanistic considerations in call-out boxes are described in the following tables and figures (blue/genetic damage, see Table 3-39; green/formaldehyde-induced proliferation without damage, see Table 3-40; red/tissue and cellular damage, see Tables 3-40 and 3-41) with evidence identified from the formaldehyde database as possibly informative of molecular mechanisms. These mechanistic considerations or modifying factors are consistent with those factors described as cancer hallmarks, enabling, or key characteristics of carcinogens (Smith et al., 2016; Hanahan and Weinberg, 2011).

Table 3-38. Concordance of temporal and dose-response relationships among formaldehyde effects induced in F344 rat nasal epithelium in vivo

F344 Rats		Time (months) 0–3	4–12	13–28	Time (months) 0–3	4–12	13–28
		Genotoxicity[a]			*Necrosis*[b]		
Exposure (mg/m^3)	0–2	+	ND	ND	–	–	–
	2–7	++	ND	ND	–/+	–	–
	>7	+++	ND	ND	++	+	+
		Hyperplasia and/or metaplasia[c]			*DNA synthesis*[d,e]		
Exposure (mg/m^3)	0–2	–	–	+	–/+	–[f]	–[f]
	2–7	–/+	+	++	+	–[f]	–[f]
	>7	+	++	+++	+++	++[f]	++[f]
		Tumorigenesis (polypoid adenoma)[g]			*Tumorigenesis (squamous cell carcinoma)*[g]		
Exposure (mg/m^3)	0–2	–	–	–	–	–	–
	2–7	–	–	+	–	–	–/+
	>7	–	–	++	–	+	+++

Male F344 rats were the most widely evaluated sex/strain/species/evaluated, but observations were comparable between rat sexes, where available. The presence or absence of treatment-related effects across all available studies (as determined by EPA review) in or near the nasal anterior lateral meatus (ALM, where specified, generally within Level II), were depicted as follows: "–" indicates the absence of effects; "ND" indicates no data available for the specified endpoint/dose/time combination; –/+ indicates an equivocal response, or evidence limited to the highest extreme of the exposure range indicated; +, ++, +++ indicate the presence of an exposure-related effect, with symbol number corresponding to increasing magnitude, incidence, or severity, relative to concurrent controls and other exposure level/duration entries within an effect category (see Section 3.2.4 and Appendix C.3).

[a]Includes DNA-protein and DNA-DNA crosslinks or increases in N^2-hmdG DNA adducts attributed to exogenous formaldehyde exposure.

[b]Direct evaluation necrosis was not frequently reported, and apoptosis has not been directly measured; significant exposure-related tissue destruction was inferred from pathological determination of necrosis, erosion, disarrangement, or atrophy of the nasal epithelium.

[c]Tissue reactive or adaptive responses to irritant or cytotoxic effects were determined by evaluating hyperplasia or squamous metaplasia (typically combined in reporting by study authors) of the nasal respiratory or transitional epithelium; however, the biochemical stimulus of this tissue reaction remains unclear, as such areas of hyperplasia could also include areas of dedicated preneoplastic foci.

[d]DNA label incorporation as a measure of proliferation at the individual cell level in the ALM was measured by incorporation of BrdU, [^{3}H]-thymidine or [^{14}C]-formaldehyde into DNA, and reported as an index normalizing affected (positive) cells as a fraction of the total respiratory epithelium (see detailed summary in Appendix C.7.1).

[e]DNA synthesis has been evaluated following both continuous and intermittent exposures; while effects of continuous exposure are depicted herein for purposes of drawing comparisons across similar exposure scenarios, intermittent exposure may be also informative for some human exposure scenarios.

[f]Results from a single study reporting rat nasal epithelial cell DNA label incorporation following 26, 52, or 78 weeks of exposure (Monticello et al., 1996).

[g]Both polypoid adenomas (PA) and squamous cell carcinomas (SCC) were described as likely arising from the respiratory or transitional epithelium, typically on or near the ALM. However, SCCs were typically associated with areas of hyperplasia or squamous metaplasia, whereas PAs were not.

Formaldehyde directly adducts DNA and proteins, causing dose-responsive increases in DNA-protein (DPX) or DNA-DNA (DDC) crosslinks, as well as DNA mono deoxyguanosine (hmdG) adducts (see Table 3-38, also see Appendix C.3). Evidence from humans and rodents suggests that formaldehyde exposure can lead to increasing levels of reactive oxidative species (ROS) and possibly inhibit cellular detoxification mechanisms (see Appendix C.7), which would be expected to further exacerbate oxidative damage to cellular constituents and DPX formation. Following these initial effects, single-strand DNA breaks could be created more frequently, and DNA repair could be inhibited, possibly leading to an accumulation of genetic damage at the chromosome (clastogenicity) and sequence level (gene mutations). While the specific nature of persistent genetic damage leading to URT cancer following formaldehyde exposure is unclear, heritable changes in genetic material are a prerequisite step for carcinogenesis following a mutagenic mode of action. The observations most relevant to genotoxic effects and sequelae to URT neoplasia are summarized in Table 3-39.

Table 3-39. Genotoxicity and mutagenicity in the upper respiratory tract

Observations from the available in vivo database *(see Appendix C.3 for details)*[a,b]	**Exposure level (mg/m^3)[c]**	**Statistical associations[d]**
Human		
Acute or short-term exposure: controlled		
• No effect or limited ↑ on MN incidence in nasal/buccal epithelial tissue	*≤1, or 17 mg/m^3-hrs[e]*	NR
Subchronic exposure: repeat environmental (pathology and medical students)		
• ↑ MN incidence in nasal and buccal epithelium, stronger association in centromere-negative MN	0.5–2 [0.07–5]	NR and –/+ assoc. w/↑ CE
Chronic exposure: repeat occupational/environmental		
• ↑ Binucleation, but not nuclear bud or MN frequency, in buccal epithelium from furniture workers	0.04–0.1 [NR]	+ assoc. w/↑ [C] No assoc. w/↑ D
• ↑ MN frequency in nasal epithelium from workers	0.1–1 [0.05–5]	NR
• ↑ MN frequency in buccal epithelium from anatomy/pathology faculty and staff, laboratory or factory workers	0.2–NR [0.05–5]	+ assoc. exposed:referent + association w/↑ D

Observations from the available in vivo database *(see Appendix C.3 for details)*[a,b]	**Exposure level (mg/m^3)[c]**	**Statistical associations[d]**
Nonhuman primate		
Acute or short-term exposure: controlled		
• ↑ DPX in the nasal mucosa; larynx, trachea, and/or carina; maxillary sinuses and lower respiratory tract of rhesus monkeys	≥0.9; ≥2; 7	− assoc. w/↑ distance from POE
• ↑ Exogenous FA $^{13}CD_2$-N^2-hmdG adducts and DPXs in maxilloturbinates of cynomolgus monkeys	≥2	+ assoc. w/↑ [C]
Rodent		
Acute or short-term exposure: controlled		
• ↑ DPX in the nasal epithelium; no effect in bronchoalveolar lavage fluid or nasal olfactory mucosa of F344 rats	≥0.4; *≥18*	− assoc. w/↑ distance from POE
• ↑ Exogenous FA $^{13}CD_2$-N^2-hmdG adducts and DPXs in nasal epithelium of F344 rats	≥0.9	+ assoc. w/↑ [C], D
Subchronic exposure: controlled		
• ↑ DPX in the nasal epithelium of F344 rats	≥0.9	− assoc. w/↑ distance from POE
• No effect on MN incidence in nasal epithelium of F344 rats	*≤18*	NR

[a]Treatment-associated increase (↑), micronucleus (MN), DNA-protein crosslinks (DPX), DNA monomethyl deoxyguanosine adducts resulting from exogenously administered formaldehyde (FA $^{13}CD_2$-N^2-hmdG), single-strand DNA breaks (SSBs).

[b]The earliest duration reported by the study authors to elicit the specified effect is noted for controlled exposure studies, or the mean duration reported in epidemiological studies; multiple values are provided in cases where the study authors described only a range of exposure durations, or to represent a range of average durations from a collection of similar epidemiological or experimental reports.

[c] For experimental studies, lowest effective concentrations (LEC) are presented, while for individual epidemiological studies, mean exposures are listed, otherwise the range of mean exposures is presented to represent a collection of studies reporting similar effects, with the overall range reported in individual studies or collections in [ ]; determinations were made by EPA review considering potentially biologically relevant effects that were attributed by the study authors to formaldehyde exposure; "≥" indicates that higher exposures were evaluated that also indicated an exposure-related effect. Where no effect was reported, the highest ineffective concentrations (*HIC*), or ranges of exposure are indicated; "≤" indicates that concentrations lower than the HIC were also evaluated.

[d]Results of association, regression, correlation, or trend analysis as reported by study authors; "NR" indicates that either associations were not evaluated or that no significant associations (assoc.) were reported; positive (+), weakly positive (−/+) associations, inverse association (−); with (w/), exposure duration (D), cumulative exposure (CE), exposure concentration ([C]), apical portal of entry (POE).

[e]This study employed a complex and variable exposure protocol, with individuals experiencing 17 mg/m^3-hours of cumulative formaldehyde exposure distributed throughout a period of 40 hours over 10 workdays (2 weeks).

[f]Results presented from respiratory or transitional epithelial tissue generally described as located in "Level II" of the anterior rodent nasal passages, including the nasal lateral meatus, septum, naso- and maxilloturbinates, as described in Section 3.2.4.

In addition to directly damaging DNA, formaldehyde inhalation can cause a number of pathological cellular changes in the URT, such as inhibited mucous flow and decreased ciliary beat, rhinitis and inflammation, ciliastasis, cilia loss, and possibly sporadic epithelial proliferation at low-to-moderate exposure levels that elicit marginal increases in frank tissue toxicity as evidenced by a

lack of necrosis, epithelial degeneration, or squamous metaplasia in the nasal passageways (see Section 3.2.4). Any molecular mechanisms responsible for such respiratory epithelial proliferation remain to be determined, but could include some of the cytokines and eicosanoids associated with URT inflammation and leukocyte extravasation, epigenetic activation, or suppression of cell cycle regulatory machinery through changes in gene regulation, including miRNA, loss of contact-inhibition signaling, or even direct stimulation of epithelial mitosis via adduction of growth factor-signaling mediators (see Appendix C.7 for the evidence available on some of these potential events). Accelerated cell cycle progression can increase the rate of random genotoxic events in proliferating cells (indirect genotoxicity), which—if improperly repaired due to insufficient delay in G1 phase, failure to arrest in S phase, or deficiency of DNA repair machinery—could lead to heritable mutations and eventually URT neoplasia (Branzei and Foiani, 2008). Tissue stem cell proliferation rate and the contribution of this random or "background" mutagenesis to human lifetime cancer risk has been proposed to be significant for a variety of tissues (Tomasetti and Vogelstein, 2015), although the relevance, magnitude, and scope are still under debate (Wodarz and Zauber, 2015; Wild et al., 2015; Rozhok et al., 2015). Experimentally, the magnitude of formaldehyde-induced DNA synthesis is dramatically increased as a function of concentration and, to a lesser extent, duration, reaches maximal levels after 1–3 months with short-term or subchronic exposure, and then appears to diminish in the only study that looked at changes after exposure longer than 13 weeks (see Appendix C.7). Observations from direct DNA labeling studies are summarized in Table 3-40 (scenarios involving cytotoxic exposures are described below).

Table 3-40. Direct measurements of DNA synthesis in the upper respiratory tract

Observations from the available in vivo database *(see Appendix C.7.1 for details on proliferation)*[a,b]	Exposure level (mg/m^3)[c]	Statistical associations[d]
Nonhuman primate		
Acute—subchronic exposure: controlled		
• ↑ Epithelial cell proliferation in nasal and extranasal transitional and respiratory epithelium of rhesus monkeys	7	– assoc. w/↑ D, distance from POE
Rodent[e]		
Acute exposure: controlled		
• ↑ Epithelial cell proliferation in nasal septum, lateral meatus, or turbinates of Wistar rats; in the anterior nose (not otherwise specified) in Sprague Dawley rats	≥4; ≥3	NR; NR
• ↑ Epithelial cell proliferation in the nasal lateral meatus, or maxilloturbinates in F344 rats	≥7	– assoc. w/↑ D + assoc. w/↑ CE[f]
• ↑ Epithelial cell proliferation in the nasal lateral meatus, or nasoturbinates in $B6C3F_1$ mice	≥15	– assoc. w/↑ D + assoc. w/↑ CE[f]

Observations from the available in vivo database ***(see Appendix C.7.1 for details on proliferation)***[a,b]	**Exposure level (mg/m^3)**[c]	**Statistical associations**[d]
Subchronic exposure: controlled		
• ↑ Epithelial cell proliferation in nasal septum, turbinates, or lateral meatus of Wistar rats	≥4	+ assoc. w/↑ [C] and not CE
• ↑ Epithelial cell proliferation in the nasal lateral meatus, septum, and/or turbinates of F344 rats	≥3–7[g]	– assoc. w/↑ distance from POE + assoc. w/↑ [C], D
Chronic exposure: controlled		
• ↑ Epithelial cell proliferation in the nasal lateral meatus in F344 rats	≥12	– assoc. w/↑ D, distance from POE

[a]Treatment-associated increase (↑).
[b]The durations reported by the study authors to elicit the specified effect are noted for controlled exposure studies; multiple values represent different durations from several experimental reports.
[c]Lowest effective concentrations (LEC) are presented for experimental studies, as determined by EPA review considering potentially biologically relevant effects that were attributed by the study authors to formaldehyde exposure; "≥" indicates that higher exposures were evaluated which also indicated an exposure-related effect.
[d]Results of association, regression, correlation, or trend analysis as reported by study authors; "NR" indicates that either associations were not evaluated or that no significant associations (assoc.) were reported; positive (+) or inverse association (–); with (w/), exposure duration (D), cumulative exposure (CE), exposure concentration ([C]), apical portal of entry (POE).
[e]Results presented from respiratory or transitional epithelial tissue generally described as located in "Level II" of the anterior rodent nasal passages, including the nasal lateral meatus, septum, naso- and maxilloturbinates, whereas "Level I" commonly included the high-flux region and nose tip, as described in Section 3.2.4.
[f]These associations are for "Level I" epithelial cells; only exposure concentration ([C]) was positively associated with cells in "Level II."
[g]LEC reported varied among reports from different authors and following exposures of different durations.

At higher, cytotoxic exposure levels, regenerative tissue proliferation concomitant with and resulting from cytotoxic epithelial pathology (including squamous hyperplasia, metaplasia, and dysplasia, with or without evidence of frank necrosis; discussed in Section 3.2.4) occurs in an exposure concentration- and duration-dependent manner. The relative contribution of exposure concentration and duration to this process may not be equal, particularly for events that segue from hyperplasia (exposure duration appears to be substantially more important to the development of metaplasia in laboratory animals than to the development of hyperplasia; see Section 3.2.4); however, specific data defining the relative contributions are unavailable. Metaplasia or hyperplasia is induced at moderate to high exposure levels after even short-term exposure, and extending the duration generally both increases the severity of nasal tissue pathology observed and decreases the exposure concentration necessary to elicit significant cytotoxicity (see Section 3.2.4). Pathological indications of significant epithelial necrosis in F344 rats are primarily reported following exposure to relatively high concentrations, with similar results in Wistar or Sprague Dawley rats, although occasionally necrosis is reported at more moderate exposure levels. Under these conditions, the tissue rhinitis/inflammation, macromolecule adduction, or inhibition of cellular function is presumably severe enough, possibly in conjunction with tissue glutathione

(GSH) depletion, to trigger cell death and significant regenerative pathology in the nasal respiratory or transitional epithelium. Together, these effects can increase damage from all sources to cellular constituents (e.g., membrane lipids and proteins, cytosolic proteins, DNA), and amplify genotoxicity while simultaneously decreasing the capacity for and fidelity of DNA repair. Thus, both direct and indirect effects of formaldehyde exposure at these levels can feed forward to increase insurmountable cellular toxicity. Cytotoxicity and death of more sensitive cells in the respiratory epithelial tissue compartment could select for and trigger compensatory proliferation among more resistant cells in the population, possibly including the division and differentiation of local pluripotent stem cells, all of which may replicate to replenish the damaged nasal mucosa. The magnitude of these tissue proliferative effects may also fluctuate as the result of epithelial tissue responses to chronic, continuous (i.e., metaplastic differentiation to a squamous phenotype) versus episodic (variable pathology) exposure scenarios. In this manner, formaldehyde exposure may accelerate proliferation as a field effect at the epithelial tissue level, causing genotoxicity and mutagenesis in both actively proliferating (direct and indirect genotoxicity) and more quiescent cells (direct genotoxicity only). Observations relevant to cytotoxic tissue pathology and regenerative proliferation are summarized in Table 3-41.

Table 3-41. Epithelial pathology, cytotoxicity, and regenerative proliferation in the upper respiratory tract

Observations from the available in vivo database *(see Appendix C.7 for details)*[a,b]	Exposure level (mg/m^3)[c]	Statistical associations[d]
Human		
Acute Exposure: Controlled[e]		
• ↑ Nasal mucosal membrane swelling; nasal and throat irritation	≥0.07; ≥0.3	NR; + assoc. w/↑ [C]
• ↓ Nasal mucociliary function, mucus flow rate; ↑ rhinitis and permeability index	≥0.3; ≥0.5	No assoc. w/D; NR
Chronic Exposure: Repeat Occupational/Residential		
• ↓ Nasal patency (airway volume)	0.01 [0.003–0.02]	– assoc. w/dust, NO_2, mold
• ↑ General symptoms of rhinitis, URT irritation, or inflammation	0.05–1 [0.01–2]	+ assoc. w/↑ [C], No assoc. w/D
• ↓ Nasal mucociliary function	0.3 [0.05–0.5]	No assoc. w/D
• ↑ Nasal hyperplasia, keratinization, or squamous metaplasia	0.3–NR [0.02–2.5]	No assoc. w/D + assoc. w/age >50
Nonhuman Primate		
Acute Exposure: Controlled		

Observations from the available in vivo database *(see Appendix C.7 for details)*[a,b]	Exposure level (mg/m^3)[c]	Statistical associations[d]
• ↓ Cilia content and ↑ hyperplasia or squamous metaplasia in nasal epithelium, nasopharynx, and larynx of rhesus monkeys	7	− assoc. w/↑ distance from POE
Subchronic Exposure: Controlled		
• ↑ Squamous metaplasia and hyperplasia in nasal epithelium, nasopharynx, and larynx of rhesus monkeys	7	+ severity w/↑ D − assoc. w/↑ distance from POE
• ↑ Squamous metaplasia and hyperplasia in nasal turbinates of cynomolgus monkeys	≥4	+ assoc. w/↑ [C]
Rodent[f]		
Acute Exposure: Controlled[g]		
• ↑ Nasal rhinitis, hyperplasia, or squamous metaplasia in Wistar rats	4	NR
• ↓ Microvilli content in nasal epithelial cells, ↓ nasal mucociliary function, flow rate; ↑ nasal squamous metaplasia of F344 rats	≥3; ≥7	− assoc. w/↑ [C], D; NR
• ↑ Nasal squamous metaplasia or hyperplasia in Swiss-Webster or $B6C3F_1$ mice	≥4	NR
Subchronic Exposure: Controlled		
• ↑ Nasal rhinitis, hyperplasia, or squamous metaplasia; ↓ cilia content of nasal septa epithelium in Wistar rats	≥4; 4	+ assoc. w/↑ [C] and not CE; NR
• ↑ Nasal hyperplasia or squamous metaplasia in F344 rats	≥7−12	− assoc. w/↑ distance from POE
• ↑ Nasal squamous metaplasia and seropurulent inflammation in $B6C3F_1$ mice	≥12	NR
Chronic Exposure: Controlled		
• ↑ Nasal rhinitis, hyperplasia, or squamous metaplasia in Wistar and F344 rats	≥1 and ≥3	NR and + assoc. w/↑ [C], D
• ↑ Nasal squamous metaplasia (but not rhinitis or hyperplasia) in Sprague Dawley rats	18	NR
• ↑ Nasal rhinitis, hyperplasia; nasal squamous metaplasia and dysplasia in B6C3F1 mice	≥3; ≥12	NR; NR

[a]Treatment-associated increase (↑), treatment-associated decrease (↓), hours (hrs), upper respiratory tract (URT).

[b]The earliest duration reported by the study authors to elicit the specified effect is noted for controlled exposure studies, or the mean duration reported in epidemiological studies; multiple values are provided in cases where the study authors described only a range of exposure durations, or to represent a range of average durations from a collection of similar epidemiological or experimental reports.

[c]For experimental studies, lowest effective concentrations (LEC) are presented, while for individual epidemiological studies, mean exposures are listed, otherwise the range of LECs or mean exposures are presented to represent a collection of studies reporting similar effects, with the overall range reported in individual epidemiological studies or collections shown in brackets ([ ]); determinations were made by EPA review considering potentially biologically relevant effects that were attributed by the

study authors to formaldehyde exposure; "≥" indicates that higher exposures were evaluated that also indicated an exposure-related effect.

[d]Results of association, regression, correlation, or trend analysis as reported by study authors; "NR" indicates that either associations were not evaluated or that no significant associations (assoc.) were reported; positive (+), inverse association (−); with (w/), exposure duration (D), cumulative exposure (CE), exposure concentration ([C]); apical portal of entry (POE).

[e]Due to the abundance of acute exposure human studies, only those rated as high or medium confidence are summarized, as described in Appendix C.7.

[f]Results presented from respiratory or transitional epithelial tissue generally described as located in "Level II" of the anterior rodent nasal passages, including the nasal lateral meatus, septum, naso- and maxilloturbinates, as described in Section 3.2.4.

[g]Due to the abundance of acute exposure rodent studies, only those rated as high or medium confidence are summarized, as described in Appendix C.7.

Relationships among the various events discussed above are integrated into a mechanistic network depicted in Figure 3-25, along with the modifying factors of chronic airway inflammation, oxidative stress, and epigenetic effects, which are also likely to stimulate or enhance URT tumorigenesis. Together, these primary mechanistic events and modifying factors form potential adverse outcome pathways (AOP), which are illustrated as a network of interconnected events [adverse outcome network (AON)], with some duplication of events across individual pathways for clarity (see Figure 3-26). These figures highlight various interactions among mechanistic elements for which some evidence exists in the formaldehyde database. They also facilitate the discussion and evaluation of this evidentiary support. The figures are not intended to illustrate every possible relationship among various aspects of formaldehyde toxicity and do not represent an attempt to exhaustively list all possible carcinogenic mechanisms. Furthermore, the understanding of how such signaling circuits actually operate in human carcinogenesis is still fragmentary and the current subject of intense study (Weinberg, 2014). The following section serves to evaluate the supporting evidentiary data pertaining to the events depicted in these figures.

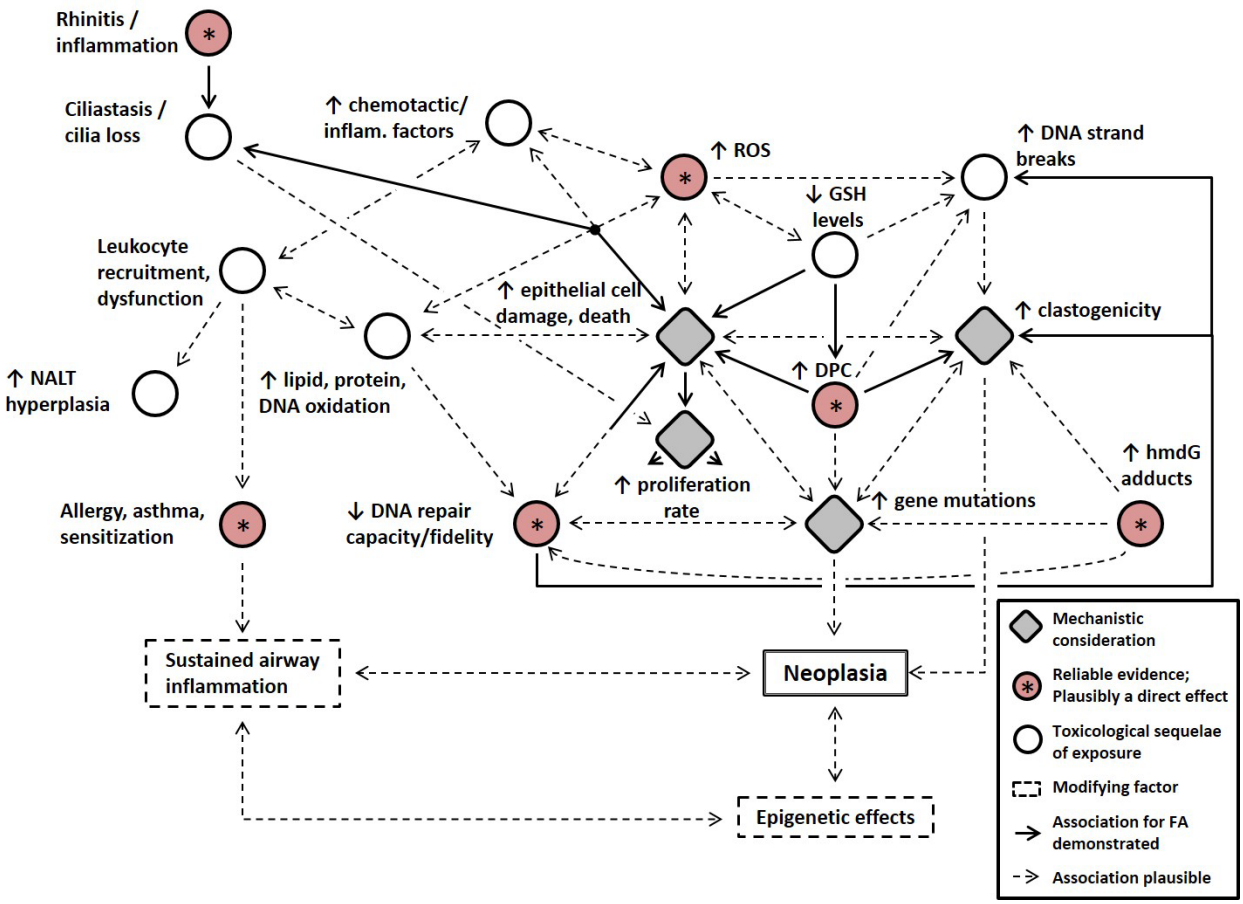


Figure 3-25. Mechanistic relationships relevant to URT carcinogenesis.

Integration of the molecular evidence available for the spectrum of formaldehyde- [FA-] related health effects pertinent to upper respiratory tract carcinogenesis summarized in the previous sections. Endpoints are depicted with varying degrees of support (with solid lines representing evidence from exposure in vivo, or consistent findings across multiple types of in vitro evidence). The identification of "reliable evidence" and related conclusions depicted in this figure are based primarily on evaluations conducted elsewhere (i.e., robust or moderate evidence described in Appendix C.7). Plausible relationships are illustrated in a manner consistent with the cancer MOA schematic in Figure 3-24, including the hallmarks and enabling characteristics of cancer outlined therein.

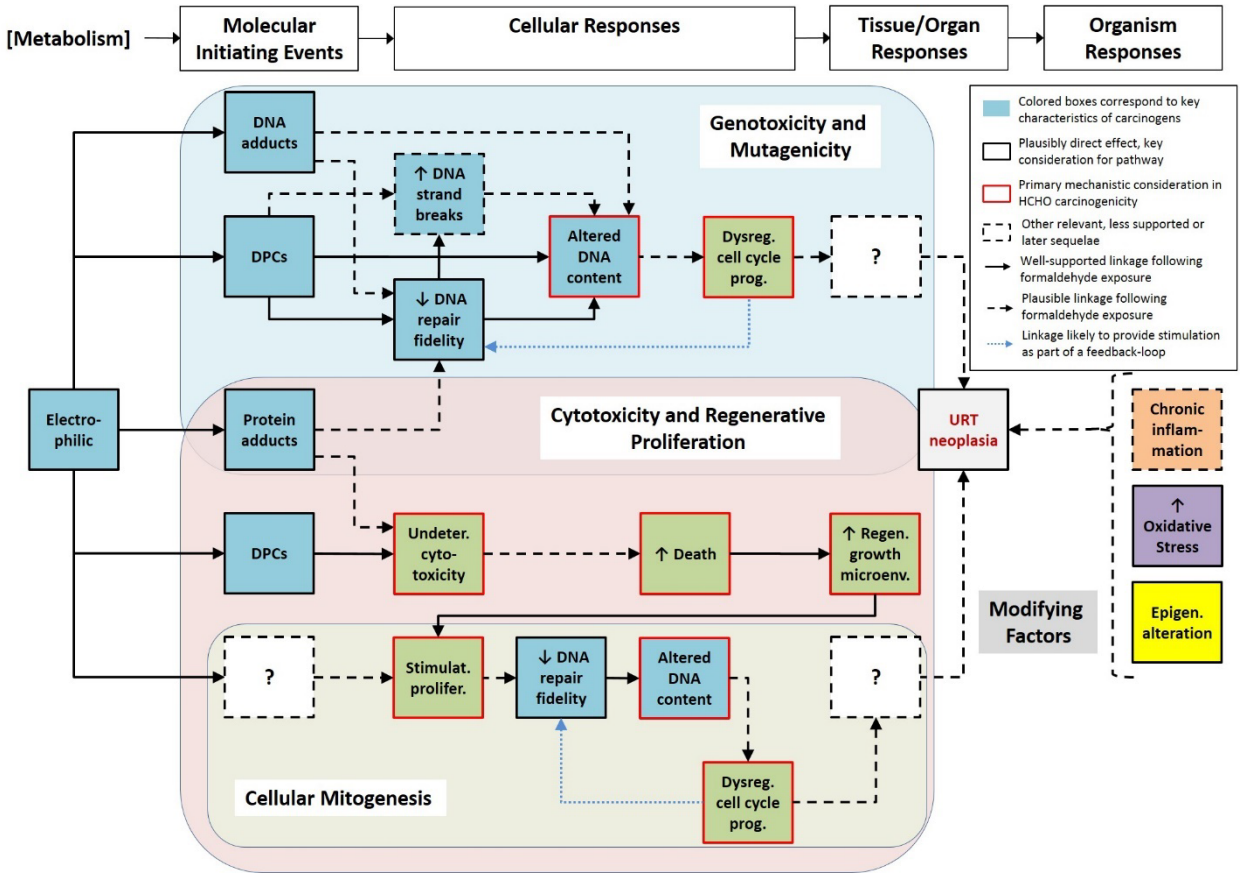


Figure 3-26. Network of adverse outcome pathways relevant to URT carcinogenesis.

Integration of the possible key events in pathways describing the role of genotoxicity and mutagenicity, cellular mitogenesis, and cytotoxicity and regenerative tissue proliferation in URT carcinogenesis following formaldehyde exposure. Endpoints are depicted with varying degrees of support (with solid lines representing evidence from exposure in vivo, or consistent findings across multiple types of in vitro evidence), with plausible relationships as hashed arrows, and possible feed-back loops illustrated as dotted reverse-facing blue lines. Boxes of varying colors represent events associated with related groups of key characteristics of carcinogens (Smith et al., 2016); electrophilicity, genotoxicity, and DNA repair elements are in blue, cell death and proliferation elements are in green, while the influence of chronic inflammation, oxidative stress, and epigenetic alterations are depicted as factors modifying the network in orange, purple, and yellow, respectively.

Evaluation of experimental support for the hypothesized mode of action

Genotoxicity

DNA-protein crosslinks (DPXs) were significantly elevated in the respiratory tracts of rhesus monkeys after 3 days of inhalation exposure, with lowest effective concentrations (LEC) increasing with anatomical distance from the apical POE, from 0.9 mg/m^3 in the nasal turbinates, to 2 mg/m^3 in the larynx, trachea, and carina (pooled samples), and 7 mg/m^3 in maxillary sinuses and lungs (Casanova et al., 1991), demonstrating direct genotoxicity as an early effect in tissues

analogous with sites of tumor formation in humans. In rats, increased DPX levels from exogenous formaldehyde were observed in the nasal lateral, medial, and posterior meatus (Casanova et al., 1994) or the entire nasal cavity of rats after ≥0.86 mg/m^3 ^{14}C-formaldehyde inhalation (Casanova et al., 1989), following single and multiple inhalation exposures over 0.25–81 days. Exogenous DPXs resulting from exposure to ^{13}C, d_2-labeled formaldehyde was reported in nasal passages from both nonhuman primates and rats. In rat nasal passages, DPX levels accumulated several-fold following 28 days of exposure to 2.5 mg/m^3 and remained largely unchanged following 7 days of recovery postexposure (different time points were not evaluated in nonhuman primate studies, (Lai et al., 2016)). Interestingly, while DPX levels increased by 2-fold to 30-fold over control levels from 0.9 to 18 mg/m^3 in rat nasal passages (NTP, 2010; Liteplo and Meek, 2003), the rate of DPX formation per unit of formaldehyde exposure (DPX/ppm exogenous formaldehyde) increased to a plateau at 7 mg/m^3, where it remained constant from 7 to 18 mg/m^3 (Swenberg et al., 2013; Casanova-Schmitz et al., 1984b). In both rhesus monkeys and F344 rats, DPX incidence was inversely associated with increasing anatomical distance from apical POE (Lam et al., 1985; Casanova-Schmitz and Heck, 1983; Casanova-Schmitz et al., 1984b; Casanova et al., 1989; Casanova et al., 1991; Casanova et al., 1994; Casanova and Heck, 1997). While increased DPX formation in human peripheral white blood cells (WBCs) has been positively associated with duration of exposure to concentrations ≥0.3 mg/m^3 [(Shaham et al., 1996; Shaham et al., 1997; Shaham et al., 2003; Lin et al., 2013); see Appendix A.4], DPX levels have not been evaluated in analogous human POE tissues (i.e., nasal, buccal, or nasopharyngeal epithelium).

Bulky DNA adducts, such as DPX, can block progression of the DNA polymerase complex, possibly contributing to genotoxicity or cell death in the URT (for further discussions see Appendices A.4 and A.5.6; (Wong et al., 2012; Heck and Casanova, 1999)). After a single exposure in rats, the inhibition of DNA replication due to DPX blockage was also predicted to be significant at >7 mg/m^3 (Heck and Casanova, 1999). While DNA replication was thought to be only marginally affected after a single exposure to lower concentrations (<1% at 1 mg/m^3 in rats), this effect may increase in magnitude or impact with the accumulation of DPXs and DNA adducts resulting from repeated exposure, as discussed below. Although the mechanisms regulating these effects remain undetermined, exposures ≥7 mg/m^3 are associated with increasingly severe epithelial pathology, cell death, and hyperproliferation in rat nasal passages following subchronic exposure, as well as dramatic increases in SCC formation after chronic exposure (see discussions of the specific animal evidence in Section 3.2.4 and earlier in this section, 3.2.5).

In addition to forming crosslinks, biochemical investigations have demonstrated that formaldehyde can react with DNA to form predominantly N^6-hydroxymethyl-deoxyadenosine (N^6-hmdA) and N^2-hydroxymethyl-deoxyguanosine (N^2-hmdG) adducts, with dA adducts more abundant than dG (Zhong and Hee, 2004; Cheng et al., 2008; Beland et al., 1984). While both DNA adducts have been detected in various tissues in vivo, likely resulting from endogenous formaldehyde reactivity, studies administering deuterium-labeled formaldehyde (^{13}C, d_2) have

detected labeled N^2-hmdG, but not N^6-hmdA, in the URT epithelium of both rodents and nonhuman primates (see Table 3-42; (Lu et al., 2010b; Lu et al., 2011; Lu et al., 2012); see Appendix A.4; (Yu et al., 2015b; Swenberg et al., 2013; Moeller et al., 2011), as well as human HeLa cells in culture (Lu et al., 2012). The inability to detect ^{13}C, d_2-N^6-hmdA was surprising, since ^{13}C, d_2-N^2-hmdG is reliably quantifiable following low levels of exposure, and increases in an exposure-dependent manner in both rodents and nonhuman primates (Yu et al., 2015b; Swenberg et al., 2013); the reason for the apparent absence of ^{13}C, d_2-N^6-hmdA adducts formed by reaction with exogenous formaldehyde remains unknown (see Appendix C.1). N^2-hmdG adducts resulting from exogenous exposure were positively associated with exposure concentration in the nasal maxilloturbinates of cynomolgus monkeys after 2 days, with an LEC of 2 mg/m^3 (Moeller et al., 2011), and also in the nasal epithelium of F344 rats after 1 to 28 days, with an LEC of 0.86 mg/m^3 (Yu et al., 2015b; Lu et al., 2010b; Lu et al., 2011). However, formaldehyde exposure up to 0.37 mg/m^3 in F344 rats failed to induce DPXs or hmDNA adducts in the nasal epithelium or in systemic tissues (Leng et al., 2019). As with DPXs, rat nasal N^2-hmdG adduct formation was also positively associated with exposure duration, with adducts accumulating to levels ≥5 times higher after 28 days of exposure to 2.5 mg/m^3 compared with single exposures; different time points were not evaluated in nonhuman primate studies (Yu et al., 2015b; Swenberg et al., 2013; Lu et al., 2010b). No studies have assessed the formation of exogenous hmDNA adducts in any tissues from humans exposed to formaldehyde.

Together with the above, acute exposure in rats and nonhuman primates appears to be sufficient to significantly increase formation of DPXs at an LEC of approximately 0.86 mg/m^3 and exogenous N^2-hmdG adducts at LECs of 0.86 and 2 mg/m^3 in analogous nasal tissues from both species. The observation that both DPXs and N^2-hmdG adducts are positively associated with exposure concentration in both nonhuman primates and rats (Yu et al., 2015b; Swenberg et al., 2013; Moeller et al., 2011; Lu et al., 2010b; Lu et al., 2011; Lai et al., 2016), and that they accumulate in rat nasal passages with repeat exposure (Yu et al., 2015b; Lai et al., 2016), is consistent with the hypothesis that DPXs may undergo spontaneous hydrolysis to form N^2-hmdG adducts (Yu et al., 2015b). While some DPXs may undergo hydrolysis to form N^2-hmdG adducts following exogenous formaldehyde exposure, other DPXs appear to be quite stable in vivo; it may be these latter DPXs that play a more important role in formaldehyde-mediated respiratory tract mutagenicity and carcinogenicity (NRC, 2011; Lai et al., 2016).

In addition to DNA adducts, strand breaks and cytogenetic endpoints have also been observed following formaldehyde exposure, and such damage can lead to heritable mutations, deletions, amplification, or chromosomal abnormalities if not successfully repaired. While DNA strand breaks have not been evaluated in apical POE tissues from rats or nonhuman primates, DNA SSB incidence was significantly increased in a concentration-dependent manner in both lung epithelial cells and PBLs from Sprague Dawley rats after 14 days of exposure to ≥6 mg/m^3, in the absence of significant protein or lipid oxidation in lung tissue (Sul et al., 2007; Im et al., 2006), corresponding with increased lung cell apoptosis observed following 28 days of exposure to

≥7 mg/m^3 (Aydin et al., 2014). Likewise, while strand breaks have not been measured in adult human URT tissues, increased SSBs have been reported in PBLs following occupational exposure to ≥0.3 mg/m^3 (Lin et al., 2013; Costa et al., 2008; Aydın et al., 2013), (see Appendix C.3).

Unlike DNA stand-breaks, clastogenicity (in particular, MN formation) has been evaluated in human URT tissues. Acute, controlled exposures in healthy human volunteers yielded equivocal results; furthermore, MN incidences fell dramatically in both tissues during 21 days of postexposure monitoring (Zeller et al., 2011; Speit et al., 2007). Binucleation only, a proposed early event in MN formation, was elevated in buccal tissues from workers repeatedly exposed to low formaldehyde levels (mean location-specific concentrations of 0.04–0.11 mg/m3; (Peteffi et al., 2015). Although MN incidence was not significantly elevated in rat URT tissues after 28 days of exposure to ≤18 mg/m^3 (see Table 3-42) (Speit et al., 2011; Neuss et al., 2010), the majority of human studies have reported significant MN induction in the buccal epithelium after 5–35 years of occupational exposures to higher concentrations, averaging ≥0.2 mg/m^3 (see Table 3-42) (Viegas et al., 2010; Ladeira et al., 2011; Ladeira et al., 2013; Costa et al., 2019; Burgaz et al., 2001; Burgaz et al., 2002; Aglan and Mansour, 2018), and in the nasal epithelium of adults after an average of 7–11 years at ≥0.1 mg/m^3 (Ye et al., 2005; Costa et al., 2008; Ballarin et al., 1992). Results in students from shorter- duration classroom exposures (60–90 days) to 0.5–2 mg/m^3 have been lower in magnitude and less consistently positive, showing a stronger association between cumulative exposure and buccal versus nasal MN incidence and a stronger association with centromere-negative MN incidence, consistent with MN formation following DNA strand breakage (Ying et al., 1997; Titenko-Holland et al., 1996; Suruda et al., 1993). This hypothesized mechanism is consistent with the gene expression profile of human B-lymphoblastoid cells (Tk6) directly exposed to cytotoxic concentrations of formaldehyde in vitro, with transcript changes more akin to DNA-alkylating clastogenic agents than aneugenic spindle poisons (Kuehner et al., 2013). In buccal epithelium from human students or factory workers, MN incidence was positively correlated with exposure duration ($p < 0.01$) following exposure to 0.06–0.6 mg/m^3 for ≥1 year (Viegas et al., 2010), and positively correlated with cumulative exposure in male ($p = 0.01$) or male + female ($p = 0.06$) student populations exposed to 0.5–2 mg/m^3 for 90 days (Titenko-Holland et al., 1996; Suruda et al., 1993). Compared with the evaluations of URT tissues, cytogenetic endpoints have been more frequently evaluated in PBLs from occupational exposure cohorts (for further discussion, see Section 3.3.3 *Evidence on Mode of Action,* and Appendix C.3). Most of the studies conducted over the past 20 years have reported increased PBL MN incidence in formaldehyde-exposed humans, including the majority of studies reporting formaldehyde-associated increases in buccal or nasal MN incidence (Kirsch-Volders et al., 2014). Together with the above, the existing evidence consistently supports the association of MN induction in nasal and buccal tissue from human cohorts occupationally exposed to formaldehyde, in a manner temporally, biologically, and dose-responsively concordant with observations of

nasopharyngeal and sinonasal carcinogenesis across a range of exposure scenarios and concentrations.

Similar MN induction in epithelial cells of the URT has also been associated with increased human cancer risk in other populations (Ramirez and Saldanha, 2002; Lippman et al., 1990). Independent of formaldehyde exposure, a strong correlation between POE (buccal) and systemic (PBL) MN incidence has also been reported in samples collected from >6,500 healthy human subjects across 10 countries (r = 0.86; (Kirsch-Volders et al., 2014; Ceppi et al., 2010), suggesting that increases in PBL genotoxicity are relevant to human URT cancer risk, although the magnitude of MN induction in buccal cells is typically less than in PBLs (Holland et al., 2008). Elevated PBL MN and nuclear bud incidence, such as that observed in cohorts of formaldehyde-exposed workers, are predictive for lung cancer risk in smokers (Fenech et al., 2011; El-Zein et al., 2006) and are associated with increased cancer incidence in otherwise healthy individuals (Kirsch-Volders et al., 2014; Holland et al., 2008; El-Zein et al., 2006; Bonassi et al., 2008); see Section 3.3.3 *Evidence on Mode of Action*). Parallel increases in buccal and PBL MN incidence have also been observed in human workers chronically exposed to wood dust, another URT carcinogen (Rekhadevi et al., 2009). Similarly, in radon-exposed miners, a 1% increase in the frequency of aberrant PBLs was associated with a 60% increase in lung cancer risk (Smerhovsky et al., 2001; Smerhovsky et al., 2002). Together, this evidence supports associations between local and peripheral clastogenicity and between tissue clastogenicity and human respiratory carcinogenesis.

The mutation profile of formaldehyde-induced rodent tumors has not been well characterized, and it is unclear which of the various genotoxic endpoints elicited by formaldehyde exposure may lead to permissive mutations in either rodent or human URT carcinogenesis. *P53* mutations were specifically evaluated in SCCs isolated from the nasal passages of F344 rats following 2 years of exposure to 18 mg/m^3 formaldehyde (Wolf et al., 1995a; Recio et al., 1992), and in hyperplastic nasal tissues following 90 days of exposure to similar concentrations (Meng et al., 2010). While not detected in hyperplastic epithelium, the *p53* mutations at codon 271 detected in five of the 11 rat URT SCCs have also been described in human URT cancers (Wolf et al., 1995a; Recio et al., 1992; Hollstein et al., 1991; Audrezet et al., 1993). At 18 mg/m^3, nasal squamous metaplasia preceding or concomitant with hyperplasia is significantly elevated early after first exposure (within 7 days; see Section 3.2.4), prior to the emergence of dysplasia at 365 days, in the nasal regions of F344 rats, which eventually harbor SCC after 330−548 days (Monticello et al., 1996; Kerns et al., 1983; Kamata et al., 1997). The absence of *p53* mutations in reactive nasal mucosa after 90 days of exposure is consistent with *p53* mutations acting as a selective or permissive factor acquired during the latter stages of formaldehyde-initiated carcinogenesis, facilitating increased genetic instability and the progression of nascent neoplasms to SCCs, which emerge months later (Hanahan and Weinberg, 2000, 2011). Perhaps consistent with this potential temporal relationship, a recent study of short-term (i.e., 8-week) exposure to high levels of formaldehyde in two strains of *p53* deficient mice failed to observe any treatment-related increases in nasal tumors at 32 weeks

post-exposure, despite pronounced metaplasia (Morgan et al., 2017). Additional study using longer-term exposures, ideally in rat models (as mice are demonstrably less sensitive), would help clarify the role of *p53* in URT carcinogenesis.

The proportion of human URT SCCs exhibiting *p53* mutations is similar to that reported in formaldehyde-elicited rat URT SCC (~45%), and codons orthologous to those with mutations in rat nasal SCC are also mutated in human URT SCC (Catalogue of Somatic Mutations in Cancer [COSMIC] build v73; filters: upper aerodigestive tract, all subtissues, carcinoma, squamous cell; accessed 10 July, 2015; http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/). However, this has not been examined specifically in formaldehyde-exposed humans. The observation that formaldehyde-induced rat URT carcinomas share similar *p53* mutations with cancers in analogous human tissues suggests that rat and human URT tissues may be subjected to similar initiating or selective biological processes, which further supports the relevance of rodent URT tumors in informing human cancer risk.

Summary

Genotoxicity in the respiratory or transitional epithelium temporally and dose-responsively precedes and anatomically coincides with sites of significant SCC and PA induction (see above synthesis of the animal evidence) in rats following chronic formaldehyde exposure as a function of increasing concentration (NTP, 2010; Liteplo and Meek, 2003). In both rats and nonhuman primates, nasal DPX and exogenous formaldehyde N_2-hmdG adducts were elevated in an exposure concentration- or duration-related manner after 1–28 days of experimental exposure to formaldehyde concentrations ≥ 0.9 mg/m^3 within the range of average occupational exposures associated with increased DPXs in human PBLs (0.5–4 mg/m^3) after various durations of exposure (see Appendix C.3) and increased MNs in human nasal (0.1–1 mg/m^3) or buccal tissue (0.2–0.5 mg/m^3) after ≥5 years (Appendix C.3). Human mortality risks from nasopharyngeal cancer were also elevated with both increasing exposure concentration and duration, with elevated risks evident at concentrations ≥1.23 mg/m^3 and after ~20 years following first exposure (see above synthesis of the human evidence). The coherence of strong and consistent evidence for genotoxicity spans multiple evidence types from exposed humans to relevant model systems and species, in analogous POE and surrogate tissues, incorporating pertinent aspects of dose-response and temporality (i.e., preceding other mechanistic events), all of which strongly supports a role for direct DNA damage leading to mutagenicity in formaldehyde-induced URT carcinogenesis.

Cellular proliferation

Studies employing labeled nucleotides or analogs have reported increased epithelial cell proliferation in the nasal and extranasal passageways of rhesus monkeys after 7 or 42 days of exposure to 7 mg/m^3, concurrent with increased tissue hyperplasia and metaplasia in the nasal epithelium, nasopharynx, and larynx (see Section 3.2.4 and Appendix C.7.1). Acute exposure (1–9 days) to similar concentrations also stimulated epithelial proliferation in the anterior nasal

passages of F344, Wistar, and Sprague Dawley rats, while only exposures to ≥15 mg/m^3 increased proliferation in similar tissue from B6C3F$_1$ mice. This difference in exposure concentrations required to induce proliferation in nasal epithelium across rodent species may result from the increased reflex bradypnea observed in mice compared to similarly exposed rats. Respiratory minute volumes of mice acutely exposed to 15–18 mg/m^3 decrease such that they are roughly equivalent to a 7 mg/m^3 exposure in rats (see Appendix C.2) (Swenberg et al., 2013). This difference in rodent physiology between mice and rats is also consistent with the reported SCC incidence of 1–2% following chronic exposure to 18 and 7 mg/m^3, respectively (see above synthesis of the animal evidence), and with the apparent resistance of mice to formaldehyde-elicited cytotoxic nasal pathology (see Section 3.2.4).

In general, the exposure level marking increased proliferation was inconsistent across studies (see Appendix C.7.4 and the quantitative "Characterization of uncertainty and variability in cell replication rates" in Appendix D.2.2); in some cases, as discussed under "Biological plausibility of alternate assumptions" in Appendix D.2.2, the cell proliferation data appear to be more representative of a monotonic increasing dose response without a threshold. In Wistar rats, proliferation was increased in the anterior nasal passages after 28 or 90 days of exposure with an LEC of 4 mg/m^3, a concentration not frequently evaluated in other species (see specific evaluations of proliferation in Appendix A.5.6) (Zwart et al., 1988; Wilmer et al., 1987, 1989). In F344 rats, cellular proliferation was induced to a similar extent after 90 days at ≥12 mg/m^3 (Monticello et al., 1996; Andersen et al., 2010) or 7 mg/m^3 in some studies (Casanova et al., 1994). A lesser magnitude of proliferation was also apparent following exposure to ≥3 mg/m^3 (Monticello et al., 1996; Meng et al., 2010; Andersen et al., 2010). In both strains, some evidence supports that increases in proliferation may occur at 0.8–2.5 mg/m^3 (Zwart et al., 1988; Meng et al., 2010; Casanova et al., 1994; Andersen et al., 2010). While proliferation in the anterior nasal passages may appear to be stimulated to a greater extent at slightly lower exposure levels in Wistar versus F344 rats (due in part to choice of exposure concentrations evaluated), the strain sensitivity to nasal SCC induction was reversed: nasal tumors were present in only 4% of Wistar rats after 28 months of exposure to 12 mg/m^3, while 22% of F344 rats developed tumors after 24 months of exposure to the same concentration ((Woutersen et al., 1989; Monticello et al., 1996). This pattern also appears in PA incidence, where PAs were reported in ~1% (1 rat) of Wistar rats exposed to 11 mg/m^3 for ≤28 months (with lifetime observations), versus 6% of F344 rats exposed to 12 mg/m^3 for 24 months (Woutersen et al., 1989; Monticello et al., 1996; Feron et al., 1988). Unlike the differences seen with Wistar rats, incidence of both nasal SCCs and PAs appear to be generally similar between Sprague Dawley and F344 rats exposed to 18 mg/m^3 for 24–28 months, although the limited evidence in Sprague Dawley rats precludes a comparison of URT proliferation with F344 rats following repeat exposure (see above synthesis of the animal evidence). While limited, the available data suggest that some strain differences exist in the URT tumor response in Wistar versus F344 rats, while proliferation appears to be similarly induced in both rat strains.

Integrating across all available studies, the magnitude of proliferation induced in F344 rats was generally similar following exposure durations of 4–90 days (see Appendix C.7.1). In the single study available reporting URT epithelial proliferation in rats following chronic as well as subchronic exposures, the proliferation response declined between 45 and 90 days, most strikingly at 7 mg/m^3, and then decreased gradually throughout 548 days of continuous exposure (Monticello et al., 1996). An inverse association between nasal epithelium DNA synthesis and exposure duration was reported between 7 and 42 days of exposure in rhesus monkeys (Monticello et al., 1989), suggesting that a proliferative peak may have been reached fairly rapidly in primates (≤7 days).

Investigations into the relative mitogenic versus cytotoxic consequences of formaldehyde exposure in vitro have revealed that while significant cytolethality was observed at >1 mM in cultured human colon carcinoma (HT-29), T lymphocyte (Jurkat E6-1) and umbilical vein endothelial cells (HUVEC) (Tyihák et al., 2001; Saito et al., 2005), lower and more physiologically relevant dose levels (0.1 mM) induced proliferation in both HT-29 and HUVEC cells, and to a greater extent in the neoplastic HT-29 cells compared with the nonneoplastic HUVEC (Tyihák et al., 2001). However, ≥0.1 mM induced endoplasmic reticulum (ER) stress and increased the ratio of proapoptotic to antiapoptotic markers in both human lung carcinoma (A549; (Lim et al., 2013) and lymphoblast cell lines, with greater sensitivity observed in DNA repair deficient cells (Ren et al., 2013) (see Appendix C.3 and C.7). Increased sensitivity to formaldehyde-induced cell death has been consistently reported in eukaryotic cell lines deficient in excision, DNA crosslink, or chromosomal breakage repair (Rosado et al., 2011; Ridpath et al., 2007; Ren et al., 2013; Noda et al., 2011; Mchale et al., 2014; de Graaf et al., 2009), suggesting that unresolved genotoxicity could contribute to some of the cytotoxicity observed with increasing levels of formaldehyde exposure. Formaldehyde-stimulated cell cycle progression may be highly context dependent and only observed in circumstances where the concomitant genotoxicity and low-level toxicity (e.g., ER stress) are adequately controlled. This variable proliferation response in vitro is consistent with some in vivo observations of increased epithelial proliferation in the nasal passages of F344 rats following subchronic exposure at subcytotoxic exposure levels (~0.8–3 mg/m^3; see Section 3.2.4 and specific proliferation analyses in Appendix C.7.1 and Appendix D.2.2). However, nasal epithelial proliferation in the absence of cytotoxic nasal pathology was not consistently observed, and cell-density adjusted cellular proliferation indices correlate well with tumor formation following chronic exposures to ≥7 mg/m^3, concentrations that induced significant epithelial pathology in rodent nasal passages (see Section 3.2.4).

Summary

Nasal epithelial cell proliferation was positively associated with the induction of squamous metaplasia and necrosis or epithelial erosion in F344 rats (Andersen et al., 2010) and correlated with SCC incidence as a function of both anatomical location and exposure concentration following exposures ≤19 mg/m^3 for up to 548 days (Swenberg et al., 2013; Monticello et al., 1996). The

association between chemical carcinogenicity and epithelial cell proliferation has been described for several respiratory tract carcinogens and rodent models of human cancers (Monticello et al., 1993). Such a relationship can accelerate the acquisition of traits consistent with a current understanding of the carcinogenic process (Sonnenschein and Soto, 2013; Hanahan and Weinberg, 2011; Goodson et al., 2015), as exemplified in the well-described etiology of mutagen-induced rat mammary gland tumorigenesis (Russo et al., 1990). The available data suggest that formaldehyde may elicit some mitogenicity at low-to-moderate exposures through an unknown cellular mechanism independent from the regenerative tissue proliferation associated with cytotoxicity following exposure to higher concentrations (see Figures 3-24–3-26). However, the evidence supporting proliferation as an effect independent from cytotoxic tissue pathology is not strong or consistent as the evidence supporting regenerative proliferation in response to cell death; furthermore, while the database contains several reports evaluating cellular proliferation at a molecular level (i.e., DNA nucleotide analog incorporation), it suffers from a dearth of molecular evaluations on other cellular functions, such as markers of toxicity, cell cycle regulation, or death, which prevents a more precise delineation of mitogenic effects at a cellular level from compensatory proliferation at a tissue level.

URT cytotoxicity, pathology

In humans, nasal airway function may be impaired at average exposures as low as 0.01 mg/m^3, suggesting that pathological URT changes occur even at low exposures (see Table 3-42) (Norback et al., 2000), while increasingly severe nasal histopathology (including hyperplasia, keratinization, and metaplasia) is associated with average chronic exposures ≥0.3 mg/m^3 (see Table 3-42) (Odkvist et al., 1985; Holmstrom et al., 1989c; Edling et al., 1988; Boysen et al., 1990; Ballarin et al., 1992). The incidence of distinct dysplasia, a dedicated preneoplastic lesion, was elevated in study participants with higher average chronic exposure, ranging from 0.1 to 3 mg/m^3 (see Section 3.2.4). Human nasal and throat irritation and cytotoxicity was positively associated with exposure concentrations ≥0.2 mg/m^3 in controlled acute exposure trials or after a single 8-hour work shift (see Table 3-42) (Priha et al., 2004; Kulle et al., 1987) and average exposure to 0.05–1 mg/m^3 in occupational cohort studies (Horvath et al., 1988; Holness and Nethercott, 1989). Consistent with these observations, fluctuation in ciliary beat frequency was also reported in primary human nasal cells exposed to 0.5–3 mg/m^3 following differentiation into a functional ciliated epithelium and cultured on an air-liquid interface (ALI) in vitro (Wang et al., 2014b). However, unlike the positive association between human MN induction and exposure duration, or the clear relationship between rat squamous metaplasia induction and formaldehyde exposure duration (see Section 1.2.4), no significant associations were reported between exposure duration and various indications of human nasal mucosal pathology (see Table 3-42).

Similar to observations following chronic human exposure, the incidence of squamous metaplasia and hyperplasia in the nasal turbinates of cynomolgus monkeys was also positively associated with exposure concentrations ≥1 mg/m^3 (Rusch et al., 1983). Although lesion severity in

rhesus monkeys was positively associated with extending exposure duration from 7 to 42 days at 7 mg/m^3 (Monticello et al., 1989), this observation is not necessarily discordant with the human data set, which generally evaluated pathology resulting from chronic durations as a function of differences in years of exposure versus days, as was evaluated in the nonhuman primates. Nonhuman primates may be more resistant to nasal irritation and cytotoxicity than humans, as squamous metaplasia and hyperplasia were observed following 42 days exposure to 7 mg/m^3 in rhesus monkeys (Monticello et al., 1989), or 180 days of exposure to 4 mg/m^3 to cynomolgus monkeys, with 1 of 6 monkeys affected at 1 mg/m^3 (vs. 0/12 in controls), and no effects observed at 0.2 mg/m^3 (Rusch et al., 1983), although no studies have evaluated exposure durations directly analogous to chronic human exposure.

In F344 rats, nasal mucociliary function and flow rate decreased in an exposure concentration- and duration-associated manner following acute exposures to ≥3 mg/m^3 (Morgan et al., 1986a; Morgan et al., 1986c). Incidence or severity of squamous metaplasia also increased in both a duration- and concentration-dependent manner following exposures ≥3 mg/m^3 (Kerns et al., 1983); all effects were inversely associated with increasing distance from the apical POE (Casanova et al., 1994). Nasal pathology in Wistar rats was positively associated with exposure concentration, but not cumulative exposure, following subchronic exposures (Wilmer et al., 1987, 1989). This result is consistent with similar relationships reported between DNA synthesis rates and exposure concentration in the same anatomical regions (i.e., Level II) in both Wistar and F344 rats (see Table 3-42) (Zwart et al., 1988; Wilmer et al., 1987, 1989; Swenberg et al., 1986). Generally, formaldehyde exposure elicited similar pathology and ultrastructural changes in the analogous nasal passages of both nonhuman primates and rats (see Section 3.2.4). F344 rats appear to be similarly sensitive to the onset of nasal cytotoxicity induced by chronically inhaled formaldehyde compared with nonhuman primates, since a similar duration of exposure (180–365 days) induced nasal squamous metaplasia or hyperplasia in both species at ≥3 mg/m^3, while higher concentrations of ≥7–12 mg/m^3 were generally required to induce similar pathology following shorter durations (30–90 days; see Table 3-42). However, nasal damage in nonhuman primates (rhesus monkeys) became more developed, covered the URT epithelium to a greater extent, progressed to posterior nasal regions, and involved the larynx/trachea in less time (1.5 months) and at lower exposure levels (Monticello et al., 1989) than similar changes observed in rats (Kerns et al., 1983). Likewise, nasal squamous metaplasia in cynomolgus monkeys was detected in all animals exposed to 4 mg/m^3 after 6 months (Rusch et al., 1983), while a comparable prevalence of analogous pathology in F344 rats required exposure to 18 mg/m^3 and ≥18 months to develop (see Section 3.2.4).

Other rodent species appear to be less sensitive to formaldehyde-induced nasal dysplasia, SCC and PA (in order of decreasing sensitivity): F334 and Sprague Dawley rats > Wistar rats > B6C3F1 mice > hamsters (see synthesis of animal evidence in this section). Necrosis, inflammation, hyperplasia, or squamous metaplasia were observed in the anterior nasal passages of F344 rats,

Wistar rats, and B6C3F_1 mice after short-term high-concentration exposures, as well as in the posterior nasal cavity of F344 rats after 6 months, and in the larynx/trachea after 18 months of exposure to 18 mg/m^3, although tumors of the larynx or trachea have not been associated with formaldehyde exposure in rodents (see Section 3.2.4). Conditions that induced nasal dysplasia in rats and mice consistently resulted in SCC formation after an additional 6–12 months of exposure, whereas neither dysplasia nor SCCs were observed in hamsters. While formaldehyde-associated benign PAs and malignant SCCs may share similar tissue level origins (i.e., the transitional or respiratory but not olfactory epithelium), this reflects a neoplastic fate arising from morphologically different epithelial populations and does not imply that PAs are precursor lesions to SCC. In the rodent nasal cavity, SCCs are thought to arise directly from hyperplastic or dysplastic tissue (i.e., atypical squamous metaplasia) and do not necessarily progress through a benign tumor intermediate (McConnell et al., 1986).

Summary

Progressive tissue cytotoxicity and induction of proliferative pathological lesions in the URT respiratory or transitional epithelium temporally and dose-responsively precede and anatomically coincide with sites of significant SCC and PA induction (see Section 3.2.4) in rats following chronic formaldehyde exposure as a function of increasing concentration (NTP, 2010; Liteplo and Meek, 2003). Similar lesions were also observed in the URT of nonhuman primates exposed up to 180 days, which appeared to progress farther along the primate respiratory tract. In humans, some indications of URT cellular toxicity have been reported at very low concentrations, with hyperplasia, keratinization, and metaplasia observed following chronic exposures ≥0.3 mg/m^3, which are concentrations approximately 10-fold lower than those eliciting similar effects in experimental animal models. Together, strong and consistent evidence exists associating URT epithelial pathology-driven tissue proliferation with SCC induction in rodent experimental models. Along with limited information from both nonhuman primates and occupationally exposed humans, these observations support a significant role for regenerative tissue proliferation in URT carcinogenesis associated with formaldehyde exposures high enough to induce cytotoxic URT pathology. However, the evidence from animal studies indicates uncertainty regarding the exposure concentration at which this proliferation occurs (see Figure 5-6).

Summary of evidence supporting the primary mechanistic considerations:

In F344 rats chronically exposed to formaldehyde, there is a clear temporal, dose-responsive, and biological relationship in the appearance of exposure-related genotoxicity, sustained epithelial damage, cellular proliferation, and eventual SCC or PA development, consistent with similar relationships evident in analogous URT tissues from both the nonhuman primate and human databases. Furthermore, the chronic formaldehyde exposure concentrations reported to elicit nasal cytotoxic pathology appear to be higher in the rats and nonhuman primates evaluated experimentally (≥3 mg/m^3), compared with the results from human epidemiological cohorts

(≥0.3 mg/m^3; see Table 3-42), whereas formaldehyde-associated genotoxicity has been induced in analogous POE tissues from rats, nonhuman primates, and humans exposed to similar formaldehyde concentrations (see Table 3-42). Together, genotoxicity, cellular proliferation, and cytotoxicity-induced tissue regenerative proliferation exhibit multiple layers of coherence as a function of species and anatomy, temporality, concentration, and duration of exposure. When integrated, this evidence forms a biologically relevant MOA for formaldehyde exposure-induced URT carcinogenesis (U.S. EPA, 2005a).

Other factors modifying the mode of action

Oxidative stress, immune disease, and dysfunction

Increased rhinitis, nasal irritation, URT inflammation, and some indications of increased oxidative stress were observed in human cohorts after environmental or occupational exposures at the lower end of the range of average formaldehyde exposures associated with nasal hyperplasia and metaplasia. Rhinitis has been observed following subchronic or longer exposure in F344 rats and B6C3F1 mice, as well as chronically exposed human workers, and some observations suggest that oxidative stress may in part evolve as an effect secondary to the activation of inflammatory leukocytes in the human respiratory tract (see Section 3.2.3 and Appendix C.7). The prevalence of allergic conditions and asthma symptoms are increased in both children and adults exposed to formaldehyde, suggesting that immune dysfunction occurs to some extent in respiratory tract tissues following formaldehyde exposure (see Section 3.2.3). These observations may imply a decreased functional activity of immune effector cells. Whether these effects are due to immunosuppression, inappropriate polarization, or exposure-related cytotoxicity, such immune dysfunction could promote a chronic inflammatory environment and permit cancer progression (Mantovani et al., 2008; Jia et al., 2014; Coussens et al., 2013a, b; Balkwill et al., 2012).

In experimental rodent studies, depletion of nonprotein sulfhydryls (NP-SH, primarily GSH) increased DPX formation in the nasal mucosa of F344 rats following formaldehyde exposure to >1 mg/m^3 (Casanova and Heck, 1987), while GSH coadministration attenuated increases in DPX formation in systemic tissues from formalin-exposed BALB/c mice [Ye et al. (2013a); see also Appendix C.3 and C.7]. Although alterations in cellular GSH content may affect DPX formation and the mutagenic potential of formaldehyde exposure, it is unclear whether formaldehyde exposure itself will reduce URT glutathione levels in rodents. For example, even though glutathione reductase activity was decreased in the rat URT following short-term exposure to ≥4 mg/m^3, total non-NP-SH content actually increased (Cassee et al., 1996). A few other rodent studies have reported increased oxidative stress from the lower respiratory tract (LRT) following short-term exposures; however, data on oxidative stress endpoints from evaluation of URT tissues is limited, and it remains unclear whether LRT responses indicate analogous responses in URT passages (see Appendix C.7). In vitro, cellular GSH concentration was inversely correlated with formaldehyde cytotoxicity in human oral fibroblast cells and rat hepatocytes (Nilsson et al., 1998; Ku and Billings, 1984). In conditions where

GSH was sufficiently decreased, formaldehyde inhibited mitochondrial respiration and led to increased lipid peroxidation and ROS production (IARC 88; (Teng et al., 2001), which could trigger NF-κB activation (Zhang et al., 2013a) and thus initiate an inflammatory signaling cascade. While formaldehyde may directly deplete cellular GSH pools to some extent, the resulting impact on cellular cytotoxicity can be amplified by other sources of oxidative stress (Saito et al., 2005). Taken together, formaldehyde exposure may exacerbate oxidative stress primarily resulting from inflammation, cytotoxicity, or sulfhydryl depletion, which could further augment DPX-mediated genotoxicity as well as increasing ROS-mediated genetic instability and cell death. This could result in an amplification of both direct and indirect mutagenicity in the nasal epithelium.

Tumor immunosurveillance may play an important role specifically in limiting human nasopharyngeal carcinoma development; for example, patients with acquired immune deficiency syndrome (AIDS) are at significantly higher risk of developing both nonkeratinizing (commonly associated with Epstein-Barr virus [EBV] infection) as well as keratinizing nasopharyngeal carcinoma (Shebl et al., 2010). In vitro, formaldehyde attenuates the perforin secretion and cell lytic activity of cultured mouse and human natural killer (NK) cells at subcytotoxic concentrations (Li et al., 2013b; Kim et al., 2013a), which would limit NK-mediated destruction of infected epithelial cells and prolong URT infection, possibly inhibiting any tumor-suppressive function of these cytotoxic lymphocytes. Consistent with this theory, 2 weeks of formaldehyde exposure attenuated both NK cell numbers and activity in the lungs of both naïve and tumor-bearing mice. This attenuation was associated with enhanced malignancy, growth, and neutrophil involvement of lung metastases formed by injected syngeneic melanoma cells (Kim et al., 2013a). Additional evidence for other formaldehyde-induced immune dysfunction comes from allergic sensitization studies and reports of exacerbated immune-mediated airway hyperresponsiveness presensitized rodents (see Section 1.2.3). Further, evidence exists to suggest the possibility that formaldehyde exposure may alter immune cell phenotypes, maturation, and survival at a systemic level (see relevant mechanistic discussions in Sections 3.2.3 and 3.3.3); however, few studies have examined such evidence specifically within respiratory tissues, and those testing endpoints that might otherwise be most informative to this possibility (Zhao et al., 2020a) had methodological limitations that prevent clear interpretation. Together, however, the available data suggest that formaldehyde exposure may induce immune suppression or dysfunction in both experimental animals and humans, which could reduce the effectiveness of local immunosurveillance in suppressing tumor progression and metastasis, thus enabling URT carcinogenesis (Hanahan and Weinberg, 2000, 2011).

In summary, nasal infection and allergic symptoms are exacerbated in humans following exposure to fairly low formaldehyde levels, concomitant with or preceding epithelial tissue distress, inflammation, and preneoplastic lesion formation. Chronic inflammation is highly relevant to and positively associated with human risk of respiratory tract cancers; however, the specific

mechanistic relationships between formaldehyde-induced inflammation, immune dysfunction, infection, allergy, oxidative damage, and URT cancer remain unclear.

DNA repair inhibition

The primary effects of formaldehyde interactions with DNA are N^2-hmdG adducts, DPXs and DDCs, and strand breaks, and repair of such formaldehyde-mediated genotoxicity appears to be crucial to cell survival. Consistent with this hypothesis, DNA repair genes are rapidly induced in rat nasal mucosa following acute or subchronic exposure in vivo (Rager et al., 2014; Hester et al., 2005; Andersen et al., 2008) and human B-lymphoblastoid cells in vitro (Kuehner et al., 2013).

The primary mechanism for repair of N^2-hmdG adducts is unclear. While nucleotide or base excision repair (NER/BER) may be responsible, the removal of small DNA adducts species may also result from nonspecific cellular processes (Lindahl, 1993; Brooks and Zakhari, 2014). The existence of two phases in the elimination of formaldehyde N^2-hmdG adducts from the rat nasal mucosa in vivo also supports a role for multiple removal mechanisms (Swenberg et al., 2013). DPXs are unlikely candidates for direct removal via excision repair in mammalian cells, although a fraction of smaller crosslink products (likely DDCs) may be removed via NER activity or proteolysis (see Appendix C.3 and C.7 for detailed discussions). DPXs are more likely repaired via activity of the BRCA/Fanconi anemia family (FANC) proteins, components of the homologous recombination repair pathway, which regulate DPX repair following chronic or lower formaldehyde concentrations in mammalian cells and can attenuate the formation of DSBs and some chromosomal abnormalities (see Appendix C.3) (Rosado et al., 2011; Ren et al., 2013; Nakano et al., 2009). If unresolved, DPXs could lead to SSBs, DSBs, various cytogenetic abnormalities, and genomic instability (Ridpath et al., 2007; Ren et al., 2013; Noda et al., 2011; Nakano et al., 2009; Langevin et al., 2011; Kumari et al., 2015; Kirsch-Volders et al., 2014; Brooks and Zakhari, 2014). Additionally, DNA repair pathways are differentially engaged as a function of damage location in relation to DNA replication machinery, supporting a role for the context of DNA damage in determining the manner of its resolution (de Graaf et al., 2009).

In cultured human fibroblasts, exogenous formaldehyde directly interfered with DNA-binding damage sensor complex recruitment to DNA adducts and inhibited the repair of DNA lesions induced by either ultraviolet light or cisplatin adduction (Luch et al., 2014), consistent with similar observations in other human tissues and cells (see Appendix C.3 for a detailed discussion). This interaction also inhibited the migration and function of BER, and consequently inhibited the repair of oxidative DNA lesions. These results suggest that formaldehyde may inhibit excision repair by directly interfering with the DNA damage detection apparatus, which could delay the recognition and repair of DNA damage induced by both formaldehyde as well as other agents. However, any direct impact on the BRCA/FANC-mediated DNA repair pathway, which is likely to be responsible for removing formaldehyde-induced DPXs following chronic exposure, remains to be elucidated.

Members of the X-ray repair cross-complementing gene (XRCC) family serve as scaffolding proteins for the repair of single- and double-strand DNA breaks, including those caused by oxidative or UV-induced DNA damage (Kirsch-Volders et al., 2014). Despite several correlations between XRCC polymorphisms and increased sensitivity to formaldehyde-induced genotoxicity in human tissues and cells, the role for XRCC family proteins in regulating formaldehyde mutagenicity remains unclear (see Appendix C.3 for a detailed discussion). The molecular mechanisms by which formaldehyde causes MN are also unknown, but incomplete repair of DNA-protein or DNA-DNA crosslinks, and the consequent stress from stalled replication forks, could result in DNA strand breaks and possibly centromere-negative MN formation (Nakano et al., 2009; Kirsch-Volders et al., 2014; Brooks and Zakhari, 2014). Taken together, the available data suggest that formaldehyde exposure may inhibit the detection and repair of lesions resulting directly from formaldehyde-DNA interactions, as well as genotoxicity resulting from other sources, and may thereby accelerate tissue carcinogenesis by exacerbating both direct and indirect mutagenesis. However, the available data are insufficient to determine any independent contribution of such interference in DNA repair to URT carcinogenesis.

Epigenetics and toxicogenomics

Changes in message RNA (mRNA) transcript levels from pathways relevant to URT carcinogenesis (e.g., cell cycle, proliferation signaling, apoptosis, and DNA repair) have been reported in URT tissues following formaldehyde exposure, possibly mediated by microRNA (miRNA) regulation, changes in DNA/histone modifying marks including methylation, acetylation and formylation, or by responses to cellular toxicity and tissue distress (see Appendix C.7 for a detailed discussion). After repeated exposure, mRNA levels for genes involved in growth signaling pathways increased in a concentration- or duration-related manner in F344 rats (Rager et al., 2014; Andersen et al., 2010), and some of these pathway perturbations were also reported in nonhuman primates (Rager et al., 2013).

In nasal tissues from acutely exposed nonhuman primates, significant induction of miR-125b and suppression of miR-29a were observed (Swenberg et al., 2013; Rager et al., 2013). Expressions of several candidate mRNA targets of miR-125b were also decreased in this study, consistent with miR-125b induction, including two that were also reported to be affected in subchronically exposed rats (Andersen et al., 2010) (see Appendix C.7). In analogous rat nasal tissues, expression of several members from the growth-suppressing miRNA family let-7 decreased following subchronic exposure (Rager et al., 2014), consistent with observations from exposed A549 lung carcinoma cells (Rager et al., 2011). Decreased expression of let-7 family members was found in nasopharyngeal carcinomas compared with healthy tissue (Li et al., 2011), and this effect has been reported to promote proliferative and oncogenic cellular signaling pathways in respiratory tract cancers (Jakopovic et al., 2013). Despite the numerous significant changes in miRNA expression levels reported following formaldehyde exposure, miR-203 was the only target reported to be similarly affected (decreased) in analogous nasal tissue from both rats and

nonhuman primates (Rager et al., 2013; Rager et al., 2014) (see Appendix C.7). Overall, changes in expression of these miRNAs are generally consistent with observations in human lung, prostate, breast, and bone marrow cancers (Ma and Weinberg, 2008; Garzon et al., 2009; Fabbri et al., 2007). The abundance of highly significant changes in specific targets within individual arrays or experiments, but limited concordance across expression array data sets or species, is not unusual; however, it greatly complicates interpretation and integration of various data streams (Weinberg, 2014).

DNA methylation and histone modification can promote carcinogenesis through steric regulation of enhancer/promoter binding and transcription factor-DNA association, thereby affecting gene transcription (Vaissière et al., 2008). DNA methylation was globally decreased in human bronchial epithelial cells exposed to formaldehyde in vitro for up to 24 weeks, which may have been mediated by the down-regulation of de novo methyltransferase genes (Liu et al., 2011b). Formaldehyde may affect gene transcription via posttranslational modification (PTM) of histone proteins, in part by directly adducting unmodified lysine residues in histones to form N^6-formyllysine, thus preventing acetylation of this residue (Lu et al., 2008; Edrissi et al., 2013a). Such irreversible adduction could interfere with transcriptional activation, nucleosome organization (Wisniewski et al., 2008), and DNA lesion repair activity (Luch et al., 2014). Levels of these formylated lysine adducts increase in a concentration-dependent manner in the URT of rats exposed to ≥0.9 mg/m^3 (Edrissi et al., 2013b), levels at which increased DPXs are also observed (see Table 3-39, and Appendix C.3). In addition, exogenous formaldehyde can induce histone phosphorylation through activation of MAP kinase signaling in vitro (Yoshida and Ibuki, 2014). In A549 cells, as histone serine phosphorylation increased, lysine acetylation levels correspondingly decreased, providing an additional (indirect) mechanism by which exogenous formaldehyde attenuates histone acetylation and potentially modulates gene transcription. c-Jun N-terminal protein kinase (JNK) was the primary regulator of this histone phosphorylation, which led to elevated nuclear c-Fos and c-Jun protein expression (Yoshida and Ibuki, 2014; Shi et al., 2014). Together, c-Fos and c-Jun comprise the transcription factor AP-1, which can play an early role in human respiratory tract carcinogenesis (Karamouzis et al., 2007). Likewise, increased histone phosphorylation may be an important mechanism specifically in human nasopharyngeal carcinogenesis (Li et al., 2013a), suggesting that these epigenetic effects may play a causal role in human URT cancer formation.

The existing evidence illustrates myriad time- and concentration-dependent effects following formaldehyde exposure, indicating the potential for both direct and indirect impacts on transcriptional activity, in addition to inhibiting protein translation via miRNA dysregulation. What is lacking, however, are conceptual paradigms and computational strategies for integrating systems and cancer biology data streams (Weinberg, 2014). While provocative, in the absence of direct hypothesis evaluation and more explicit phenotypic anchoring, the causal contribution of

epigenetic effects to URT carcinogenesis cannot be evaluated independently from the primary mechanistic considerations outlined above.

Mode of action evidence integration and summary of analysis

Prolonged inflammation or irritation to the nasal mucosal surface has been associated with squamous metaplasia of the respiratory or transitional epithelium following exposure to infectious agents such as fungi or bacteria, but such exposures did not result in neoplasia (Monticello et al., 1990b; Brown et al., 1991). Likewise, chemical URT irritants such as dimethylamine, glutaraldehyde, ethylacrylate, hydrogen chloride, and chlorine gas cause rhinitis, inflammation, and cytotoxicity leading to squamous metaplasia or hyperplasia, but do not induce rat nasal tumors following chronic exposure (Wolf et al., 1995b; Sellakumar et al., 1985; NRC, 2014b; Mcgregor et al., 2006; Buckley et al., 1985; Albert et al., 1982). However, a number of genotoxic chemicals that also induce pathological changes in the rat nasal epithelium similar to formaldehyde (e.g., acetaldehyde, acrolein, 4-[N-methyl-N-nitrosamino]-1-[3-pyridyl]-1-butanone [NNK] and 1,2-epoxybutane) also induce nasal tumors including SCCs and PA-like lesions (Woutersen et al., 1986; U.S. EPA, 2003; NTP, 1988, 2011; Monticello et al., 1990b; Monticello et al., 1993). The comparison between formaldehyde and glutaraldehyde is particularly informative, as similar rat nasal cytotoxic pathology (e.g., squamous metaplasia, hyperplasia, inflammation) is elicited by exposure to both aldehydes (Hester et al., 2005), and yet glutaraldehyde exposure does not induce rat nasal tumors even after 24 months of exposure, while such tumors are induced following ≥12 months of formaldehyde exposure (Mcgregor et al., 2006). It has been proposed that glutaraldehyde exposure causes more epithelial cell death in the nasal mucosa compared with formaldehyde, possibly resulting in part from the greater inability of cells to repair or otherwise resolve any glutaraldehyde-DNA adducts (Mcgregor et al., 2006; Hester et al., 2005). The observation that a more effectively cytotoxic but less effectively mutagenic agent, glutaraldehyde, induces similar cytotoxicity-induced regenerative URT pathology to formaldehyde, yet appears unable to elicit rat URT tumors, suggests that cytotoxicity-induced regenerative proliferation alone is insufficient to induce URT carcinogenesis resulting from formaldehyde exposure.

The underlying balance between formaldehyde-associated cytotoxicity and genotoxicity may not only be responsible for the induction of these rare URT tumors in rats, but may also be key to the difference in phenotype between formaldehyde-induced nasal squamous metaplasia and that normally encountered in the aging rat. Gamma-glutamyl transpeptidase activity, present in normal and metaplastic epithelium in unexposed animals, is absent in the frequently atypical squamous metaplasia associated with formaldehyde exposure (Dinsdale et al., 1993; Brown et al., 1991). Such atypical squamous metaplasia (i.e., dysplasia) has been noted as a possible precursor to SCC in the rat URT (Monticello et al., 1990b). Together with the above, several lines of evidence converge to support the conclusion that while inflammation, squamous metaplasia, or hyperplasia alone are clearly not sufficient to induce nasal cancer in rats (Monticello et al., 1993), the amplified cellular proliferation occurring in regenerating tissues may be a mechanism by which genotoxicity-induced

DNA mutation rates are augmented, facilitating neoplastic transformation. The marked increase in formaldehyde-initiated clones observed in vitro following growth stimulation by 12-O-tetradecanoylphorbol-13-acetate (TPA) in two-stage transformation studies (Ragan and Boreiko, 1981; Boreiko and Ragan, 1983) is also consistent with this conceptual model.

Strong and consistent evidence for formaldehyde-induced direct genotoxicity and mutagenicity comes from studies in mammalian cell lines, controlled inhalation studies in rodents and nonhuman primates, and occupationally exposed humans, wherein mutagenicity anatomically coincides with and temporally precedes URT tumorigenesis. Strong and consistent evidence associates URT tissue pathology of increasing severity and regenerative proliferation with squamous cell carcinoma (SCC) formation in experimental rodent studies at moderate-to-high exposure levels, consistent with some measurements of cytotoxicity reported in analogous nasal or buccal tissues from formaldehyde-exposed humans (see Table 3-43). Experimental evidence also links polypoid adenoma (PA) formation to formaldehyde exposure in several rat strains that also develop SCCs, and limited evidence associates increased PA incidence across a range of exposure concentrations in F344 rats. Limited evidence from a subset of experimental rodent studies also supports nasal epithelial cell proliferation in the absence of significant epithelial tissue pathology following acute, discontinuous, or moderate concentration exposure scenarios; however, while even intermittent proliferative stimuli could promote the growth of both nascent and malignant clones, the specific role for formaldehyde-induced cellular proliferation as an effect independent from either concomitant genotoxicity or tissue pathology remains undetermined. Evidence supporting the URT cancer MOA depends not only on temporality, duration, and concentration of exposure, but also anatomical location within the URT (i.e., incidence or severity of all primary mechanistic considerations decreases following an anterior-to-posterior gradient within the URT). While significant evidence supports some association between formaldehyde exposure and immune disease or dysfunction, including chronic inflammation and increased oxidative stress, the existing database is not sufficient to evaluate the independent contribution of these effects to URT carcinogenesis. Likewise, while formaldehyde appears to inhibit various cellular DNA repair pathways, the independent contribution of this effect to URT carcinogenesis remains to be determined.

Based on this detailed analysis conducted according to EPA's cancer MOA framework (U.S. EPA, 2005a), there is sufficient evidence to conclude that formaldehyde induces URT carcinogenicity via at least two primary mechanistic considerations: genotoxicity-associated mutagenicity and cytotoxicity-induced regenerative proliferation. By means of its fundamentally mutagenic activity, formaldehyde damages DNA and increases the mutational burden of the URT mucosa when this damage is not adequately repaired, while mucosal cytotoxicity creates a tissue microenvironment driving continuous proliferation, facilitating the accumulation of mutations arising from both direct and indirect genotoxicity, thereby increasing the rate at which initiated clones are formed as well as stimulating the expansion of existing neoplastic colonies (see

Table 3-43). The involvement of both mutagenicity and cytotoxicity-induced proliferation in the URT cancer MOA is strongly supported and internally consistent with the available formaldehyde evidence, and is also externally consistent with the described activities of other reported URT toxins and carcinogens.

Table 3-42. Summary considerations for upper respiratory tract (URT) carcinogenesis

Hypothesized mechanistic event	Experimental support for mechanistic event	Human relevance	Weight-of-evidence conclusion and biological plausibility
Direct genotoxicity and mutagenicity (see Table 3-39 and Appendix C.3)	• ↑ MN incidence in URT mucosa from human students and workers following subchronic-to-chronic exposure • ↑ DPX and/or hmdG adducts in URT tissues of rhesus or cynomolgus monkeys, following acute exposure • ↑ DPX or hmdG adducts and accumulation in URT tissues of F344 rats following acute to subchronic exposure • No effect on MN incidence URT tissues of F344 rats follow subchronic exposure	Yes. Markers of direct genotoxicity correspond anatomically and temporally with subsequent URT neoplasia in experimental animal models, are consistent with increased MN induction following exposure in humans, and are presumed relevant to human carcinogenesis.	Strong and consistent evidence for formaldehyde-induced direct genotoxicity and mutagenicity exists from both experimental animal models and human molecular epidemiology to support a significant role for mutagenicity in URT carcinogenesis.
Cytotoxicity-induced regenerative proliferation (see Tables 3-40 and 3-41)	• ↓ Nasal mucociliary function, ↑ nasal hyperplasia, keratinization and/or squamous metaplasia, URT rhinitis, irritation, and inflammation in humans following acute to chronic exposure • ↓ Nasal cilia content, ↑ hyperplasia and squamous metaplasia in URT tissues from monkeys following acute to subchronic exposure • Associated with ↑ URT cell proliferation in rhesus monkeys • ↓ Nasal mucociliary function, ↑ nasal rhinitis, hyperplasia and squamous metaplasia and/or dysplasia in various rat	Yes. Increasing incidence or severity of URT dysfunction or pathology is positively associated with formaldehyde exposure in humans, nonhuman primates, and rats. A continuum of similar epithelial pathology is observed across affected species at POE tissues, and therefore the resulting increased cellular turnover observed in experimental models is presumed relevant to human carcinogenesis.	Strong and consistent evidence exists which associates the nasal epithelial pathology-driven proliferation with SCC abundance following formaldehyde exposure in rodent experimental models to support a significant role for regenerative proliferation in URT carcinogenesis.

Hypothesized mechanistic event	Experimental support for mechanistic event	Human relevance	Weight-of-evidence conclusion and biological plausibility
	strains and B6C3F1 mice following acute to chronic exposure • Associated with ↑ URT cell proliferation rats and mice		
Cellular mitogenesis in the absence of cytotoxic tissue pathology (see Table 3-41)	• Clear evidence of ↑ URT cell proliferation under conditions also resulting in tissue pathology in rhesus monkeys • Exposure to subcytotoxic concentrations not evaluated • Clear evidence of ↑ URT cell proliferation under conditions also resulting in tissue pathology in Wistar and F344 rats (≥4 mg/m^3) • Suggestive evidence of ↑ URT cell proliferation under conditions not clearly causing tissue pathology (<4 mg/m^3; *see Appendix C.7)*	Yes. Cellular proliferation may be increased at lower exposures and/or following shorter durations of exposure than that eliciting tissue pathology, which suggests that mitogenesis may be directly stimulated by formaldehyde exposure. Proliferation is expected to accelerate and enhance carcinogenesis in both humans and model systems, and is therefore presumed relevant to human carcinogenesis.	Limited and inconsistent evidence associates cellular proliferation with formaldehyde exposures below those eliciting cytotoxic pathology in the rat nasal epithelium, which precludes a determination as to the importance of this phenomenon in URT carcinogenesis.
Oxidative stress, immune disease and dysfunction in the URT (see Appendix C.7)	• ↑ LRT infection frequency, inflammation, allergic outcomes in children; ↑ leukocyte activation, allergy symptoms, chronic URT inflammation and ↓ infection resistance in adult workers following subchronic-chronic exposure • ↑ LRT oxidative stress, markers of inflammation and leukocyte recruitment in rats and mice; ↑ airway wall thickening or remodeling in mice and rats following OVA sensitization • ↑ Malignancy and neutrophil involvement of lung metastases, ↓ lung NK cell numbers and activity in C57BL/6 mice	Yes. Nasal infection, markers of persistent inflammation and/or immune dysfunction are positively associated with a range of formaldehyde exposure in both humans and rodents. Oxidative stress and chronic inflammatory diseases, including immunosuppression, are presumed relevant to human carcinogenesis. The relevance of other immune system dysfunctions to human carcinogenesis, such as allergy, is less clear.	While significant evidence exists supporting oxidative stress, chronic inflammation and various immune dysfunctions following formaldehyde exposure in humans and experimental animal models *(see Appendix A.5.6)*, the evidence supporting associations between these effects and URT carcinogenesis is insufficient to evaluate the contribution of these effects independently in either humans or experimental animal models.

Summary of Inferences Regarding Mode of Action

Support for the hypothesized mode of action in experimental animal models

Strong, consistent evidence from rodent and nonhuman primate models supports the role for both direct (i.e., potentially DPX or hmDNA adduct-associated) mutagenicity, as well as indirect genotoxicity, mutagenicity, and regenerative proliferation resulting from respiratory tissue pathology, in rodent URT carcinogenesis. DNA labeling studies in rodent nasal epithelium suggest that cell division may also accelerate in response to marginally cytotoxic tissue concentrations resulting from short-term, lower level, or discontinuous exposure scenarios, although this evidence was neither strong nor consistent across similar studies and model systems. Observations of mutagenicity, cytotoxic epithelial pathology, and proliferation correspond histologically, anatomically, temporally, and dose-responsively with subsequent SCC and PA formation, consistent with contribution of both mutagenesis and regenerative proliferation to rodent URT carcinogenesis following formaldehyde exposure.

Relevance and applicability of the hypothesized mode of action to human cancer

Mutagenicity is presumed to be a relevant component of URT carcinogenesis in humans, supported by strong evidence of direct genotoxicity in both rodent and nonhuman primate experimental models and consistent observations of direct genotoxicity and mutagenicity from human epidemiological studies. Increased nasal epithelial cell proliferation (in rats and nonhuman primates) coincides anatomically with dysplastic lesions found in tissues from similar species, as well as with progressive, proliferative lesions in the nasal/buccal epithelium and nasopharynx of chronically exposed humans. This cross-species concordance, combined with the observation that cellular proliferation may be induced at lower exposures or following shorter durations of exposure than those eliciting tissue metaplasia, suggests that cellular proliferation in the presence of marginal tissue toxicity may also be potentially relevant to human URT carcinogenesis, as this episodic exposure scenario may be more frequently encountered in human populations than the continuous, chronic high-level exposures traditionally employed in rodent cancer bioassays. Increasing incidence or severity of nasal dysfunction and progressive pathology is associated with escalating formaldehyde exposure concentration or duration in humans, nonhuman primates, and rats. While POE tissue sensitivity to formaldehyde toxicity may quantitatively differ in humans versus rats and other rodents, qualitatively similar nasal dysfunction and pathology consistent with preneoplastic stages of cancer progression are observed across analogous tissues from all affected species, and therefore conclusions derived from these model systems are presumed relevant to human URT carcinogenesis. Given this presumed relevance, the potential for an increased susceptibility of specific human populations to developing URT cancers can be informed by both the human data and relevant mechanistic evidence from experimental model systems.

In general, URT findings in animals are found to be relevant to the URT cancer types and locations observed in humans despite significant differences in the occurrence of the individual

cancer types. Firstly, site concordance is not required (U.S. EPA, 2005a). Secondly, the lack of a clear site-specific correspondence may be attributed to large interspecies differences in anatomy and airflow which in turn dictates formaldehyde distribution.

Regarding human NPC, the observed formaldehyde exposure-induced nasal tumors and mechanistic changes in animals are considered directly applicable to interpreting changes in the human nasopharynx. The nasopharynx is part of the nasal cavity and a recognized target of inhaled nasal toxicants across species (Chamanza and Wright, 2015).

Similarly, the URT MOA is considered relevant and applicable to the interpretation of human SNC, although some uncertainties remain. Across species, the sinuses are positioned close to the nasal cavity and encounter inspired air (Reznik, 1990). Analyses of sinonasal cancer cases indicate that most sinonasal cancers are squamous cell carcinomas (the primary tumor type in animals) and the upper nasal cavity is generally the primary site of tumor occurrence, in more than 40% of cases (the maxillary sinus is the next most common site), although it is often difficult to pinpoint the exact anatomical location from which the cancers developed (Turner and Reh, 2012; Llorente et al., 2014; Dutta et al., 2015). While these similarities support the relevance of the animal data to human SNC, it is necessary to consider the anatomy of the rodent and human URT given the importance of the distribution of inhaled formaldehyde and, as compared to the nasopharynx and other parts of the nasal cavity, a reduced flow of inspired air reaches sinonasal regions and the sinuses specifically (via narrow channels from the nasal cavity) (Xiong et al., 2008; Kumar et al., 2016). Although tumors in the sinonasal regions of exposed rodents or monkeys were not observed, this may be partially explained by differences in anatomy. Specifically, while humans have four paranasal sinuses, rodents and monkeys only have one, and the sinus in rodents is much smaller, thus presenting a smaller target for potential cancer development and a reduced capacity for detection as compared to in humans. Additional uncertainties in drawing interpretations across species include differences in airflow and tissue/cellular composition, which cannot be easily evaluated. Taken together, while there is some uncertainty in the applicability of the MOA to SNC, the mechanistic evidence (as well as the evidence on nasal cancers in animals) is interpreted as applicable to and supportive of human SNC.

The hypopharynx and oropharynx, and to a greater extent the larynx, are more distal from the POE than the nasopharynx and sinonasal tissues. Oronasal breathing in humans, as compared to nasal-only breathing in rodents, may suggest a greater relevance of tissue sites close to the oral cavity for human exposure; thus, mechanistic changes in rostral parts of the URT (i.e., the nasal cavity) in animals may be more relevant to human oropharyngeal cancer. In general, however, based on the known reactivity and distribution of inhaled formaldehyde, a greater level of uncertainty in the applicability of the animal nasal findings is inferred for these human cancer types, most notably laryngeal cancer, as compared to NPC or SNC.

Utility of mechanistic data for informing hazard quantification decisions

Since strong and consistent evidence supports the contribution of both direct genotoxicity and mutagenicity as well as cytotoxicity-induced regenerative proliferation as primary mechanistic considerations relevant to the pathogenesis of formaldehyde-associated URT cancer in rodents, mechanistic data relevant to these endpoints may be useful for informing quantification of nasal cancers in experimental animals following chronic formaldehyde exposure. In particular, quantitative evaluation of these mechanisms may inform a biological response basis for guiding dose-response extrapolations of rodent SCCs, as described in Section 5.2.1.

Evidence Integration Summary

Table 3-43 summarizes the evidence integration judgments and supporting rationale for the individual URT cancers.

Epidemiological findings provide *robust* evidence for nasopharyngeal cancers (NPCs), based on groups with occupational exposure. Consistent increases in NPC risk were reported by numerous *high* and *medium* confidence studies involving occupational exposure to formaldehyde among diverse populations in different geographic locations and exposure settings that accounted for expected temporal relationships for cancer induction and progression, with several reporting a large magnitude of relative risk (RR ≥3). A dose-response gradient was reported for various measures of exposure, including cumulative exposure, duration of exposure, and peak exposure. *Robust* evidence for nasal cancers is provided from studies in experimental animals (rats and mice). In animals, the incidence of lesions, as well as the tumor invasiveness and latency, was reproducibly shown to worsen with increasing formaldehyde exposure level. The distribution of tumors was dependent on duration of exposure as well as formaldehyde concentration. Mechanistic changes associated with the development of cancer in the nasal cavity were consistently observed in humans and experimental systems, including genotoxicity, epithelial damage and proliferation, and eventual cancer development in relevant URT tissues. The mechanistic changes and URT lesions exhibited a temporal and dose-response relationship coherent with carcinogenesis and supportive of a mutagenic MOA (see *Evidence on MOA for upper respiratory tract cancers)*. The observed formaldehyde exposure-induced nasal tumors and mechanistic changes in animals are considered directly relevant to changes in the human nasopharynx (the nasopharynx is part of the nasal cavity and a recognized target of inhaled nasal toxicants). Thus, based on *robust* human evidence, *robust* animal evidence, and mechanistic evidence supporting a mutagenic MOA for NPC, the **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer in humans. This conclusion is primarily based on studies of groups exposed to occupational formaldehyde levels and coherent findings in animals, with tumors in rodents generally only observed at formaldehyde concentrations above 6 mg/m^3.

Epidemiological findings also provide *robust* evidence for sinonasal cancer (SNC), based on groups with occupational exposure. The *robust* judgment for SNC is supported by a smaller set of

epidemiological studies than for NPC, although a large, pooled analysis of 12 case-control studies included a large number of cases and greater detail on formaldehyde exposures, which increased confidence. This study observed an increasing trend in risk for adenocarcinoma with higher cumulative exposure among men and women in analyses that controlled for key confounders including exposure to wood dust. The studies were conducted in different geographic locations and exposure settings that accounted for expected temporal relationships for cancer induction and progression. Rodent nasal cancers and related mechanistic changes in the nasal cavity are considered relevant to human SNC (see discussion in *Evidence on MOA for upper respiratory tract cancers*), although some uncertainty in their applicability to SNC, as compared to NPC remains, and thus judgments of both *robust* and *moderate* animal evidence were considered. Ultimately, given this uncertainty in applicability, while the animal and mechanistic evidence cited for NPC is judged as informative and supportive for interpreting SNC, including providing sufficient support for a mutagenic MOA for this cancer type, the animal evidence overall is interpreted as *moderate* rather than *robust*. Based on *robust* human evidence, *moderate* animal evidence, and mechanistic evidence supporting a mutagenic MOA for SNC, the **evidence demonstrates** that formaldehyde inhalation causes sinonasal cancer in humans. This conclusion is primarily based on studies of groups exposed to occupational formaldehyde levels.

For oropharyngeal/hypopharyngeal cancers, the human evidence is *slight*, based on data from highly exposed workers, and s*light* animal evidence is provided from relevant observations of preneoplastic lesions and mechanistic changes. Taken together, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause oropharyngeal/hypopharyngeal cancers.

The human and animal evidence is *indeterminate* for laryngeal cancers and, overall, the **evidence** is **inadequate** to determine whether formaldehyde inhalation may cause this cancer.

Table 3-43. Evidence integration summary for effects of formaldehyde inhalation on URT cancers

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Nasopharyngeal cancer (NPC)					
Human	*Consistency and Study Confidence*	• Consistent increases in risk across numerous *high*, *medium,* and *low* confidence studies		*Robust* Based on large, consistent, and dose-dependent increases in risk across numerous *high* and *medium* confidence studies in different populations, with strong mechanistic support.	The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer in humans. Primarily based on studies of groups of workers exposed to occupational formaldehyde levels, coherent findings in animals (with tumors in rodents generally only at formaldehyde levels above 6 mg/m^3), and a well-supported MOA for nasal tumor development *Potential Susceptibilities*: There is very little evidence to evaluate the potential risk to sensitive populations and/or lifestages. However, several animal studies
	Strength and Precision	• Very strong associations (eight studies reported at least a threefold increase in risk for some exposure categories, three of the eight were of *high* or *medium* confidence, direction of potential bias toward the null)			
	Dose-Response	• Evidence of exposure-response relationships across multiple measures of increased exposure			
	Coherence	• A temporal relationship consistent with causality (i.e., allowing for cancer induction, latency, and mortality)			
	Biological Plausibility	• Although not as strong as the animal database of mechanistic studies, mechanistic evidence from human studies indicates a clear biological relationship with genotoxicity, epithelial damage and proliferation, and eventual cancer development in relevant URT tissues.			

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Animal	*Consistency and Study Confidence*	• Tumors of the respiratory tract (predominantly nasal squamous cell carcinomas, SCCs, but including other epithelial and nonepithelial tumors) were consistently observed in mice and in several strains of rats in numerous *high* and *medium* confidence studies. • The development of these lesions, particularly the SCCs, depended on the duration of observation and, based on an increasing incidence and severity of lesions in animals exposed for longer periods of time, the formaldehyde exposure duration. • Studies of subchronic formaldehyde exposure without follow-up consistently failed to observe dysplasia or neoplasms. Studies with a long observation period were not identified to inform the possibility of cancer development in nonhuman primates exposed to formaldehyde. Given the long development time for these cancers, these findings did not decrease certainty.	• A single *medium* confidence study in hamsters did not observe tumors.	*Robust* Based on consistent, dose-dependent, and biologically plausible findings of nasal tumors, primarily SCCs, in mice and rats in numerous high and medium confidence studies, in general after at least 12 months of exposure at formaldehyde levels above 6 mg/m^3. These lesions were not observed in other regions, such as the larynx and lung.	suggest that prior damage to the nasal epithelium might increase the development of cancer in these damaged regions.
	Strength and Precision	N/A			
	Dose-Response	• The lesion incidence, as well as the tumor invasiveness and latency, was reproducibly shown to worsen with increasing formaldehyde exposure level. • The lesions increased in severity and progressed to more posterior locations with			

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
		increasing duration and concentration of formaldehyde exposure.			
	Coherence	• Precancerous dysplastic lesions were induced in rats and mice, sometimes at lower formaldehyde concentrations.			
	Biological Plausibility	• Mechanistic changes consistent with cancer development in nasal tissues were observed across species, including rats, mice, and monkeys. In F344 rats chronically exposed to formaldehyde, a clear temporal, dose-responsive, and biological relationship was observed in the appearance of genotoxicity, sustained epithelial damage, cellular proliferation, and eventual tumor development.			
Other inferences	• *Relevance to humans*: The types of findings were consistent and coherent across species (including humans). Although site concordance is not essential (U.S. EPA, 2005a), considering the anatomy of the rodent and human URT and the importance of the distribution of inhaled formaldehyde, the observed formaldehyde exposure-induced nasal tumors and mechanistic changes in animals are considered directly relevant to changes in the human nasopharynx. • *MOA*: Together, genotoxicity, cellular proliferation, and cytotoxicity-induced regenerative proliferation exhibit multiple layers of coherence as a function of species, anatomy, temporality, concentration, and duration of exposure, and when integrated, form a biologically relevant MOA for formaldehyde-induced URT carcinogenesis (U.S. EPA, 2005a). While the chronic formaldehyde exposure concentrations reported to elicit nasal cytotoxic pathology appear to be higher in the rats and nonhuman primates evaluated experimentally (≥4 mg/m^3), compared with the results from human epidemiological cohorts (≥0.3 mg/m^3), formaldehyde-associated genotoxicity has been induced in analogous POE tissues from rats, nonhuman primates and humans exposed similarly (≤0.9 mg/m^3).			
Sinonasal cancer (SNC)					
Human	*Consistency and Study Confidence*	• Consistent increases in risk across a set of four *medium* confidence studies, with		*Robust*	The **evidence demonstrates** that

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
		consistent findings in 4 *low* confidence studies. • Increased risk of lower magnitude reported by two other medium confidence studies. • Null results in 3 insensitive low confidence studies did not reduce certainty.		Based on large, consistent, and dose-dependent increases in risk across four medium confidence studies in different populations, with strong mechanistic support.	formaldehyde inhalation causes sinonasal cancer in humans Primarily based on studies of groups of workers exposed to occupational formaldehyde levels. Although less certain than the support provided for NPCs, animal and MOA evidence provide support for the human evidence. *Potential Susceptibilities*: There is very little evidence to evaluate the potential risk to sensitive populations and/or lifestages. However, several animal studies suggest that prior damage to the nasal epithelium might increase the development of cancer in these damaged regions.
	Strength and Precision	• 2 *medium* and *2 low* confidence studies reported at least a threefold increase in risk, primarily for adenocarcinoma, including the largest study, a pooled analysis of 12 case-control studies			
	Dose-Response	• Four studies above demonstrated a clear exposure-response relationship.			
	Coherence	*N/A*			
	Biological Plausibility	• The human mechanistic evidence cited for NPC is informative and supportive for interpreting the biological plausibility of SNC (see discussion in MOA analysis).			
Animal	*Consistency and Study Confidence*	• (Same evidence base as for NPC; see "Other inferences below, relevance of the animal evidence to human SNC" for justification) [Note: tumors were not reported in the maxillary sinus of exposed animals]		*Robust* [see description for animal evidence supporting NPC above]	
	Strength and Precision				
	Dose-Response				

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
	Coherence				
	Biological Plausibility	• (Same mechanistic evidence base as for NPC) • Although infrequently examined, studies that measured noncancer lesions in the maxillary sinus did not detect treatment-related respiratory tract pathology, although cell proliferation was observed (see Section 3.2.4). • Although also poorly studied, some mechanistic changes consistent with the MOA for nasal cancers, including increased DPX in the monkey maxillary sinus, have been observed.			
Other inferences	• *Relevance of the animal evidence to human SNC*: The types of findings were consistent and coherent across species (including humans). The strong animal and mechanistic evidence for nasal cancers across species is interpreted to provide *moderate* evidence supportive of sinonasal cancer (a judgment of *moderate* rather than *robust* reflects some uncertainty in interpreting the nasal cavity findings in animals as fully applicable to human sinonasal cancer specifically; see discussion in MOA analysis). • *MOA*: Similar to the inference above, although there is uncertainty in the application of the identified MOA to SNC, the evidence overall is interpreted to provide reasonable support for the mutagenic MOA as applicable to SNC.				
Oropharyngeal/ Hypopharyngeal cancer (OHPC)					
Human	*Consistency and Study Confidence*	• Increased risks in two of three *medium confidence* studies that evaluated multiple metrics of exposure.	• Little evidence of increases in risk (near the null) across one medium and two low confidence results	*Slight* Based on coherent and large increases in risk in two studies, with	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
	Strength and Precision	• Three- to five-fold increases in those highly exposed		some inconsistent findings in other studies.	oropharyngeal /hypopharyngeal cancer[a]
	Dose-Response	• A medium confidence study demonstrated clear exposure-response relationships across several exposure metrics			
	Coherence	*N/A*			
	Biological Plausibility	• Although cells from exposed humans in tissues closely apposed to the oropharynx and, more indirectly, the hypopharynx (e.g., buccal cells) demonstrate mechanistic changes consistent with the development of cancer, including genotoxicity, these data were not interpreted as sufficient to further strengthen the human evidence judgment beyond *slight*.			
Animal	*Consistency and Study Confidence*	• Some data suggest that changes in more caudal (e.g., in the trachea) regions, including evidence of dysplasia (a dedicated pre-neoplastic lesion) in one study, can occur with very high formaldehyde exposures and/or different breathing patterns (e.g., oronasal breathing in monkeys).	• The majority of findings in well-conducted animal studies were localized to the nasal cavity.	*Slight* Based primarily on supportive mechanistic changes and indirect cancer indicators (the latter only at very high formaldehyde levels) in regions of the respiratory tract most relevant to human OHC.	
	Strength and Precision		• Changes in the more caudal URT tissues most relevant to OHPC were generally less		

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
			direct indicators of cancer development, were less severe, or occurred only at very high exposure levels.		
	Dose-Response	*N/A*			
	Coherence	*N/A*			
	Biological Plausibility	• Mechanistic changes within caudal portions of the rodent and monkey URT have been observed, and oronasal breathing in humans (contrasting nasal-only breathing in rodents) infers an increased potential relevance of mechanistic changes in rostral (anterior) regions of the rodent to human OHPC. However, this was not interpreted as sufficient to further strengthen the evidence judgment beyond *slight*.			
Other inferences	• *Relevance of the animal evidence to human OHPC*: While cancer site concordance is not required for hazard determination (U.S. EPA, 2005a), given the known reactivity and distribution of inhaled formaldehyde, a lesser level of confidence in the applicability of the animal nasal findings is inferred for OHPC as compared to NPC or SNC. • *MOA*: While aspects of the MOA for nasal cancers, including NPC and SNC, may be operant for OHPC, the evidence overall is not interpreted to provide reasonable support for a MOA that is relevant to OHPC.				
Laryngeal cancer					
Human	*Consistency and Study Confidence*	• Suggestive associations reported in two *medium* confidence studies		*Indeterminate* Based on a lack of	There is **inadequate evidence** to determine whether formaldehyde

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
		Note: The moderate survival rate for laryngeal cancer may indicate that mortality data are not as good a proxy for incidence.		definitive observations of laryngeal cancer after formaldehyde exposure.	inhalation may be capable of causing laryngeal cancer in humans
	Strength and Precision	*N/A*			
	Dose-Response		• Inconsistent evidence on exposure-response relationships		
	Coherence	*N/A*			
	Biological Plausibility	Human mechanistic data specifically related to this cancer type are lacking.			
Animal	*Consistency and Study Confidence*		• No studies observed tumors in the rodent or monkey larynx, nor were preneoplastic lesions such as dysplasia detected.	*Indeterminate* While some mechanistic changes indicate potential tissue changes in the larynx and related regions in animals, there is an overwhelmingly consistent lack of tumors observed in such areas.	
	Strength and Precision	*N/A*			
	Dose-Response	*N/A*			
	Coherence	*N/A*			

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
	Biological Plausibility	• The evidence for mechanistic changes specifically within the larynx included findings in rodents and monkeys consistent with the MOA for nasal cancers, specifically noncancer lesions (e.g., tissue damage, hyperplasia, and squamous metaplasia) and genotoxicity (i.e., increased DPX). Although these mechanistic changes alone could support a judgment of *slight*, in the absence of experimental confirmation (or a biological understanding) that these mechanistic changes are likely to lead to cancer or preneoplastic lesions at sublethal formaldehyde concentrations, the animal evidence was judged as *indeterminate*.			
Other inferences	• *Relevance of the animal evidence to human laryngeal cancer*: The mechanistic changes observed in similar regions of the rodent and monkey URT are considered relevant to the interpretation of laryngeal cancer. • MOA: No potential MOA was identified for this cancer type.				

N/A = indicates the factor was not applicable to (i.e., did not influence) the judgment drawn.

[a]Given the uncertainty in this judgment and the available evidence, this assessment does not attempt to define a quantitative estimate for this cancer type (see Section 5.2).

3.3. EVIDENCE FOR NONRESPIRATORY EFFECTS

This section synthesizes research on nervous system effects (see Section 3.3.1), developmental and reproductive toxicity (see Section 3.3.2), and cancer effects beyond the respiratory tract (see Section 3.3.3), specifically in the lymphohematopoietic (LHP) system. Very little information has been reported concerning cancer associations at other nonrespiratory sites (e.g., brain; see Appendix B.3.9 for details). Evidence relevant to assessing carcinogenicity is synthesized for LHP cancer subtypes in Section 3.3.3 (i.e., myeloid leukemia, lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma; note: non-Hodgkin lymphoma was not systematically evaluated: see Appendix B.3.9).

3.3.1. Nervous System Effects

Numerous studies suggest that formaldehyde inhalation might result in noncancer nervous system effects; however, the evidence across studies is generally weak and the database is incomplete. Few studies in humans are available, but they reported that formaldehyde exposure was associated with neurobehavioral deficiencies as indicated by poorer performance in tests of short-term memory and psychomotor responses, and with the motor neuron disease, amyotrophic lateral sclerosis (ALS). Observations in rodents include altered performance in tests of locomotion and anxiety, and in learning and memory tests. In many of these animal neurobehavioral studies, a confounding factor was introduced when test animals were exposed to the known neurotoxicant, methanol, in formalin solutions. Experimental animal studies without methanol coexposure suggest that repeated formaldehyde exposure may lead to amplified behavioral responses to certain challenges (e.g., pharmacological), possibly through persistent modifications to neural pathways. Similarly, studies from one laboratory suggest that developmental exposure to formaldehyde at concentrations well above those causing adverse effects on the respiratory system (see Sections 3.2.1−3.2.4) results in long-lasting changes in brain structure. To date, none of these potential nervous system changes are supported by an experimentally verified mechanistic hypothesis outlining how formaldehyde might elicit neurotoxicity without systemic distribution. Overall, a definitive association between formaldehyde inhalation and neurotoxicity could not be concluded. Most of the available experiments had significant study design deficiencies and corroboration across the database was incomplete; thus, overall, the **evidence suggests**, but is not sufficient to infer, the potential for formaldehyde inhalation to cause nervous system effects in humans (i.e., based on *slight* evidence from human or animal health effect studies). Additional research is needed to draw a more certain evidence integration judgment.

Human Studies

The identified studies describing results of neurobehavioral tests, as well as the occurrence or mortality from neurological disease, are described in this section. These studies are summarized

in Tables 3-44 and 3-45. The tables are organized by study design (observational, acute controlled exposure), confidence in study results, and publication year. Three studies were considered not informative (Schenker et al., 1982; Kilburn, 2000; Broder et al., 1988c). The study evaluations are included in Appendix B.3.7.

While several observational epidemiology and controlled exposure studies report nervous system impairment in humans following exposure to formaldehyde, there are notable limitations in the available data and the results from some of the studies are potentially confounded by coexposures. Specifically, data from both observational and experimental studies showed an association between formaldehyde exposure and impaired performance in neurobehavioral tests of memory, dexterity, and psychomotor function (Lang et al., 2008; Kilburn et al., 1987; Kilburn et al., 1989b; Kilburn and Warshaw, 1992; Bach et al., 1990). In prospective studies from one research group, Weisskopf et al. (2009) and Roberts et al. (2015) both noted an association between formaldehyde exposure and death from the fatal motor neuron disease, ALS, in different study populations in the United States; a separate case-control study from another research group in Sweden also identified an association among individuals younger than 65 years of age, but not in the overall analysis using national registry data (Peters et al., 2017). A national registry-based case-control study in Denmark by the same research group in the United States also observed an association (Seals et al., 2017), but a subsequent analysis using the same cases examining joint effects by multiple health and chemical risk factors observed an inverse association in both men and women, although only the latter reached statistical significance (Bellavia et al., 2021). Two other studies failed to identify an association (Pinkerton et al., 2013; Fang et al., 2009). All of the studies were limited by uncertainty in individual exposure assignments, except for the study by Pinkerton et al. (2013), which evaluated a cohort of garment workers with known formaldehyde exposure and detailed information on employment history. The cohort studies were limited by a very low number of exposed cases.

Neurobehavioral tests

A series of epidemiology studies examined neurobehavior in histology technicians using standardized test batteries designed to assess higher brain functions (Kilburn et al., 1987; Kilburn et al., 1989b; Kilburn and Warshaw, 1992) (see Table 3–44). It is important to note that the majority of formaldehyde exposure in this occupation is from formalin (containing methanol), which introduced bias due to confounding of unknown magnitude and thus reduced the reliability of the results for interpreting the effects of formaldehyde exposure. All of these studies were ultimately considered to be of *low* confidence during study evaluation. Decreased performance in multiple tests of memory and tests of dexterity, balance, coordination, motor control, and reaction time was observed with increased daily hours of formaldehyde exposure (Kilburn et al., 1987; Kilburn et al., 1989b). Although these workers were also exposed to solvents that can affect behavior (e.g., xylene), hours of daily exposure to solvents was only correlated with decreased performance in a single memory test (Kilburn et al., 1987; Kilburn et al., 1989b). The effects of

formaldehyde exposure on neurobehavior were not verified when a comparable test battery was performed in a slightly larger (350 versus 305 technicians), but possibly overlapping, study (Kilburn and Warshaw, 1992). In addition, a smaller group (n = 19) tested yearly over a 4-year period did not experience worsening effects with continued work exposure, but this analysis did not specifically address formaldehyde exposure (Kilburn and Warshaw, 1992). These latter results suggest a lack of worsening effects with cumulative exposure, but they did not incorporate a consideration of the relative magnitude of exposure (e.g., hours of daily exposure to formaldehyde).

Three acute, controlled exposure studies evaluated performance in standardized neurobehavioral tests (see Table 3–44). Two of these studies included multiple tests assessing concentration, short-term memory, and motor control (Bach et al., 1990; Andersen and Molhave, 1983), while the third focused on decision reaction time (Lang et al., 2008). Although Bach et al. (1990) reported decreased performance in multiple neurobehavioral tests following controlled exposures at ≥0.480 mg/m^3, particularly in workers with previous chronic formaldehyde exposure, the exposure groups were not well matched for a number of variables relevant to test performance, most of the responses were not concentration dependent, and distractibility due to possible irritation cannot be ruled out (irritation measurements were subjective). In contrast to these results, Andersen and Molhave (1983) indicated that they found no effects of exposure on performance in cognitive tests, but the supporting data were not provided. Increased decision reaction times in response to visual, auditory, or combined visual/auditory stimuli were observed with exposure to 0.369 mg/m^3 formaldehyde by Lang et al. (2008); the motor component of the reaction times was unaffected by exposure. These increases were not observed at higher exposure levels and did not exhibit the same dose-response pattern as effects on irritation; thus, additional experiments are needed to better explain the findings.

Taken together, the epidemiological and human-controlled exposure studies provide mixed results suggesting that formaldehyde exposure might be associated with deficits in performance in neurobehavioral tests related to learning and memory and motor behavior. However, the reliability of these results is unclear and additional experiments are needed to clarify the potential contributions of variables that are known to affect these measures, but which were poorly controlled in these studies, including coexposures to neurotoxicants, irritation, and differences in population characteristics such as age or education.

Table 3-44. Summary of alterations in neurobehavioral tests in relation to formaldehyde exposure in observational epidemiology and controlled exposure studies

Reference and study design	Exposure measures	Results
Observational epidemiology studies		
Reference: Kilburn and Warshaw (1992) (United States) Prospective study; histology technicians attending histology conferences between 1982 and 1987; 19 histology technicians tested yearly across 4 years (46–50 years old); 299 technicians tested 2–3 times across 4 years (44–47.9 years old); 350 histology technicians tested once (38–40.4 years old); sex not reported. **Outcome:** 2–3 h neurobehavioral battery; testers blinded to exposure status. **Analysis:** Multiple regression, adjusting for age. Other variables considered were sex, years of employment, smoking, and nonoccupational exposures. **Evaluation:**[a] *Low* confidence Potential selection bias, limited detail presented in results. Longitudinal analysis limited by sample size and did not specifically address formaldehyde exposure.	Duration of formaldehyde exposure up to 37 years. Self-rated exposure scales. Source of formaldehyde is most likely formalin (containing methanol).	For single test analysis (n = 250), formaldehyde exposure was not associated with age-related change in performance in tests encompassing memory, cognition, pattern recognition, dexterity, decision-making, motor speed, or balance (beta and SE not provided; reported as not statistically significant). No decline seen in smaller group (n = 19) tested across 4 years.
Reference: Kilburn et al. (1987); Kilburn et al. (1989b) (United States) Survey, n = 305 female histology technicians attending histology conference in Boston (167 of 658 in 1982, 25.4% or Anaheim (218 of 704, 31%, in 1983. Age 23–78 years, mean 40 years. Work duration, mean 17 years. Seventy-nine female referent laboratory technicians in Los Angeles (participation rate not reported). **Outcome:** Neurobehavioral battery (10 tests) administered in 1 hour by trained personnel. **Analysis:** Multiple regression, formaldehyde (hours) controlling for age, education, smoking, home solvent	Self-reported estimated formaldehyde exposure (average 4.3 hr/d) and xylenes (average 112 cover-slipped slides). Most recent exposures were at least several days prior. Hour formaldehyde/day correlated with number of slides/day, $p < 0.05$. Source of formaldehyde is most likely formalin (containing methanol).	Statistically significant association ($p < 0.05$) between hr/d formaldehyde exposure: Recall memory (stories): One of two tests Visual memory (diagram): One of three tests Associative memory (digit span): One of two tests Dexterity (pegboard): One of one test Balance (sharpened Romberg): One of one test Perceptual motor speed (trail making): One of two tests Age associated with performance decrements in nine tests; solvent exposure (# of slides cover-slipped) associated with one test ($p < 0.05$)

Reference and study design	Exposure measures	Results
exposure and number of cover-slipped slides. **Evaluation:**[a] *Low* confidence Potential selection bias (could be influenced by perceived exposure and effects), limited detail presented in results.		No association with formaldehyde observed for choice reaction time, peripheral nerve function, or spatial relation tests.
Acute, controlled exposure studies		
Reference: Lang et al. (2008) (Germany) *N* = 21 (of 26 volunteers selected based on screening; five left study), 10 women, 11 men (results were combined), age 19–39 years, healthy nonsmokers. Exposure order randomly assigned; double blinded. Ten 4-hour exposures, one per day, over 10 days. **Outcome**: Reaction times (Vienna Test System) to visual and acoustic stimuli measured before and after exposures. **Evaluation**: *Medium* confidence Tested immediately after exposure.	Four hours in groups of four. Formaldehyde levels[a]: Clean air, 0.185, 0.369, and 0.615 mg/m^3; additional 0.369 and 0.615 mg/m^3 with peaks up to 1.23 mg/m^3. Additional 0.0, 0.369, and 0.615 mg/m^3 with ethyl acetate introduced as a "mask" for formaldehyde. (Analytical concentrations achieved were measured). Formaldehyde generated from paraformaldehyde, exposure under quasi-static conditions; ethyl acetate at 12–16 ppm (irritant threshold of EA reported at 20 ppm, identified from scientific literature).	↑ in decision reaction time upon visual stimulus at 0.3 and 0.3+ethyle acetate (data presented graphically, $p < 0.05$). ↑ in decision reaction time upon acoustic or audio-visual stimulus at 0.3 ppm only (data presented graphically, $p < 0.05$; comparison group for contrast not stated). The motor speed component of the decision reaction time was unaffected by exposure.
Reference: Andersen and Molhave (1983) (Denmark) *N* = 16 healthy students, age 30–33, 68.8% male, 31.2% smokers, groups of four over 4 days. Exposure order determined by Latin square design, blinding not indicated. **Outcome**: Numerical addition: tested 3×/d (once in clean air; twice during exposure); multiplication: tested 1×/d during exposure; card punching tested 2×/d (once in clean air; once during exposure). **Evaluation**: *Low* confidence Tested during exposure; results not reported.	Five hours; 0.3, 0.5, 1.0, and 2.0 mg/m^3 (analytical concentrations achieved were not reported: indicated as within 20% of target concentrations). Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber.	The study authors reported no change in performance in addition (speed and accuracy), multiplication, or transfer of numbers to punch cards, but data were not provided.
Reference: Bach et al. (1990) (Denmark) 32 with occupational exposure to formaldehyde (>5year); age 18−64 years; selected from 108 workers (recruitment and selection not described). Referent	Formaldehyde concentrations 0, 0.15, 0.4, and 1.2 mg/m^3 [analytical concentrations achieved: 0.04, 0.21, 0.48, and 1.10 mg/m^3].	Occupational group showed significantly ↓ performance on the digit symbol test ($p < 0.025$ for pooled exposure groups, 0, 0.15, and 0.4 compared to 1.2 mg/m^3); controls showed an inverse

Reference and study design	Exposure measures	Results
group (*n* = 29 from 546 selected randomly from a population registry); attempted frequency matching by average age, education, and smoking prevalence but workers had higher smoking prevalence and lower education (detailed demographic data not reported). Formaldehyde-exposed excluded from referent group. Exposure order by balanced Latin square design; double blinded—Furfuryl mercaptan (coffee aroma) used to mask odor. **Outcome:** Four performance tests twice during exposure. **Evaluation:** *Low* confidence Education and smoking imbalance in workers and referents; tested during acute exposure.	5.5 hr (0.5 hr pre-exposure in chamber and gradual increase in formaldehyde). Formaldehyde vapor generation not reported; however, assumed to be from depolymerization of paraformaldehyde based on protocols used in the same exposure chamber as reported by a coauthor (Andersen and Molhave, 1983).	relationship; digit span ($p < 0.025$) for total digit sum in one of the six test components—lowest scores in 0.4 mg/m^3 group, and graphic continuous line test ($p < 0.05$ only for the 0.4 mg/m^3 group); effects were not dose-related. Addition test: Dose-related performance decrements (↓ # of additions and ↑ reaction time). Data were presented graphically. Matching was not completely successful; due to last-minute substitutions, the exposed workers, particularly the 1.2 mg/m^3 group, had a lower education and different proportion of smokers; the 1.2 mg/m^3 group had a lower average age and fewer smokers overall. Exposure groups were not comparable.

Organized by study confidence, then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.
[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.7).
Results from *low* confidence studies are shaded; these findings are considered less reliable.
[b]Formaldehyde levels in the study converted to mg/m^3 from ppm (1 ppm = 1.23 mg/m^3).

Nervous system disease

In a large and well-designed, prospective study of risk factors associated with amyotrophic lateral sclerosis (ALS) mortality, years of self-reported exposure to formaldehyde was associated with a 2.5−fold (95% CI 1.58, 3.86) increased mortality risk when examined across individuals reporting duration data (this information was available for 22 of the 36 cases reporting formaldehyde exposure) (Weisskopf et al., 2009) (see Table 3−45). The overall risk was no longer significantly elevated when individuals who reported exposure but did not report duration were included in the analysis (all 36 cases; RR = 1.34; 95% CI 0.93,1.92). Risk increased with increasing duration of formaldehyde exposure, with a fourfold risk seen with >10 years of exposure (13 cases). In total, Weisskopf et al. (2009) followed 987,229 people and identified 1,156 ALS deaths (1,120 of these cases reported that they were not exposed to formaldehyde), but formaldehyde intensity was not assessed, and the duration of exposure was self-reported. A second study from the same research group also identified some evidence of an association between formaldehyde exposure and ALS death in a national study (Roberts et al., 2015). An odds ratio (OR) of 4.43 was observed among individuals with a high probability, high intensity exposure, based on only two cases of ALS; no cases were observed among individuals with high probability, medium intensity exposure. Formaldehyde exposure assignments were made by industrial hygienists using a job-exposure

matrix with estimates of intensity and probability of exposure for the most recent job held by participants, although duration was not assessed. More recently, two registry-based studies in Sweden and Denmark observed associations of similar magnitude between ALS diagnosis and occupational formaldehyde exposure analyzing all incident ALS cases occurring over a 20- to almost 30-year period. Both studies used a job-exposure matrix (JEM) developed for the Nordic Occupational Cancer Study (NOCCA) with exposure data specific to each country. The Swedish study observed no association in the entire analytic group of blue-collar workers and farmers, however an odds ratio of 1.28 (95% CI 1.02, 1.61) was observed when the analysis was restricted to persons younger than 65 years of age (Peters et al., 2017). In Denmark, occupational exposure to formaldehyde was associated with ALS incidence in the entire cohort using a nonspecific exposure definition (ever/never) (RR 1.3, 95% CI 1.2, 1.4) and associations of the same magnitude were observed across all exposure quartiles in comparison to nonexposed (Seals et al., 2017). Hence neither study observed an (exposure-response trend. Also, the potential effect of confounding by smoking on the formaldehyde—ALS association (Wang et al., 2011; Armon, 2009) was not addressed. Paradoxically, the direction of the association was reversed when investigators used a machine learning method to select joint predictors and interaction terms and then included these health and chemical risk factors for ALS in the model (Bellavia et al., 2021). An OR of similar magnitude but less precise than that reported by Peters et al. (2017) (OR = 1.3; 95% CI 0.5, 3.2) was observed for participants with a high probability of exposure in a small case-control study, although no association with exposure duration was observed (Fang et al., 2009). Although the longitudinal design of the prospective studies makes it unlikely that the association between formaldehyde exposure and ALS death is attributable to some types of bias, a study with detailed evaluations of formaldehyde exposure (probability, frequency) and duration of exposure in the exposed populations failed to confirm an association (Pinkerton et al., 2013). Exposure in the cohort of garment workers (Pinkerton et al., 2013), in particular, was more certain, based on monitoring data in the 1980s, year of hire, and years of employment. However, all of the studies, except Peters et al. (2017) and Seals et al. (2017) were limited by small numbers of exposed cases, which leads to decreased sensitivity to detect an association that might exist, or decreased stability in effect estimates (see Figure 3-27). Overall, evidence is emerging that formaldehyde exposure may pose a hazard for ALS, but there is a large degree of uncertainty due to the mixed nature of the findings. As risk factors for increased risk of ALS are complex and poorly defined, it remains possible that the findings of Weisskopf et al. (2009), and the less robust but supportive findings by Roberts et al. (2015), Peters et al. (2017) and Seals et al. (2017), identify a true risk of formaldehyde exposure. However, additional research designed to address the identified limitations would help to clarify these study results.

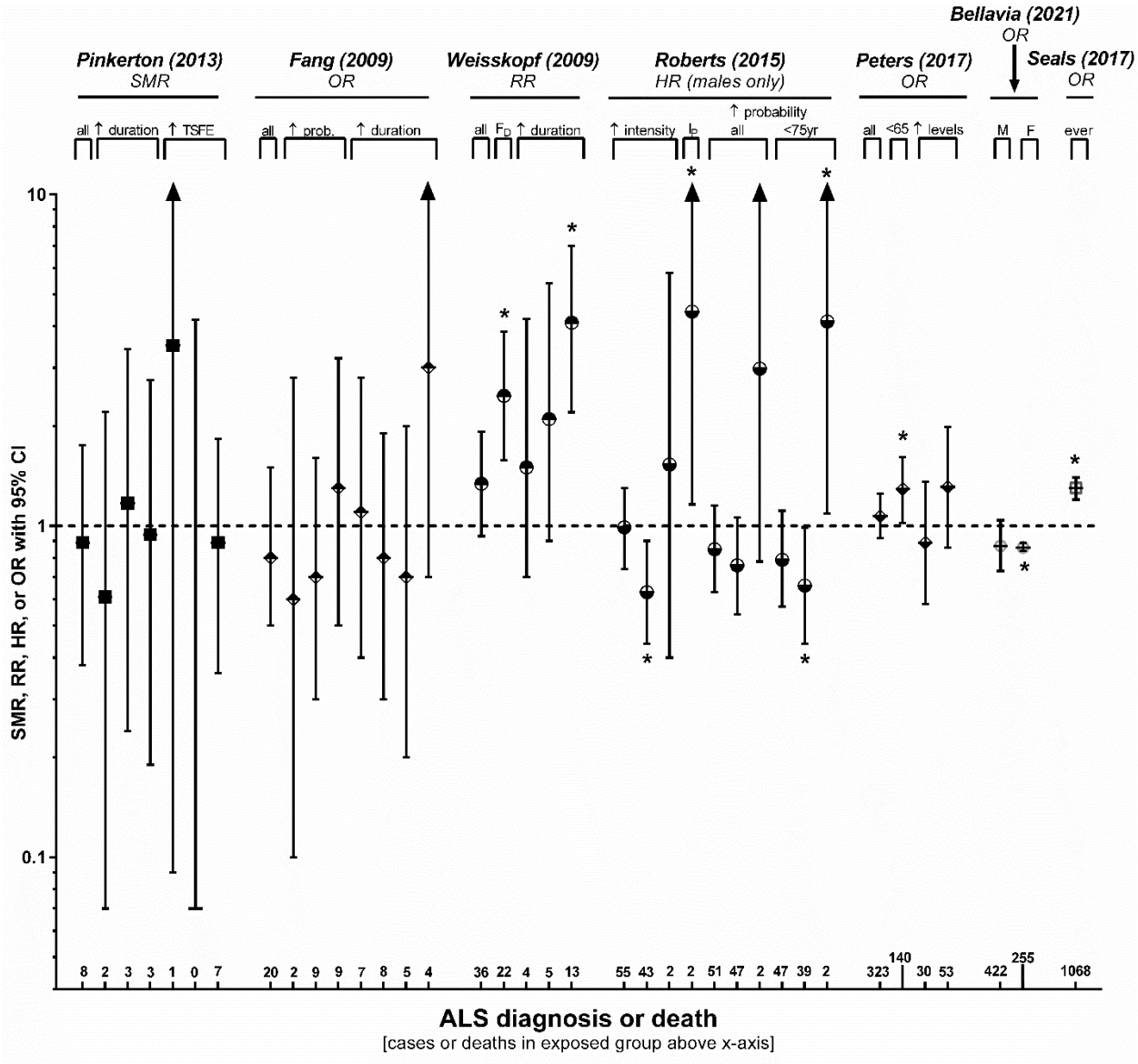


Figure 3-27. Human studies of *medium* confidence examining the potential for formaldehyde exposure to cause ALS.

Seven epidemiological studies of *medium* confidence were identified, all of which examined potential associations with amyotrophic lateral sclerosis (ALS) [notes: a *medium* confidence, acute controlled exposure study of neurobehavior, Lang et al. (2008), is not presented; results from Roberts et al. (2015) are only presented for males as all results in females were null]. Estimates of risk (i.e., odds ratios [ORs], standardized mortality ratios [SMRs], relative risks [RRs], or hazard ratios [HRs]), 95% confidence intervals (CIs), and number of exposed cases or deaths are presented for different comparisons within the studies, including full cohort (e.g., ever/never exposed) comparisons (unlabeled) and comparisons across multiple groups by: increasing duration, probability (prob.), time since first exposure (TFSE) [note: null results comparing date of first exposure in Pinkerton et al. (2013) are not shown], or age-restricted (e.g., younger than 65 years: ≤65). Different shapes reflect different research groups. Other abbreviations: F_D = full cohort comparison excluding persons not providing duration information; I_P = maximum intensity in persons with a high probability of exposure compared to controls; M = males; F = females; all = overall (full cohort comparisons).

Table 3-45. Summary of human studies of nervous system disease risk in relation to formaldehyde exposure

Reference and study design	Exposure measures	Results
Observational epidemiology studies		
Reference: Pinkerton et al. (2013) (United States) Prospective cohort, 11,098 garment workers (82% women) exposed to formaldehyde-treated fabric for ≥3 mo. (late 1950s to early 1980s). **Outcome:** Vital status through 2008, underlying cause of death, ICD-10 G12.2, ICD-9 335.2, ICD-8 348.0 and ICD-7 356.1. **Analysis:** Life-table analysis based on U.S. population, excluded missing birth date (*n* = 55), deaths (*n* = 8), lost to follow-up prior to date file begin date (*n* = 13); SMRs and 95% CI, adjusted for age, calendar time, sex, race; no information on smoking. **Evaluation:**[a] *Medium* confidence Small number of cases.	Monitoring in 1980s, geometric mean 0.15 ppm (GSD 1.9 ppm), constant levels across departments and facilities, year of first exposure (42% before 1963), time since first exposure (median 39.4 years) and exposure duration (median 3.3 years); no other exposures associated with ALS.	**Amyotrophic lateral sclerosis mortality** *N* = 11,022, 414,313 person-years at risk; eight ALS deaths; mortality for COPD and lung cancer in cohort was similar or greater than national rates (Meyers et al., 2013) indicating that possible confounding by smoking would be in direction away from the null, not a concern for these null results. All eight deaths were recorded due to ALS in death certificates. Overall: 8 deaths, SMR 0.89 (0.38, 1.75) Year of 1st exposure Before 1963: 5, 0.84 (0.27, 1.96) 1963–70: 3, 1.29 (0.27, 3.78) ≥1973: 0, 0.00 (0.00, 4.92) Duration <3 year: 2, 0.61 (0.07, 2.21) 3–9 year: 3, 1.17 (0.24, 3.41) 10+ year: 3, 0.94 (0.19, 2.75) TSFE[a] <10 year: 1, 3.50 (0.09, 19.52) 10–19 year: 0, 0.00 (0.00, 4.19) 20+ year: 7, 0.89 (0.36, 1.83) [a]TSFE: time since first exposure
Reference: Bellavia et al. (2021) (Denmark) Population-based case-control ALS cases, 1982-2009, from Seals et al. (2017) with complete data for several health factors and environmental risk factors previously linked with ALS (N = 1086). Controls, 100 per case matched on being alive on index date for case diagnosis, same birth year and sex (N = 111,507). Excluded individuals with less than 5 years work experience. **Outcome:** see Seals et al. (2017) **Analysis:** Selected joint predictors and interactions using boosted regression trees and Logic regression, which were included in a logistic regression model adjusting for age, SES, and geography. Model used a 3-year lag. Evaluated diabetes, obesity, physical/ stress trauma, CVD (1977-2009) and lead, diesel exhaust and solvents.	see Seals et al. (2017) Formaldehyde exposure metric was ever/never exposed. Anticipate exposure misclassification and large variation in prevalence and intensity of exposure across individuals. In men, correlations between formaldehyde, diesel exhaust and solvents were 0.22 and 0.41, respectively (Phi coefficients)	**Amyotrophic lateral sclerosis** Ever formaldehyde Exposed Men: Controls N (%) 43,760 (0.64); Cases N (%) 422 (0.63); OR (95% CI) 0.87 (0.73, 1.04) Women: 28.100 (0.65); 255 (0.61); 0.86 (0.84,0.89) Logistic regression mutually adjusting for age, SES, and geography, diesel exhaust (male), solvents, trauma, CVD, diesel*CVD (male), solvents*trauma (male), diesel*trauma (male), and diesel*solvents (male), lead (female), lead*solvents (female) and trauma*formaldehyde (female).

Reference and study design	Exposure measures	Results
Evaluation:[a] *Low* confidence Large uncertainty regarding exposure assessment (ever/never exposed). Adequacy of 3-year lag is unknown.		
Reference: Seals et al. (2017) (Denmark) Population-based case-control study, Registry-based case identification using the Danish National Patient Register, 1982-2009 (3650 incident cases). Controls obtained from Central Person Registry (All Denmark residents since 1968), 4 per case matched on sex, age, and no ALS diagnosis in Hospital Register as of date of diagnosis for matched case (index date). **Outcome:** Cases identified from Danish National Patient Register, discharge diagnosis ICD-8 348.0 or ICD-10 G12.2. Case definition was 1st diagnoses on or after 1/1/1982–12/31/2009. **Analysis:** Conditional logistic regression adjusted for age, sex, index date, SES, marital status and residence. No information on smoking status. **Evaluation:**[a] *Medium* confidence Uncertainty regarding exposure assessment. JEM not validated to predict formaldehyde exposure level.	Occupational histories obtained from Danish Pension Fund databases. Used NOCCA (Nordic Occupational Cancer Study)- Danish JEM for periods 1960-74, 1975-84, and 1985 and after. Inputs year and industry code and outputs prevalence of exposure for each job along with expected exposure level (ppm) in exposed. The JEM has not been validated to estimate levels. Cumulative expected exposure calculated (prevalence multiplied by expected level) summed over jobs and time (3- and 5-year lags). Exposure misclassification expected due to variation of tasks within industries.	**Amyotrophic lateral sclerosis** Exposure / Controls N (%) / Cases N (%) / RR (95% CI) None: 10,934 (75) / 2582 (71) / 1.0 (ref) Ever: 3666 (25) / 1068 (29) / 1.3 (1.2, 1.4) Quartiles (mg/m^3) <0.016: 935 (6.4) / 262 (7.2) / 1.3 (1.1, 1.5) 0.016-0.1: 976 (6.7) / 272 (7.5) / 1.2 (1.1, 1.4) 0.1- 0.34: 873 (6.0) / 268 (7.3) / 1.4 (1.2, 1.6) >0.34: 882 (6.0) / 266 (7.3) / 1.3 (1.1, 1.5)
Reference: Peters et al. (2017) (Sweden) Nested case-control study, 5,020 patients diagnosed with ALS between 1991 and 2010 and 25,100 Swedish controls (5 per ALS case) matched by birth year and sex, alive on case's date of diagnosis; source population born 1901−1970 and included in the 1990 Swedish Population and Household Census (includes persons living in Sweden for ≥1 year). **Outcome:** Cases identified from National Patient Register (primary or secondary diagnosis) through 2010 (ICD-9 335C; ICD-10 G12.2). **Analysis:** Conditional logistic regression with adjustment for education and other 11 exposures examined; restricted to individuals with at least one occupation registered in any of the censuses, occupations listed in censuses 10 years before diagnosis, and either blue collar	Individual occupational histories obtained from 1970, 1980, and 1990 censuses; Swedish version of Nordic Occupational Cancer Study JEM (industrial hygienist estimates of prevalence and level of specific exposures at specific calendar times). Dose-response: exposure metric calculated: prevalence multiplied by annual mean level of exposure in a specific occupation at the time of a census, averaged over all three censuses,	**Amyotrophic lateral sclerosis** Cases / Control / OR (95% Ci) Restricted analytic sample (2,647 cases) All: 323 / 1,579 / 1.07 (0.92–1.25) Exposure metric (mg/m^3) Not exposed: 659 / 3,341 / 1.0 (Reference) ≤0.013: 30 / 185 / 0.89 (0.58–1.36) ≥0.013: 53 / 210 / 1.31 (0.86–1.99) Restricted to individuals <65 years old at diagnosis (1,014 cases) All: 140 / 576 / 1.28 (1.02–1.61)

Reference and study design	Exposure measures	Results
workers or farmers (2,647 cases, 13,378 controls). **Evaluation:**[a] *Medium* confidence Uncertainty regarding exposure assessment.	dichotomized at mean level in controls.	
Reference: Roberts et al. (2015) (United States) Prospective cohort, 1,469,235 occupational workers (46% women); National Longitudinal Mortality Study (NLMS) restricted to age 25+ at initial survey. Participants provided follow-up from survey until 2011 or death. **Outcome:** NLMS records matched to the National Death Index (1979–2011) with underlying cause of death as ALS: ICD-10 G12.2 or ICD-9 335.2. **Analysis:** HRs estimated for each exposure level using survival analyses with age as the time variable, separate models for men and women, adjusted for education, race/ethnicity, and income. **Evaluation:**[a] *Medium* confidence Uncertainty regarding exposure assessment, including the influence of duration, no information about job history prior to most recent job; very small number of exposed cases (*n* = 2 in jobs with high probability and intensity of formaldehyde exposure). Note: same laboratory, data handling, and analysis methods as Weisskopf et al. (2009).	Exposure matrix by industrial hygienists at the National Cancer Institute (see (Wang et al., 2009)) was constructed based on participant survey at enrollment regarding their last or most recent job; no information or adjustments for other potential exposures.	**Amytrophic lateral sclerosis mortality** *N* = 757 total ALS deaths (472 deaths in men, with 100 exposed cases and 12,930,240 total person-years in men). Duration not evaluated. No information on mortality from smoking-related disease or smoking in the general cohort. Deaths matched to ALS in death certificates. No increased risk of ALS in women (data not shown): authors attribute this to occupation role. *ALS deaths in men* Intensity Unexposed 372 1.0 (Reference) Low 55 0.99 (0.74, 1.30) Medium 43 0.63 (0.44, 0.90) High 2 1.53 (0.4, 5.80) Intensity, restricted to probability = high Unexposed 372 1.0 (Referent) Low 0 - Medium 0 - High 2 4.43 (1.16, 16.85) Probability Unexposed 372 1.0 (Reference) Low 51 0.85 (0.63, 1.15) Medium 47 0.76 (0.54, 1.06) High 2 2.98 (0.78, 11.30) Probability, follow-up to age 75 only Unexposed 332 1.0 (Reference) Low 41 0.79 (0.57, 1.11) Medium 40 0.66 (0.44, 0.99) High 2 4.13 (1.09, 15.69) Probability, aged 50–75 at enrollment Unexposed 197 1.0 (Reference) Low 31 1.00 (0.67, 1.49) Medium 27 0.75 (0.47, 1.19) High 2 4.76 (1.16, 19.49) Probability analyses excluding the first 5 years of follow-up or restricted to men aged 35–75 at enrollment, or to those employed at enrollment, are not shown (results were similar to the overall probability analysis).

Reference and study design	Exposure measures	Results
Reference: Fang et al. (2009) (United States) Case-control study, 111 cases and 256 controls; sequential ALS cases recruited, 1993–1996, from two major referral centers; cases and controls lived in New England at least 50% of year, mentally competent, English speakers; 71% of eligible cases participated; controls by random telephone screening, frequency matched on sex, age (three groups), and region, 76% of eligible (256 of 270 completed questionnaires). **Outcome:** Diagnoses by board-certified specialists in motor neuron disease using World Federation of Neurology El Escorial criteria (Brooks, 1994). **Analysis:** Unconditional logistic regression models; tested linear trend with lifetime exposure days, probability, and weighted exposure duration (four categories); adjusted for age, sex, area of residence, smoking (ever/never), and education. **Evaluation:** [a] *Medium* confidence Uncertainty regarding exposure assessment; small number of exposed cases.	Occupational history by structured questionnaire; industry, occupation, frequency, and duration; jobs held before ALS diagnosis or 2 years before interview (controls); formaldehyde-exposed occupations identified a priori by industrial hygienist; calculated life-time hours of exposure to formaldehyde weighted by probability of exposure in specific jobs.	**Amytrophic lateral sclerosis** Association of ALS risk with occupational formaldehyde exposure (109 cases, 253 controls) Controls / Cases / OR (95% CI) Never[a]: 204 / 89 / Ref. Ever: 49 / 20 / 0.8 (0.5, 1.5) Exposure Probability[b] 0–1: 7 / 2 / 0.6 (0.1, 2.8) 1: 27 / 9 / 0.7 (0.3, 1.6) 2: 15 / 9 / 1.3 (0.5, 3.2) *Trend p-value*: 0.50 Weighted exposure duration (hr)[c] ≤10,000: 14 / 7 / 1.1 (0.4, 2.8) 10,001–40,000: 19 / 8 / 0.8 (0.3, 1.9) >40,000: 16 / 5 / 0.7 (0.2, 2.0) *Trend p-value*: 0.45 >60,000[d]: 4 / 4 / 3.0 (0.7, 12.9) [a]Referent was group with no previous. occupational exposure to formaldehyde [b]Highest probability ever experienced. [c]Weights were 0.5, 1, and 2 for probabilities 0–1, 1, and 2. [d]Additional analysis.
Reference: Weisskopf et al. (2009) (United States) Prospective cohort, 987,229 men and women. American Cancer Society Cancer Prevention Study II. No major illness at baseline in 1982. Follow-up from 1989 through 2004. **Outcome:** Cause of death obtained for >98% of known deaths; underlying or contributing cause. ICD-9 (1989–1998) code 335.3; ICD-10 (1999–2004) code G12.2 (ALS represents >98% of these categories). **Analysis:** Cox proportional hazards modeling, adjusted for age, sex, smoking, military service, education, alcohol, occupation (farmer, lab technician, machine assembler, programmer), vitamin E use, and the other chemical (and X-rays) exposures assessed at baseline.	Self-report (at baseline, 1982) of current or past regular exposure to formaldehyde (and duration); data on 10 other types of chemicals and X-ray exposure also collected. Source(s) of formaldehyde exposure were not defined; likely to be occupational settings.	**Amyotrophic lateral sclerosis mortality** 1,156 ALS deaths; mortality rate 11.3 and 6.7 per 100,000 person-years in men and women, respectively. N cases exposed / RR / (95% CI) Full cohort: 36 / 1.34 / (0.93, 1.92) With duration[a]: 22 / 2.47 / (1.58, 3.86) <4 years: 4 / 1.5 / (0.7, 4.2) 4–10: 5 / 2.1 / (0.9, 5.4) >10: 13 / 4.1 / (2.2, 7) CIs estimated from graph RR between other exposures and ALS ranged from 0.68 to 1.44.

Reference and study design	Exposure measures	Results
Evaluation:[a] *Medium* confidence Uncertainty regarding exposure assessment.		[a]"With duration" indicates the subset of the full cohort after excluding individuals not providing duration information.

Organized by study confidence, then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.7).

Abbreviations: ALS = amyotrophic lateral sclerosis; COPD = chronic obstructive pulmonary disease; GSD = geometric standard deviation; CI = confidence interval; SMR = standardized mortality ratio.

Summary of Human Evidence Synthesis Judgments

Neurobehavioral Tests

The following factors were influential to the synthesis judgment that the human studies provide *slight* evidence of formaldehyde exposure-induced neurobehavioral effects, specifically on motor behaviors and learning and memory. No human studies informed potential neural sensitization.

Motor behaviors

- *Consistency and Study Confidence*: Two *low* confidence studies, with weak support from one *medium* confidence study, observed effects on motor-related behaviors. All low confidence studies had significant coexposures and/or poorly comparable groups, reducing certainty.
- *Dose-Response*: Certainty is decreased due to a lack of dose-dependence.

Learning and Memory

- *Consistency and Study Confidence*: Three of four *low* confidence studies observed effects in tests of learning or memory. All studies had significant coexposures and/or poorly comparable groups, reducing certainty.
- *Dose-Response*: Certainty is decreased due to a lack of dose-dependence, although exposure duration was associated with decrements in learning and memory.

Nervous System Disease

The following factors, particularly the generally consistent findings across a few studies, were influential to the synthesis judgment that the human studies on nervous system disease provide *slight* evidence of a formaldehyde exposure-induced increase in amyotrophic lateral sclerosis (ALS) incidence and mortality.

- *Consistency and Study Confidence*: Clear effects were observed in one *medium* confidence study with more limited support from three other *medium* confidence studies, two of which were from the same research group. Conversely, no association was observed in a *medium* confidence study using a longitudinal design and more robust exposure assessment. Overall uncertainty exists due to small numbers of exposed cases.
- *Strength and Precision*: One *medium* confidence study observed large, precise increases.

- *Dose-Response*: Certainty is decreased by a lack of dose-response trends in the studies able to examine it, and because exposure duration was inconsistently associated with disease incidence.
- *Biological Plausibility:* Certainty is decreased because plausibility is lacking for how inhaled formaldehyde, which is not appreciably distributed to the central nervous system, could impact ALS. No MOA or informative mechanistic studies were identified.
  In addition to the judgment above, it is noted that ALS disproportionately affects males.

Developmental Neurotoxicity

No informative human studies related to developmental neurotoxicity were identified (i.e., *indeterminate* human evidence).

Animal Studies

Numerous experimental animal studies report findings of neurobehavioral and structural alterations following formaldehyde inhalation. This section discusses these studies according to the type of evaluation(s) performed, specifically by studies of neuropathology (see Table 3-46), studies examining potential sensitization of the nervous system (see Table 3-47), tests of general motor-related behaviors (see Table 3-48; as discussed below, most of the available studies used tests that evaluated responses that may be related to motor function and other behaviors, such as responses to increased anxiety), and tests of learning and memory (see Table 3-49). The evidence tables are organized by study confidence and descending publication year. The study evaluations are included in Appendix B.3.7.

As discussed below, much of the available data are difficult to interpret due to potential coexposures (e.g., methanol), possible mischaracterization of irritation-related behaviors as central nervous system- (CNS)-mediated effects, unreported or inadequate study design methods, and unclear dose-response relationships. The neurobehavioral effects reported following formaldehyde inhalation include changes in motor function, anxiety, habituation, learning and memory, and chemical sensitization in adult animals (Usanmaz et al., 2002; Sorg et al., 1998; Sorg and Hochstatter, 1999; Sorg et al., 2001b; Sorg et al., 2004; Pitten et al., 2000; Malek et al., 2003a, b, c, 2004; LICM, 2008; Boja et al., 1985). Nociception was unaffected in one study (Sorg et al., 1998). Several studies also indicate neuropathology or behavioral effects following developmental formaldehyde exposure (Songur et al., 2003; Sheveleva, 1971; Sarsilmaz et al., 2007; Aslan et al., 2006); no corresponding information on developmental nervous system effects in human studies is available.

In addition to these studies evaluating specific effects on the nervous system, one subchronic study (Woutersen et al., 1987) and three chronic studies (Tobe et al., 1985; Kerns et al., 1983; Appelman et al., 1988) designed to assess the general toxicity or carcinogenicity of formaldehyde reported general behavioral effects (e.g., uncoordinated locomotion) following exposure to high levels of formaldehyde (>12 mg/m^3). In these studies, no overt changes in

absolute brain weight, brain histopathology, or performance in simple tests of nervous system function were observed (data not shown). These general toxicity and carcinogenicity studies were not specifically designed to assess nervous system function and did not report many of the relevant procedural details or, in most cases, the specific quantitative results. Thus, a confidence rating was not assigned to these experiments, and they are not discussed further. Studies on odorant detection (not considered a potential adverse effect of formaldehyde) were also reviewed (see Appendix B.3.7) and are briefly discussed to inform the interpretation of specific nervous system effects (e.g., behavioral changes). Aside from these cursory examinations and one subchronic experiment with brief, 10-minute, daily formaldehyde exposures (Pitten et al., 2000), the remaining animal studies of the potential for nervous system effects due to formaldehyde inhalation relied on exposures of acute or short-term duration; extrapolation of these effects to long-term exposure scenarios is difficult. Studies classified as *not informative* to the animal or MOA evidence syntheses are not discussed (Yu and Blessing, 1997, 1999; Wang et al., 2014a; Tepper et al., 1995; Tani et al., 1986; Sorg et al., 1996; Sorg et al., 2002; Senichenkova, 1991a; Sari et al., 2005; Nalivaiko et al., 2003; Morgan et al., 1986a; Mei et al., 2016; Maronpot et al., 1986; Liu et al., 2009; Liu et al., 2010; Liao et al., 2010; Katsnelson et al., 2013; Gieroba et al., 1994; DHGC, 2010; Coon et al., 1970; Chonglei et al., 2012; Bokina et al., 1976; Bian et al., 2012; Apfelbach and Weiler, 1991), noting that some studies deemed *not informative* for certain endpoints were informative for other endpoints and are discussed below (see Appendix B.3.7 for details). Figure 3–28 presents all of the *medium* or *low* confidence experimental animal studies identified (no *high* confidence studies were identified), whereas the data from the *medium* confidence animal studies are summarized in greater detail in Figure 3–29.

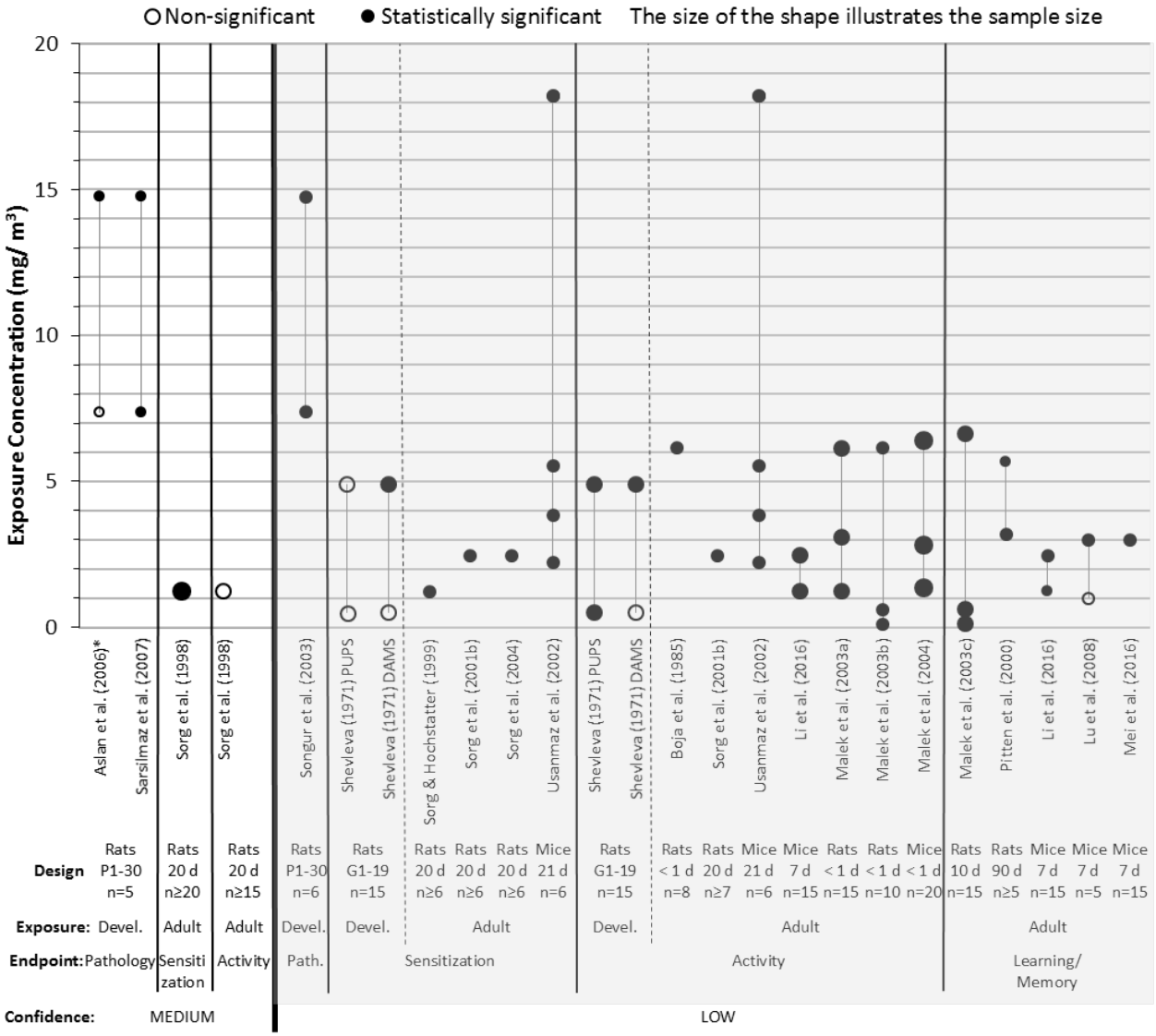


Figure 3-28. Nervous system effects in animal studies.

As no *high* confidence experimental animal studies were identified, the available studies are organized by *medium* and *low* confidence study evaluation interpretations (see Appendix B.3.7), then by endpoint, then by timing of exposure (i.e., developmental [devel.] or adult). Filled symbols indicate statistically significant effects, and the size of the points reflecting the sample size for that formaldehyde exposure group (larger size = larger *n*). The *low* confidence experiments are shown on a gray background, as the identified study limitations substantially reduce confidence in the reliability of the results; these *low* confidence experiments contribute very little to the weight of evidence for nervous system effects. Note: "Activity" refers to motor-related behaviors (e.g., open field activity). *The studies by Aslan et al. (2006) and Sarsilmaz et al. (2007) report data from the same cohort of exposed rats.

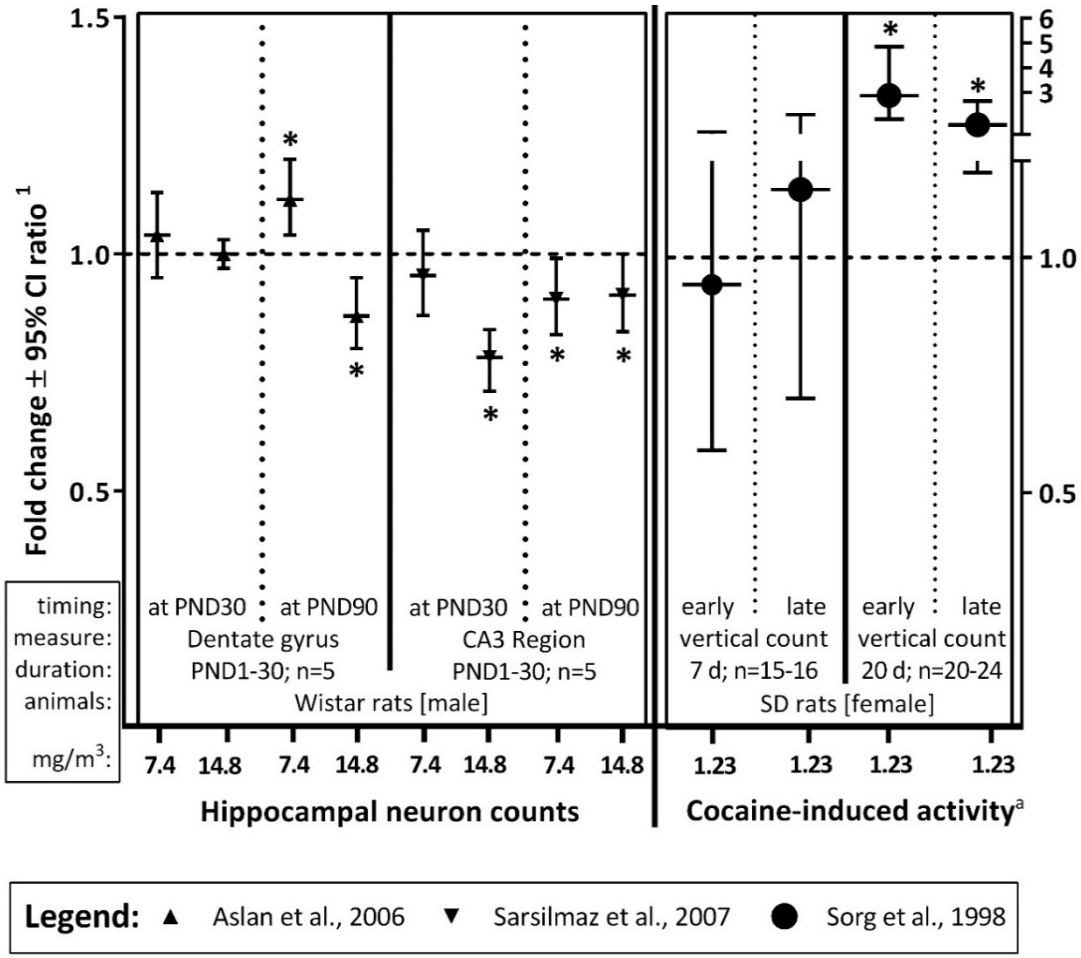


Figure 3-29. *Medium* confidence animal studies of nervous system effects.

The evidence for nervous system effects reported in *medium* or *high* confidence experimental animal studies is arrayed (note: no *high* confidence studies were identified). Two studies examined developmental neuropathology using stereological methods after postnatal exposure to 7.4–14.8 mg/m^3 formaldehyde in a single cohort of rats (Sarsilmaz et al., 2007; Aslan et al., 2006), while a third study evaluated sensitization-type responses in adult rats at 1.23 mg/m^3 (Sorg et al., 1998). [1]Results are displayed as fold change from control animals (control responses at 1 are illustrated as a dashed line), with variability in both the controls and treatment groups represented by the quotient (ratio) of the 95% CI, as calculated based on the method described by E.C. Fieller (Cox and Ruhl, 1966), which assumes Gaussian distributions. [a]Changes in vertical activity induced by stimulation with cocaine exposure following formaldehyde inhalation for 7 or 20 days and several days ("early") or several weeks ("late") of nonexposure are shown; the authors did not observe any changes in cocaine-induced horizontal activity (not shown). *$p < 0.05$, as reported by study authors. Note: all results were estimated from data presented graphically using Grab It!™, Datatrend Software.

Neuropathology, including Developmental Neurotoxicity

Several studies examined the effects of formaldehyde inhalation on brain neuropathology. Evidence of changes in brain structure and neuron number following developmental exposure to ≥7.38 mg/m^3 formaldehyde has been described in three publications from one laboratory (Songur

et al., 2003; Sarsilmaz et al., 2007; Aslan et al., 2006) (see Table 3–46). Two of these studies (Sarsilmaz et al., 2007; Aslan et al., 2006) were evaluations of the same cohort of animals. No overt changes in CNS pathology have been reported following subchronic or chronic formaldehyde exposures in adult rats at concentrations ranging from 0.369 to 18.5 mg/m^3 (Tobe et al., 1985; Pitten et al., 2000; Kerns et al., 1983; Appelman et al., 1988), although the methods employed in the adult animal studies were far less sensitive than those used by Sarsilmaz et al. (2007) and Aslan et al. (2006).

Neuropathological alterations were evident in male rats following exposure to 7.38 or 14.8 mg/m^3 formaldehyde from postnatal day (PND) 1 to PND 30. Specifically, in the cornu ammonis (CA) region of the hippocampus, a 4% (at 7.38 mg/m^3) or 22% (at 14.8 mg/m^3; statistically significant) decrease in the number of neurons in the pyramidal cell layer was observed at PND 30, and statistically significant, 8–9%, decreases were still observable at both concentrations at PND 90 (Sarsilmaz et al., 2007). Although the morphology of the cell nuclei determined by cresyl violet staining was indicated as normal in all regions of the hippocampus at PNDs 30 and 90 in Sarsilmaz et al. (2007) and Aslan et al. (2006), these decreased cell counts were consistent with separate observations of robust increases (59–322%) in the number of pyknotic (i.e., dying) CA neurons at PNDs 30 and 60 in Songur et al. (2003). A decrease in cell number is considered an adverse effect and a specific indicator of toxicity. The decreased magnitude of neuronal loss at PND 90 as compared to PND 30 (Sarsilmaz et al., 2007), along with a separate observation that pyknotic CA neuron counts were no longer elevated at PND90 (Songur et al., 2003), suggest some measure of recovery or adaptation 60 days after exposures were terminated. Notably, hippocampal cell number exhibits a natural decrease between PNDs 30 and 90, as demonstrated by Sarsilmaz et al. (2007) and Aslan et al. (2006).

Changes in the hippocampal dentate gyrus (DG) cell number and in volumetric measures were less clear. A significant increase in DG volume was observed at ≥7.36 mg/m^3 formaldehyde at PND 30, without any accompanying changes in cell number (Aslan et al., 2006). The authors attributed this finding to possible formaldehyde-triggered inflammation during postnatal growth of the DG, which continues until ~PND 28; however, this hypothesis was not evaluated by immunostaining. At PND 90, although DG cell number was decreased at 14.8 mg/m^3, DG volume and cell number were elevated at 7.36 mg/m^3. In contrast to decreases in cell number, an increase in cell number is not necessarily adverse. Although CA cell counts were decreased, the volume of the pyramidal cell layer on PND 30 was increased at 7.38 mg/m^3 but decreased at 14.8 mg/m^3; neither exposure group was significantly different from controls on PND 90. Changes in brain hemisphere volume [decreased at PND 30 and increased at PND 90; (Sarsilmaz et al., 2007)] suggest formaldehyde-induced structural changes or inflammation in nonhippocampal regions, or altered ventricular parameters, as the changes were not consistent with volume changes in the DG or CA regions. Volume changes can provide nonspecific measures of neural health. Although these changes are sometimes associated with regional atrophy and degeneration, they are also sensitive

to variations such as changes in neuron size or changes in the size or number of nonneuronal cells. Thus, decreased cell number is a more specific indicator of toxicity.

Exposure from PND 1 to PND 30 covers a sensitive window of hippocampal development, as a large percentage of hippocampal neurons, particularly in the DG, are generated or mature (e.g., establish permanent connections) during the early postnatal period. In addition, the stereological methods used by Aslan et al. (2006) and Sarsilmaz et al. (2007) are extremely sensitive and unbiased by design (e.g., sampling is random and systematic). These methods were not applied in any other studies, highlighting a key uncertainty in the database. The specific exposure window or methods employed could explain the general lack of overt neuropathological effects in rats exposed as adults. Importantly, these developmental studies did not appear to evaluate possible effects on nursing dams (i.e., dam health and behavior), who appear to have been exposed along with the pups from PND 1 to PND 14. It is plausible that the high-level exposures could lead to nutritional changes that influence measures of structural brain development. Pup health, which was affected at PND 30 (i.e., decreased body weight) but not PND 90 in the study by Songur et al. (2003), was not reported in the other two studies. However, CA neuron loss was still evident at PND 90 when no body-weight differences were evident (Songur et al., 2003). An additional significant limitation of these studies is that the sample size is very small considering that the analyses were performed on a pup basis rather than a litter basis, as would be preferred. Specifically, although 5–6 pups/group were analyzed, because litter effects may influence these measures, the data are better evaluated as representing only $N = 3$ litters (the authors indicate two pups were assessed from each of the three litters). Litter data were not available to determine whether such analyses would result in a greater or lesser magnitude of response, further complicating interpretation.

Complete recovery of the observed neuropathology following developmental exposure was not observed. Partial recovery was apparent, but examinations did not continue long enough to detect whether or when the observed pathology completely resolves. This supports the possibility that formaldehyde may cause long-lasting or permanent neuroanatomical changes in the brain following early-life exposure, which would substantiate characterizing it as a nervous system hazard according to Agency guidelines (U.S. EPA, 1998). However, these stereological data reflect a single cohort of exposed animals, and the study deficiencies described above limit the ability to attribute the results to formaldehyde exposure alone. In addition, the limited data supporting these effects were derived from studies only testing high-level formaldehyde exposure (i.e., well above levels demonstrated to cause noncancer effects in the respiratory system; see Sections 3.2.1–3.2.4), introducing additional uncertainties. Therefore, because of the possibility of long-lasting or permanent changes to the brain following developmental exposure, this is an area in need of further research.

Table 3-46. Developmental neuropathology in experimental animal studies

Reference and study design	Results (percentage change from control) and exposure levels
Medium confidence	
Reference: Sarsilmaz et al. (2007) Rat (Wistar); *N* = 3 litters (5 male pups[b]) 0, 7.38, or 14.8 mg/m^3[a] PND 1–PND 30 Test article: paraformaldehyde **Main limitations**: Small sample size; potential for litter effects; note: same cohort as Aslan et al. (2006)[b].	**(Importantly, all data were analyzed on a pup basis rather than on a litter basis.)** **0 7.38 14.8 0 7.38 14.8** *Total CA cell number assessed by stereology:* at PND 30: 0 −4[c] −22%* at PND 90: 0 −9* −8%* Note: CA cell morphology was normal at PND 30 and PND 90 *CA volume assessed by stereology:* at PND 30: 0 15* −28%* at PND 90: 0 −7 10% *Hemisphere volume assessed by stereology:* at PND 30: 0 −3* −7%* at PND 90: 0 24* 5%*
Reference: Aslan et al. (2006) Rat (Wistar); *N* = 3 litters (5 male pups) 0, 7.38, or 14.8 mg/m^3[a] PND 1–PND 30 Test article: paraformaldehyde **Main limitations**: Small sample size; potential for litter effects; note: same cohort as Sarsilmaz et al. (2007)[b]	**(Importantly, all data were analyzed on a pup basis rather than on a litter basis.)** **0 7.38 14.8 0 7.38 14.8** *Total DG cell number assessed by stereology:* at PND 30: 0 3 0% at PND 90: 0 10* −12%* Note: DG cell morphology was normal at PND 30 and PND 90. *Volume of the DG assessed by stereology:* at PND 30: 0 9* 8%* at PND 90: 0 13* −1%
Low confidence	
Reference: Songur et al. (2003) Rat (Wistar); *N* = 3 litters (6 male pups) 0, 7.38, or 14.8 mg/m^3[a] PND 1–PND 30 Test article: paraformaldehyde **Main limitations**: Small sample size; potential for sampling bias and litter effects.	**(Importantly, all data were analyzed on a pup basis rather than on a litter basis.)** **at PND 30 / at PND 60 / at PND 90** **0 7.38 14.8 0 7.38 14.8 0 7.38 14.8** *CA1 pyknotic neurons:* 0 59* 74%* 0 5 54% 0 20 −6% *CA2 pyknotic neurons:* 0 322* 336%* 0 65* 72% 0 18 9% *CA3 pyknotic neurons:* 0 273* 291%* 0 128 60%* 0 60 −19% *Body weight:* 0 −12* −21%* 0 −4 −9%* 0 −2 −5%

Organized by study confidence, then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.

Abbreviations: DG = dentate gyrus; PND = postnatal day; CA = cornu ammonis.

*$p < 0.05$ versus control exposure; formaldehyde levels are underlined.

[a]Formaldehyde levels in the study (converted to mg/m3 from ppm) were interpreted from the methods to represent the achieved mean analytical levels, although the range of measured concentrations was not reported.

[b]Sex and cohort information provided to EPA by personal communication (Kaplan, 2012, 2014).

[c]Indicated as −19% by study authors in text but estimated by EPA at −4% from data displayed graphically.

Neural sensitization

Research suggests that formaldehyde exposure might induce sensitization-like properties in neuronal networks (Usanmaz et al., 2002; Sorg et al., 1998; Sorg and Hochstatter, 1999; Sorg et al., 2001b; Sorg et al., 2004; Sheveleva, 1971) (see Table 3-47). Behavioral sensitization in animals can be initiated by drugs affecting the mesolimbic dopamine system (e.g., cocaine, morphine). Although the mechanisms are not fully understood, repeated, low-level exposures to certain chemicals and other stimuli have been hypothesized to cause a persistent modification to brain signaling, possibly due to altered dopamine levels in limbic circuits (Bell et al., 1992; Bell et al., 1999; Antelman et al.,

1980). Subsequent re-exposure to the conditioned chemical or stimulus, or challenge with other sensitizing agents, may result in amplified neural responses. These responses can be manifest as, for example, increased impulsivity, motor activity, or CNS excitability.

Possible sensitization manifest as amplified cocaine-induced locomotor activity and conditioned fear responses, as well as disrupted sleep patterns, has been reported by one group of researchers following repeated exposure to formaldehyde at 1.23–2.46 mg/m^3 (Sorg et al., 1998; Sorg and Hochstatter, 1999; Sorg et al., 2001b; Sorg et al., 2004). In the study interpreted with the highest confidence (*medium* confidence), although cross-sensitization to cocaine was not observed in female rats exposed to formaldehyde for 7 days, 4 weeks of exposure led to increased cocaine-induced vertical activity (with no difference in horizontal activity) when tested at 2–4 days (early withdrawal) and 4–6 weeks (late withdrawal) after cessation of exposure (Sorg et al., 1998). Sleep-wakefulness patterns, which are regulated in part by dopaminergic signaling (Dzirasa et al., 2006), were disrupted in male rats (females were not tested) after a 1–week withdrawal from formaldehyde inhalation (Sorg et al., 2001b); however, these results were limited by incomplete reporting (see Table 3-47). The study authors hypothesized that formaldehyde exposure may be causing a persistent stress response in the animals.

Several weeks following exposure to ≥1.23 mg/m^3 formaldehyde for 20 days, rats previously trained in a fear conditioning paradigm (a neutral odor was paired with footshock) tended to spend more time immobilized ("freezing") in the presence of the odor than did air-exposed controls, although these differences were not statistically significant (Sorg and Hochstatter, 1999). The authors concluded that the formaldehyde-treated rats had more difficulty than controls in extinguishing the fear response to the conditioned odor; however, as these changes were noted in response to odor cues, it is unclear whether formaldehyde preconditioning may have altered the sensitivity of the respiratory tract to odor. Overt damage of the nasal mucosa is not expected at these formaldehyde levels, and airway irritation at these levels is expected to be resolved two weeks after exposure (see Section 3.2.1), making causation by physical irritation unlikely. As these data could be related to observations suggesting increased anxiety following exposure (as discussed in the next subsection), the results identify the need to systematically test whether formaldehyde inhalation preconditioning influences responses related to limbic system function using olfactory-independent stimuli, and to compare any findings with responses caused by other stressors (e.g., restraint stress; chemicals with strong irritant odors, but no CNS action).

Equivocal evidence of increased CNS excitability following formaldehyde exposure has been reported in a few studies. Proconvulsant activity following acute formaldehyde exposures in mice was observed at 2.21–7.87 mg/m^3 (Usanmaz et al., 2002), but not at higher exposure levels or when formaldehyde was administered for longer durations (2–3 weeks). A critical component of sensitization was not included in this study, namely, a period of latency between the stimulus and challenge. These data are difficult to interpret because of an inability to distinguish between a "wet-dog shake" due to an irritating odor and that due to a proconvulsive movement. Changes in

pentylenetetrazole-induced seizures reported by Usanmaz et al. (2002) were also not easily interpreted, as no discernible pattern could be identified (e.g., seizure incidence was decreased at 18.2 mg/m^3 and seizure intensity was increased at 2.21 mg/m^3). In a developmental study, exposed pregnant dams displayed a significant reduction (12%) in the threshold of neuromuscular excitability at 4.92 mg/m^3, whereas neuromuscular excitability was unchanged in rat offspring exposed in utero (Sheveleva, 1971). However, the details of the study methods, including latency between exposure and testing in dams, were not provided. It is unclear whether reflex bradypnea-related responses would affect these types of measures (e.g., via transient tissue hypoxia). No other developmental studies examining these types of effects have been identified. Overall, the data indicate the potential for an effect, but the evidence is insufficient to conclude that formaldehyde exposure causes neural excitation or acts as a proconvulsant.

In some studies, it is unclear how the observed sensitization-type responses can be fully separated from potential confounders, such as responses due to irritation (the levels used are likely to elicit some irritant aversion responses) or sensitivity to the formaldehyde odor. Odor detection and irritation responses in rodents and humans differ. In general, odor detection of formaldehyde occurs at slightly lower concentrations than irritation-related responses, with human thresholds reported at 0.068–0.135 mg/m^3 (Berglund and Nordin, 1992; Berglund et al., 2012). An alternative explanation for some of the observed effects is that formaldehyde exposure, and the irritation associated with exposure, is uncontrollable or inescapable, which has the potential to modify stress and brain reward responses (Sorg et al., 1996). This is in contrast to situations of controllable stress expected to be encountered by formaldehyde-exposed humans. Additionally, explanations for sex-dependent differences in potential sensitization responses have yet to be explored. Overall, the human relevance of, and the formaldehyde-independent contributions to, the observed sensitization responses in rodents require additional research, including studies clarifying human sensitization-type responses to chemical irritants and well-controlled animal studies designed to mimic the human condition.

Table 3-47. Neural sensitization in experimental animal studies

<table>
<tr><th>Reference and study design</th><th>Results[a] and exposure levels</th></tr>
<tr><td colspan="2">Medium Confidence</td></tr>
<tr><td>Reference: Sorg et al. (1998)
Rat (Sprague-Dawley); N = 15–16 (7d) or 20–24 (20 d) females
0 or 1.23 mg/m^{3}[b]
[Actual[c]: 0 or 0.779–1.76]
7 or 20 days (5 days/week)
Test article: Paraformaldehyde
Main limitations: Blinding NR; description of methods incomplete.</td><td>Cocaine-induced vertical activity following 20-day exposures:
<table><tr><th></th><th colspan="2">Early withdrawal[d]</th><th colspan="2">Late withdrawal</th></tr><tr><th></th><th>0</th><th>1.23</th><th>0</th><th>1.23</th></tr><tr><td>Saline-induced activity (counts):</td><td>333</td><td>333</td><td>231</td><td>231</td></tr><tr><td>Cocaine-induced activity (counts):</td><td>1,233</td><td>3,467*</td><td>1,983</td><td>3,372*</td></tr><tr><td>Percentage change in activity by cocaine:</td><td>370%</td><td>1,040%*</td><td>858%</td><td>1,460%*</td></tr></table>No changes in cocaine-induced activity were noted after 7 days of exposure and no changes in horizontal activity were noted after 20 days of exposure.
No changes in nociception (hot plate test) were noted after 7 or 20 days of exposure.</td></tr>
<tr><td colspan="2">Low confidence</td></tr>
<tr><td>Reference: Sorg et al. (2004)
Rat (Sprague Dawley); N = 7–8/sex
0 or 2.46 mg/m^{3}[b]
[Actual: 0 or 2.66]
20 days (5 days/week)
Test article: Paraformaldehyde
Main limitations: Unclear influence of changes in olfactory detection.</td><td>Freezing responses to a conditioned stimulus (CS, odor)[h] in males:
<table><tr><th></th><th colspan="2">Day 1</th><th colspan="2">Day 2</th><th colspan="2">Day 3</th><th colspan="2">Day 4</th><th colspan="2">Day 5</th><th colspan="2">Renewal[i]</th></tr><tr><th></th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>0</th><th>2.46</th></tr><tr><td>Unpaired:</td><td>0</td><td>64%*</td><td>0</td><td>19%</td><td>0</td><td>7%</td><td>0</td><td>76%*</td><td>0</td><td>0%</td><td>0</td><td>86%</td></tr><tr><td>Paired:</td><td>0</td><td>26%</td><td>0</td><td>12%</td><td>0</td><td>5%</td><td>0</td><td>22%</td><td>0</td><td>50%*</td><td>0</td><td>47%</td></tr></table>No changes observed in response to the context alone (footshock or novel).
No change in female conditioned fear behaviors (to context or CS).</td></tr>
<tr><td>Reference: Usanmaz et al. (2002)
Mouse (Balb/C); N = 6 Sex NR
0, 2.21, 3.94, 7.87, 11.9, or 18.2 mg/m^{3}[j]: 3 hours
0 or 3.94 mg/m^{3}: 2 weeks
0 or 2.46 mg/m^{3}: 3 weeks
Test article: Paraformaldehyde
Main limitations: Tested immediately after exposure; blinding NR.</td><td>CNS excitability after a 3-hour exposure:
<table><tr><th></th><th>0</th><th>2.21</th><th>3.94</th><th>7.87</th><th>11.9</th><th>18.2</th></tr><tr><td>Percentage incidence of wet-dog shake[k]:</td><td>0</td><td>63*</td><td>67*</td><td>60*</td><td>25</td><td>17%</td></tr><tr><td>Percentage incidence of seizures[l]:</td><td>91</td><td>82</td><td>ND</td><td>60</td><td>ND</td><td>33%*</td></tr><tr><td>Seizure intensity (median vales):</td><td>4</td><td>6*</td><td>ND</td><td>4</td><td>ND</td><td>1</td></tr><tr><td>Seizure threshold (seconds to onset):</td><td>74</td><td>83</td><td>ND</td><td>104</td><td>ND</td><td>110%</td></tr></table>No significant effects on seizure mortality.
No significant effects on CNS excitability after 2–3 weeks of exposure.</td></tr>
<tr><td>Reference: Sorg et al. (2001b)
Rat (Sprague-Dawley); N = 6/sex
0 or 2.46 mg/m^{3}[b]
[Actual: not reported]
20 days (5 days/week)
Test article: Paraformaldehyde
Main limitations: Description of methods incomplete; no preformaldehyde exposure comparisons.</td><td>Sleep patterns, as assessed by EEG/EMG in Males 7 days after exposure:
<table><tr><th>[Dark: 1–12h/Light: 13–24h phase[g]]:</th><th colspan="2">1–6h</th><th colspan="2">7–12h</th><th colspan="2">13–18h</th><th colspan="2">19–24h</th></tr><tr><th></th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>0</th><th>2.46</th></tr><tr><td>Number of waking episodes:</td><td>0</td><td>–30%</td><td>0</td><td>–25%</td><td>0</td><td>–16%</td><td>0</td><td>–18%</td></tr><tr><td>Number of NREMS episodes:</td><td>0</td><td>–25%</td><td>0</td><td>–21%</td><td>0</td><td>–10%</td><td>0</td><td>–18%</td></tr><tr><td>Duration of waking episodes:</td><td>0</td><td>37%</td><td>0</td><td>59%</td><td>0</td><td>9%</td><td>0</td><td>12%</td></tr></table>*Significant treatment effects noted for each measure above by 2–way ANOVA.
No changes in REMS episodes or duration of NREMS episodes were noted.
[Note: a 15–min challenge with 37% formalin odor abolished all differences.]</td></tr>
</table>

Reference and study design	Results[a] and exposure levels
Reference: Sorg and Hochstatter (1999) Rat (Sprague-Dawley); *N* = 4–8 females 0 or 1.23 mg/m^3[b] [Actual: not reported] 20 days (5 days/week) Test article: Paraformaldehyde **Main limitations**: Unclear impact of altered olfactory detection or cocaine injection; note: formalin use as an aversive odor was deemed irrelevant.	**0** / **1.23** *Cocaine (10 mg/kg)-induced horizontal activity (as percentage change in induced activity):* Cocaine-induced activity 2–4 days after air or formaldehyde, as compared to cocaine-induced activity prior to exposure: 198 / 407%* *Fear-conditioned responses to odor (as percentage change from nonshocked)*[f]*:* Freezing in the context used for shock training: 433* / 476%* Freezing with the conditioned odor 2 days later: 45 / 127%* Freezing with the conditioned odor 12 days later: 54 / 181%* *$p < 0.05$, as compared to no shock condition in the same exposure group (*t*-test). [Notes: Statistically significant differences in direct comparisons of the control and HCHO pre-exposed groups were not observed for any fear conditioning tests (*N* = 4).]
Reference: Sheveleva (1971) Rat (Strain NR); *N* = 15/sex 0, 0.492, or 4.92 mg/m^3[e] [Actual: 0, 1.24, 3.09, or 6.20] GD 1–GD 19 Test article: Not reported **Main limitations**: Test article and endpoint evaluation methods NR.	**0** / **0.492** / **4.92** *Neuromuscular excitability in dams:* 0 / −7 / −19%* *No changes in offspring neuromuscular excitability.*

Organized by study confidence, then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.

Abbreviations: GD = gestational day; NREMS = nonrapid eye movement sleep; CS = conditioned stimulus; ND = not determined; NR= not reported; EEG/EMG= electroencephalogram/electromyelogram; CNS = central nervous system.

*$p < 0.05$ vs. control exposure unless otherwise indicated; formaldehyde levels are underlined.

[a]Data presented as percentage change from control, unless otherwise indicated.

[b]Formaldehyde levels in the study converted to mg/m^3 from ppm.

[c]Actual mean analytical concentrations achieved.

[d]2–4 days after discontinuing exposure, rats were given cocaine and evaluated for 2 hr (early withdrawal); an additional cocaine challenge and locomotor assessment were conducted 4–6 week later (late withdrawal).

[e]Formaldehyde levels in the study (converted to mg/m^3 from mg/L) represented the achieved analytical levels.

[f]Context = in the context the shock was delivered, rats receiving shock training vs. those not shocked were compared at 1 day after training; conditioned odor = comparison as in "context" 2 or 12 days after training except in a novel context and with the odor used for shock training (orange oil) present. Values and statistical analyses are compared against nonshocked rats within the same treatment group.

[g]Data were recorded for 6-hour periods beginning at dark phase for 24 hours; percentage change from air controls for each period is presented; air and formaldehyde groups were significantly different by two-way ANOVAs.

[h]Several weeks after treatment an orange oil odor (CS) was either Paired (with CS presentation) or Unpaired (separately and randomly from CS presentation) with footshocks, then testing performed over subsequent days

[i]CS presented in a second, completely novel context.

[j]Formaldehyde levels in the study (converted to mg/m^3 from ppm) were interpreted from the methods to represent the achieved mean analytical levels, although the range of measured concentrations was not reported.

[k]Wet-dog shake, a possible pro-convulsive sign, is a shuddering motion in rodents that can be induced pharmacologically with agents that affect glutamatergic and/or serotonergic signaling.

[l]Seizures were induced by injection of pentylenetetrazole.

Tests of general motor-related behaviors

This section encompasses a range of behavioral tests examining general locomotion (without pharmacological manipulation) as the output. These tests span a range of test environments and testing conditions, and the observed responses often involve contributions from multiple specific behavioral processes (e.g., motor function, anxiety, arousal, olfaction, acclimation

to the test environment, etc.) that can be difficult to disentangle. Motor-related tests designed to examine learning and memory processes are discussed separately in the next section.

Animal studies that included protocols of sufficient duration to specifically assess changes in motor function (Sorg et al., 1998; Sorg et al., 2001b) either did not observe effects of formaldehyde inhalation alone (Sorg et al., 1998) or were complicated by irritant effects when tested during exposure (Sorg et al., 2001b). However, open field activity testing following formaldehyde exposure revealed decreased ambulatory activity in rats and mice, as well as elevated anxiety and reduced habituation to the test environment in nearly all available studies (Usanmaz et al., 2002; Sheveleva, 1971; Malek et al., 2003a, b, 2004; Boja et al., 1985) (see Table 3-48). Open field testing is a commonplace test that can be standardized and reproducible (Broadhurst, 1969), but which often involves a somewhat arbitrary interpretation of different behavioral features. The short testing duration used in open field tests (typically 3–5 minutes) is not of sufficient length to accurately assess motor function, and the results are also affected by the initial anxiety of the animals to the novel test environment. Thus, with these tests (which vary by laboratory), it can be difficult to separate changes in motor function and interpretation of olfactory and visual cues from changes due to exploration of a novel environment and anxiety due to open spaces and bright light (e.g., increased anxiety correlates with decreased ambulation in these tests). A second test (typically 24 hours later) measures the level of habituation or learned familiarity to the test environment. Due primarily to prominent exposure-quality issues (Sheveleva, 1971; Malek et al., 2003a, b, 2004) or significant study design concerns (Usanmaz et al., 2002; Sheveleva, 1971; Boja et al., 1985), all of the data suggesting effects of exposure on motor-related behaviors are derived from *low* confidence studies (see Appendix A.5.7), limiting their interpretability.

Consistent decreases in open field locomotor activity in male mice and rats of both sexes were observed at formaldehyde concentrations as low as 0.123 mg/m^3 (with rats exhibiting enhanced sensitivity) when assessed shortly after a single, acute formaldehyde exposure (Malek et al., 2003a, b, 2004) or after exposure for 1 week (Li et al., 2016); however, these studies employed formalin exposures. From the current studies it remains unclear whether these changes persist more than a few hours after exposure, noting that motor activity testing (not open field tests) did not reveal changes several weeks after exposure (Sorg et al., 1998). A portion of this immediate response in male mice may be due to increased anxiety, as decreases in crossed inner squares occurred at notably lower levels than decreases in crossed peripheral squares (anxious animals tend to spend less time in the open and bright areas at the center of the field), suggesting an elevated stress response after acute exposure (Malek et al., 2004); however, this increased anxiety was not confirmed in a second, short-term study (Li et al., 2016), which actually reported evidence of a decrease in anxiety in both open field and elevated plus maze tests at 1.23 mg/m^3. Although, no changes were observed at 2.46 mg/m^3 and changes in plus maze activity were not observed in rats that were similarly exposed (Sorg et al., 1998). Perhaps relatedly, short-term exposure of mice to ≥1 mg/m^3 resulted in dose-dependent increases in immobility time in the forced swim test (Li et al.,

2016), a stress-related test of "behavioral despair" (Porsolt et al., 1977). When habituation to the open field was tested 24 hours after exposure, formaldehyde-treated rats and mice did not demonstrate the same degree of habituation as control animals (Malek et al., 2003a, 2004). In male rodents, the degree of habituation was reduced compared to controls. In contrast, formaldehyde-treated female rats demonstrated robust increases (50–150%) in activity at all formaldehyde exposure levels (≥1.23 mg/m^3), suggesting not only reduced habituation, but also delayed hyperactivity in these animals. These mixed results suggest a general effect on behavior across a range of tests of general motor-related behaviors, but the specifics of this effect(s) remain difficult to interpret and require clarification in studies with better-controlled formaldehyde exposures.

A serious concern that changes may be due to irritation and related phenomena (e.g., reflex bradypnea; distractibility) is raised for three of the studies which evaluated behaviors during or immediately after exposure to formaldehyde at concentrations expected to cause irritation (Usanmaz et al., 2002; Boja et al., 1985). Decreased activity from 0 to 24 hours after exposure to 6.15 mg/m^3 formaldehyde was reported using a minimally informative protocol developed for observations of rat pups (Boja et al., 1985), with activity defined as the percentage of time "active" (i.e., not sleeping or immobile). Consistent with the pattern of alterations to habituation reported by (Malek et al., 2003a, 2004), after several days of daily exposure and activity testing, vertical activity measured during exposure to 2.46 mg/m^3 formaldehyde was depressed in male rats (on exposure days 12–20) and increased in female rats (on exposure days 5 and 20), as compared to controls (Sorg et al., 2001b). Usanmaz et al. (2002) noted unexplainable formaldehyde sensitivity (gastrointestinal impairment and decreased weight gain), causing them to discontinue the study, at exposures as low as 2.5 mg/m^3 for 3 weeks, which would be expected to confound their findings of decreased activity. Owing primarily to the timing of the behavioral tests, none of the observed changes in activity can be clearly attributed to formaldehyde-induced effects on the nervous system.

Reduced spontaneous mobility at PND 30 was observed in pups exposed in utero to 0.492 or 4.92 mg/m^3 (Sheveleva, 1971). In contrast, concentration-related increases in mobility were observed in these pups at PND 60 (an increased level of spontaneous mobility was also observed in dams at 4.92 mg/m^3), with the female pups exhibiting enhanced sensitivity. Increases in activity which persist into adulthood following developmental exposure are of concern. However, the methodology was insufficiently described and the significance of these formaldehyde-induced, bidirectional changes in the activity of young animals, which were dependent either on the delay between exposure and testing or the postnatal age at testing, is unclear.

Overall, the data from basic tests of motor-related behaviors suggest an effect in formaldehyde-exposed rodents. This response may be short lived, and, at least in open field tests, rats seem to be more sensitive to changes following formaldehyde exposure than mice (which would be consistent with the known toxicokinetic differences across species; see Appendix C.1) and females seem to exhibit a different pattern of responses than their male counterparts. Somewhat

differing results across some of the studies, particularly in tests other than open field activity (i.e., elevated plus maze and forced swim test), together present a complicated picture of these potential effect(s). More importantly, however, no studies using methanol-free formaldehyde and other appropriate methodology were available to clarify and confirm the findings of behavioral changes from this set of *low* confidence studies.

Table 3-48.Tests of motor-related behaviors in experimental animal studies

Reference and study design	Results[a] and exposure levels
Medium confidence (activity); *low* confidence (elevated plus maze)	
Reference: Sorg et al. (1998) Rat (Sprague-Dawley); *N* = 15–24 females 0 or 1.23 mg/m^{3b} [Actual[c]: 0 or 0.779–1.76] 7 or 20 days (5 days/week) Test article: Paraformaldehyde **Main limitations**: Description of methods incomplete; activity could be affected, and plus maze data are likely affected, by prior manipulations; total plus maze activity NR; blinding NR.	*No change in horizontal or vertical activity were noted following saline injections 2–4 days or 4–6 weeks after discontinuing formaldehyde exposures.* Note: activities were measured over a 2–hour period after allowing the rats to acclimate to the test environment. *No statistically significant changes in elevated plus maze performance were noted.* Note: percentage open arm entries and percentage time spent in open arms were decreased 24 and 39%, respectively after 7 days [p = 0.06 for percentage time]; percentage time in open arms was increased 21% after 20 days, but this did not approach statistical significance.
Low confidence	
Reference: Li et al. (2016) Mouse (Kunming: outbred Swiss albino); *N* = 15 males 0, 1.23, or 2.46 mg/m^{3c} [Actual: levels confirmed] 7 days (2 hours/day) Test article: Formalin **Main limitations**: Formalin; blinding NR for tests other than forced swim; possible influence of multiple behavioral tests in the same animals.	**0 / 1.23 / 2.46** *Open Field Activity (2-hr postexposure):* Total Distance: 0 / −3.15 / −18.7* Total Crossings: 0 / −4.02 / −20.9* Percentage Center Time: 0 / 39.0* / −11.5 *Forced Swim (after plus maze):* Immobility Time: 0 / 42.3 / 87.6* **0 / 1.23 / 2.46** *Elevated Plus Maze (after open field):* Total Distance: 0 / 0.70 / −3.00 Number of Entries: 0 / −14.5 / −12.1 Percentage Open Arm Time: 0 / 20.9* / −4.33 Note: Statistically significant differences in body-weight gain were observed at 2.46 mg/m^3 (−3.7%, as compared to + 1.82% in controls).
Reference: Malek et al. (2003a) Rat (LEW.1K); *N* = 15/sex 0, 1.23, 3.08, or 6.15 mg/m^{3c} [Actual: 0, 1.24, 3.09, or 6.20] 2 hours Test article: Formalin **Main limitation**: Formalin. [Note: an excessive level of variability was noted for this study, possibly due to an erroneous indication of data as Mean ± SE in this study, in contrast to Mean ± SD in the other studies by (2003b, c, 2004).]	Males: **0 / 1.23 / 3.08 / 6.15**; Females: **0 / 1.23 / 3.08 / 6.15** *Open field activity and behaviors at 2 hours postexposure:* Locomotion: 0 / −63* / −22* / −41%* | 0 / −72* / −30* / −36%* Grooming: 0 / −47 / −23* / −34%* | 0 / 4 / −17* / −62%* Air sniffing: 0 / 103* / 118* / 104%* | 0 / 1 / −23* / 22%* Floor sniffing: 0 / 105* / 51* / 84% | 0 / −2 / 56 / 79% Wall climbing: 0 / −22* / −22* / −26%* | 0 / −8 / −14 / 16% Rearing: 0 / 28 / 32 / 2% | 0 / 58* / 74* / 42% Note: No changes in defecation. *Habituation to the open field at 26 hours postexposure (Trial 2/Trial 1[h]):* Locomotion: −80 / −44 / −35* / −21%* | −78 / 140* / 42* / 38%* Air sniffing: 161 / −31* / −13* / 12%* | 78 / 48* / 174* / 43% Climbing: 95 / −10* / −14* / 38%* | 73 / 118 / 105 / 46% Rearing: −14 / 6* / 9* / 24%* | 34 / 3 / 6* / −8% Note: No consistent changes in grooming, floor sniffing, or defecation.

<table>
<tr><th>Reference and study design</th><th>Results[a] and exposure levels</th></tr>
<tr><td>Reference: Malek et al. (2003b)
Rat (LEW.1K); N = 10/sex
0, 0.123, 0.615 or 6.15 mg/m^{3c}
[Actual: 0, 0.160, 0.590, or 6.37]
2 hours
Test article: Formalin
Main limitation: Formalin.</td><td>
<table>
<tr><th></th><th colspan="4">Males</th><th colspan="4">Females</th></tr>
<tr><th></th><th>0</th><th>0.123</th><th>0.615</th><th>6.15</th><th>0</th><th>0.123</th><th>0.615</th><th>6.15</th></tr>
<tr><td colspan="9">Open field activity and behaviors at 2 hours postexposure:</td></tr>
<tr><td>locomotion:</td><td>0</td><td>−17*</td><td>−48*</td><td>−65%*</td><td>0</td><td>−5</td><td>−19*</td><td>−39%*</td></tr>
<tr><td>Air sniffing:</td><td>0</td><td>8*</td><td>−22*</td><td>−55%*</td><td>0</td><td>21*</td><td>14*</td><td>−11%*</td></tr>
<tr><td>Floor sniffing:</td><td>0</td><td>−23*</td><td>−39*</td><td>−64%*</td><td>0</td><td>−5</td><td>−23*</td><td>−27%*</td></tr>
<tr><td>Wall climbing:</td><td>0</td><td>21*</td><td>−55*</td><td>−72%*</td><td>0</td><td>54*</td><td>−4</td><td>−34%*</td></tr>
<tr><td>Rearing:</td><td>0</td><td>−57*</td><td>−75*</td><td>−59%*</td><td>0</td><td>44*</td><td>−35*</td><td>−24%</td></tr>
</table>
Note: No consistent changes in grooming or defecation.
</td></tr>
<tr><td>Reference: Malek et al. (2004)
Mouse (AB); N = 20 Males
0, 1.35, 2.83 or 6.40 mg/m^{3c}
[Actual: 0, 1.37, 2.84, or 6.64]
2 hours
Test article: Formalin
Main limitation: Formalin.</td><td>
<table>
<tr><th></th><th colspan="4">Open field activity and behaviors at 2 hours postexposure:</th><th colspan="4">Habituation to the open field at 26 hours postexposure:</th></tr>
<tr><th></th><th colspan="4">2 hr (Percentage control)</th><th colspan="4">26 hr (Trial 2/Trial 1[h])</th></tr>
<tr><th></th><th>0</th><th>1.35</th><th>2.83</th><th>6.40</th><th>0</th><th>1.35</th><th>2.83</th><th>6.40</th></tr>
<tr><td>Crossed inner squares:</td><td>0</td><td>−26*</td><td>−38*</td><td>−53%*</td><td>−70</td><td>−62</td><td>−57</td><td>−40%</td></tr>
<tr><td>Crossed outer squares:</td><td>0</td><td>5</td><td>−12</td><td>−49%*</td><td>−24</td><td>−25</td><td>−10</td><td>41%</td></tr>
<tr><td>Total crossed squares:</td><td>0</td><td>−7</td><td>−22*</td><td>−51%*</td><td>−41</td><td>−36</td><td>−24</td><td>15%</td></tr>
<tr><td>Air sniffing:</td><td>0</td><td>11</td><td>−16*</td><td>−58%*</td><td>−29</td><td>−38</td><td>−23</td><td>52%</td></tr>
<tr><td>Floor sniffing:</td><td>0</td><td>26*</td><td>2</td><td>9%</td><td>3</td><td>−40*</td><td>−38*</td><td>−23%*</td></tr>
<tr><td>Grooming:</td><td>0</td><td>−11</td><td>−11</td><td>−18%</td><td>5</td><td>96*</td><td>45*</td><td>82%*</td></tr>
<tr><td>Rearing:</td><td>0</td><td>−22*</td><td>-37*</td><td>-44%*</td><td>3</td><td>−11*</td><td>8*</td><td>21%*</td></tr>
</table>
Note: No consistent changes in wall climbing or defecation.
</td></tr>
<tr><td>Reference: Usanmaz et al. (2002)
Mouse (Balb/C); N = 6 (sex NR)
0, 2.21, 3.94, 5.54, 7.87, 11.9, or 18.2 mg/m^{3}[j]: 3 hours
0 or 2.46 mg/m^{3}: 1 or 3 weeks
0, 2.46, or 3.94 mg/m^{3}: 2 weeks
Test article: Paraformaldehyde
Main limitations: Tested immediately after exposure; blinding NR.</td><td>
<table>
<tr><th></th><th>0</th><th>2.21</th><th>3.94</th><th>5.54</th><th>7.87</th><th>11.9</th><th>18.2</th></tr>
<tr><td colspan="8">Open field activity immediately after a 3-hour exposure:</td></tr>
<tr><td>Horizontal activity:</td><td>0</td><td>−10</td><td>−16</td><td>−28</td><td>−35*</td><td>−69*</td><td>−91%*</td></tr>
<tr><td>Vertical activity:</td><td>0</td><td>−26*</td><td>−43*</td><td>−48*</td><td>−48*</td><td>−83*</td><td>−88%*</td></tr>
</table>
Open field activity[k] and body-weight gain after 1- to 3-week exposures:
<table>
<tr><th></th><th colspan="2">1 week</th><th colspan="3">2 weeks</th><th colspan="2">3 weeks</th></tr>
<tr><th></th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>3.94</th><th>0</th><th>2.46</th></tr>
<tr><td>Horizontal activity:</td><td>0</td><td>−28%*</td><td>0</td><td>−3</td><td>−40%*</td><td>0</td><td>−23%</td></tr>
<tr><td>Vertical activity:</td><td>0</td><td>−37%*</td><td>0</td><td>−1</td><td>−44%*</td><td>0</td><td>−32%*</td></tr>
<tr><td>Body-weight gain:</td><td>0</td><td>33%</td><td>0</td><td>0</td><td>−150%*</td><td>0</td><td>−280%*</td></tr>
</table>
</td></tr>
<tr><td>Reference: Sorg et al. (2001b)
Rat (Sprague-Dawley); N = 7−8/sex
0 or 2.46 mg/m^{3c}
[Actual: not reported]
20 days (5 days/week)
Test article: Paraformaldehyde
Main limitations: Activity tested during exposure; description of methods incomplete.</td><td>Total vertical activity during formaldehyde exposure:
Males: ↓ at exposure days 12−20 (−25 to −55%*)
Females: ↑ at exposure days 5 (133%*) and 20 (98%*)</td></tr>
<tr><td>Reference: Boja et al. (1985)
Rat (Sprague Dawley); N = 8 males
0 or 6.15[b] mg/m^{3c}
[Actual[d]: not reported]
1−2 days (switching paradigm)
Test article: Paraformaldehyde
Main limitations: Tested immediately after exposure; uncommon protocol.</td><td>
Percentage time “active” versus “inactive”[e] during exposure relative to air controls:
<table>
<tr><th></th><th>at 30 min.</th><th>at 60 min.</th><th>at 120 min.</th></tr>
<tr><td>Day 1 HCHO (Day 1 exposed):</td><td>−34%*</td><td>−66%*</td><td>−77%*</td></tr>
<tr><td>Day 2 HCHO (Day 1 and 2 exposed):</td><td>−76%*</td><td>−70%*</td><td>24%</td></tr>
<tr><td>Day 2 HCHO (only Day 2 exposed):</td><td>−58%</td><td>−80%</td><td>122%</td></tr>
<tr><td>24h post HCHO (only Day 1 exposed):</td><td>−30%</td><td>−80%</td><td>72%[f]</td></tr>
</table>
Boja et al. (1985)
</td></tr>
</table>

Reference and study design	Results[a] and exposure levels						
Reference: Sheveleva (1971) Rat (Strain NR); *N* = 15/sex 0, 0.492, or 4.92 mg/m^3[i] [Actual: 0, 1.24, 3.09, or 6.20] GD 1–GD 19 Test article: Not reported **Main limitations**: Test article and endpoint evaluation details NR.		Males			Females		
		0	**0.492**	**4.92**	**0**	**0.492**	**4.92**
	Spontaneous mobility in offspring and dams:						
	at PND 30:	0	−48*	−2%	0	−36*	−44%*
	at PND 60:	0	16	32%	0	42	291%*
	in dams:	NA	NA	NA	0	−46	89%*

Organized by study confidence, then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: HCHO = formaldehyde; SE = standard error; SD = standard deviation; GD = gestational day; NR= not reported; PND = postnatal day.
*$p < 0.05$ vs. control exposure; formaldehyde levels are underlined.
[a]Data presented as percentage change from control, unless otherwise indicated.
[b]Additional exposure groups of 12.3 and 24.6 mg/m^3 were indicated, but data were not reported and thus, not included.
[c]Formaldehyde levels in the study converted to mg/m^3 from ppm.
[d]Actual mean analytical concentrations achieved.
[e]Active (e.g., grooming, eating, climbing, ambulating, etc.) versus inactive (i.e., immobile, sleeping).
[f]Statistical comparisons to air-air group not performed.
[g]Locomotion = crossed squares; M = changes were observed in males; F = changes were observed in females.
[h]Values presented as Trial 2 (26 hr) vs. Trial 1 (2 hr) performance in same group; * for comparisons within Trial 2.
[i]Formaldehyde levels in the study (converted to mg/m^3 from mg/L) represented the achieved analytical levels.
[j]Formaldehyde levels in the study (converted to mg/m^3 from ppm) were interpreted from the methods to represent the achieved mean analytical levels, although the range of measured concentrations was not reported.
[k]Open field activity in the short-term studies is inferred to have been conducted immediately following exposure.

Tests of learning and memory

Five studies have examined the effects of inhaled formaldehyde on learning and memory processes in experimental animals (see Table 3-49). All of the studies are expected to have significant coexposures due to the formaldehyde generation methods (see Appendix B.3.7), and thus, the effects cannot be attributed to formaldehyde inhalation alone. In addition, many of the dose-response relationships are difficult to interpret and the results are occasionally inconsistent.

Decreased performance in short-term spatial memory tasks following exposure to formaldehyde has been observed in rats across two *low* confidence studies from coauthors in the same research institute (Pitten et al., 2000; Malek et al., 2003c), with supportive, related findings from three *low* confidence mouse studies (Mei et al., 2016; LICM, 2008; Li et al., 2016). These testing paradigms involve components of memory, orientation, reward seeking, stress, olfactory and visual information processing, and motor function. In the rat studies, increased error rate and increased latency in a water maze were observed after short-term exposures to ≥0.123 mg/m^3 and ≥0.615 mg/m^3, respectively (Malek et al., 2003c), although the results were not entirely consistent across all trial days. Similarly, very brief (10-minute) formaldehyde exposures over a prolonged duration (90 days) resulted in an increased number of errors and longer running times in a land-based maze at ≥3.06 mg/m^3 (Pitten et al., 2000), with an increasing magnitude of change with increasing trial days, which suggests an additive effect of exposure. In general, excluding the latency measures reported by Malek et al. (2003c), all exposed rats were equally impaired across a broad range of exposures; no explanation for this lack of a dose-response relationship is presently

available. These observations are supported by potentially related findings in mice exposed for 1 week to similar levels of formaldehyde (i.e., 2.46 to 3 mg/m^3); specifically, exposed mice exhibited decreased performance in the Morris water maze (Mei et al., 2016) and decrements in a test of recognition memory, the novel object test (Li et al., 2016). However, it is difficult to attribute these decrements to formaldehyde exposure due to notable methodological limitations (e.g., the use of formalin and the lack of observer blinding for these nonautomated measures raise substantial concerns). In addition, the data from both studies suggest possible complicating effects on behaviors other than learning or memory in the mice exposed to formaldehyde [i.e., in Mei et al. (2016), exposed mice did not exhibit improved performance across training trials and swimming tracks suggest that they avoided the target quadrant completely during the probe trial; in Li et al. (2016), even in the absence of a novel object, exposed mice spent approximately half the time exploring objects during training than did controls]. Although vision and olfaction were not evaluated in these rodent studies, possible effects on these functions are not expected to influence performance in the studies by Malek et al. (2003c), Mei et al. (2016), and Li et al. (2016), or by Pitten et al. (2000), as assessments occurred 2–3 or 22 hours after exposure(s), respectively. In contrast, supportive observations in mice (LICM, 2008) are considered even less reliable due to the short, 30-minute delay before testing following exposure to formaldehyde and other potential contaminants (formaldehyde was released from wood baseboard) at levels that are likely to induce irritation-related responses.

In rats, the increases in maze latency are most likely reflective of the increased number of errors in treated animals as errors usually increase the distance traveled, and thus the time required, for completion of the trial. However, in the absence of data on path length or motor speed in all three of the maze-based studies, it is unclear whether hyperactivity of the formaldehyde-exposed animals may have been present (e.g., increased swim time and increased number of errors due to exposed animals swimming faster in circular or back-and-forth patterns). In the study by Malek et al. (2003c), increased swim speed is indeed evident at 0.123 mg/m^3 in females: despite making approximately four more errors than control rats on trial days 4, 5, and 8, they still had significantly shorter swimming times. Recovery following exposure was only assessed by Pitten et al. (2000), who observed that performance was still impaired 4 weeks after exposures had ended.

While the study authors interpreted these results to suggest deficits in the retention of a previously learned task or in remembering a previously explored object, these studies had significant methodological shortcomings. Thus, sole attribution of the decreases in performance to formaldehyde-induced impairment, and specifically to impairment of memory or orientation, cannot be concluded. Although two developmental studies evaluating learning and memory processes following formaldehyde exposure were identified (Senichenkova, 1991a; Liao et al., 2010), data from these studies were not considered useful for the purposes of hazard characterization (see Appendix B.3.7). Overall, while the available data suggest a potential effect on

behavior in tests of learning and memory, which may or may not reflect effects on those specific cognitive processes, no studies using methanol-free formaldehyde and other more appropriate methodology were available to clarify and confirm the findings of behavioral changes from this set of *low* confidence studies.

Table 3-49. Tests of learning and memory in experimental animal studies

Reference and study design	Results (as indicated) and exposure levels
Low confidence	
Reference: Li et al. (2016) Mouse (Kunming: outbred Swiss albino); *N* = 15 males 0, 1.23, or 2.46 mg/m^3[a] [Actual: levels confirmed] 7 days (2 hours/day) Test article: Formalin **Main limitations**: Formalin; blinding NR; possible influence of multiple behavioral tests performed in the same animals.	**0 / 1.23 / 2.46** *Novel Object Training and Testing (~ 2 days postexposure):* Training exploration (time ± SEM) of Left identical object: 94 ± 14 / 99 ± 25 / 55 ± 10 Training exploration (time ± SEM) of Right identical object: 98 ± 20 / 88 ± 23 / 51 ± 9 Familiar object exploration (seconds) 24-hr posttraining: 69.8 / 47.0, / 61.8 Novel object exploration (seconds) 24-hr posttraining (*p < 0.05 versus familiar object exploration time): 149* / 103* / 41.6 Discrimination Index [(novel object time ÷ total time) − (familiar object time ÷ total time) × 100]: 43.3 / 32.7 / −12.0* Notes: Statistically significant differences in body-weight gain were observed at 2.46 mg/m^3 (−3.7%, as compared to + 1.82% in controls). The study authors did not provide comparisons of total exploratory activity (Left + Right object) during training.
Reference: Mei et al. (2016) Mouse (Balb/c); *N* = 8 males 0 or 3 mg/m^3[a] [Actual: confirmed, 3.04 ± 0.13 mg/m^3] 7 days (8 hours/day) Test article: Formalin **Main limitations**: Formalin; blinding NR; details of behavioral protocols NR.	*Training trials escape latency (sec.; *p < 0.05: Dunnett's post hoc tests on ANOVA)*[e]: **Control / 3 mg/m^3** Day 1: 58.2 / 56.7 Day 2: 55.4 / 55.0 Day 3: 55.7 / 52.2 Day 4: 49.4 / 51.4 Day 5: 38.0 / 52.1* Day 6: 36.3 / 50.4* Day 7: 33.1 / 50.7* *Probe trial test performance on Day 8*[e]*:* **Control / 3 mg/m^3** Mean (+ SE) swim distance (cm) in target quadrant: 316 (± 42) / 154* (± 16) Mean (+ SE) time (sec) in target quadrant: 27.5 (± 3.4) / 10.0* (± 0.9)
Reference: LICM (2008) Mouse (Kun Ming: outbred Swiss albino); *N* = 5 males 0, 1, or 3 mg/m^3 [Actual[a]: 0.020, 0.990, or 3.03] 7 days beginning at ~PND 42 Test article: Wood baseboard **Main limitations**: Undefined mixture exposure; possible impact of irritation.	**0 / 1 / 3** *Escape latency across training trial days in the Morris water maze*[b]*:* Latency (percentage from control for averaged trial days): 0 / 32 / 74%*[c] Note: Magnitude of change was unrelated to duration of exposure. *Performance during probe trial test:* Time spent in the target quadrant (percentage from controls): 0 / −19 / −41% Note: Only controls spent significantly more time in the target quadrant.
Reference: Malek et al. (2003c) Rat (LEW.1K); *N* = 15/sex 0, 0.123, 0.615, or 6.64 mg/m^3[d] 10 days Test article: Formalin **Main limitations**: Formalin; protocol deficiencies, including blinding NR.	*Latency and number of errors in a water maze:* Maze errors (as #): Males **0 / .12 / .62 / 6.6**; Females **0 / .12 / .62 / 6.6** Swim time (as percentage control): Males **0 / .12 / .62 / 6.6**; Females **0 / .12 / .62 / 6.6** Day 1: 7 / 8 / 8 / 8; 8 / 7 / 8 / 8; 0 / −5 / −8* / 0; 0 / −7* / −6* / −5* Day 2: 6 / 7 / 6 / 6; 8 / 7* / 8 / 6*; 0 / −1 / 3 / 8*; 0 / −4 / −2 / 4* Day 3: 5 / 5 / 6* / 7*; 4 / 6* / 7* / 8*; 0 / −2 / 14* / 4; 0 / 4 / 8* / −2 Day 4: 2 / 5* / 5* / 6*; 1 / 6* / 5* / 6*; 0 / −11 / 29* / 14*; 0 / −24* / 16* / 14*

Reference and study design	Results (as indicated) and exposure levels
	Day 5: 1 4* 3* 5* | 1 4* 4* 5* | 0 −11 −2 23* | 0 −13* −9 −1 Day 6: 1 5* 4* 5* | 0 5* 5* 5* | 0 6 37* 111* | 0 −2 17* 88* Day 7: 0 5* 4* 5* | 0 5* 4* 5* | 0 6 38* 94* | 0 12* 11* 62* Day 8: 0 3* 3* 3* | 0 4* 3* 3* | 0 −3 −8 41* | 0 −20* −8 15* Day 9: 0 3* 3* 3* | 0 3* 3* 4* | 0 3 17* 64* | 0 18* 11* 46* Day 10: 0 3* 2* 3* | 0 3* 2* 3* | 0 −3 21* 73* | 0 15 17* 49*
Reference: Pitten et al. (2000) Rat (Wistar); *N* = 5–8/sex[f] 0, 3.06, or 5.55 mg/m^3[d] 90 days (Note: only 10 minutes/day exposures) Test article: Formalin **Main limitation**: Formalin.	*Latency and number of errors in a land maze:* Latency (as percentage control)[g]: **0** **3.06** **5.55** Errors (as percentage control): **0** **3.06** **5.55** Exposure week 0: 0 −6 4% | 0 −39 −7% Exposure week 2: 0 8 21% | ND ND ND Exposure week 4: 0 30 51% | 0 70 91% Exposure week 6: 0 48 76% | ND ND ND Exposure week 8: 0 75* 113%* | 0 116 112% Exposure week 10: 0 94* 143%* | ND ND ND Exposure week 12: 0 128* 185%* | 0 153* 184%* 2 weeks postexposure: 0 168* 241%* | ND ND ND 4 weeks postexposure: 0 215* 303%* | 0 72 89% *No CNS pathology or changes in body weight were observed.*

Organized by study confidence, then descending publication year. Results from low confidence studies are shaded; these findings are considered less reliable.
Abbreviations: SEM = standard error of the mean; PND = postnatal day; ND = not detected.
*p < 0.05 vs. control exposure (unless otherwise indicated); formaldehyde levels are underlined.
[a]Actual mean analytical concentrations achieved.
[b]Morris water maze: Four trials/day during training; Probe trial involved removal of the platform on Day 7.
[c]Significant differences between the 0 and 3 mg/m^3 groups by multiple comparison testing (LICM, 2008).
[d]Formaldehyde levels in the study (converted to mg/m^3 from ppm) represented the achieved analytical levels.
[e]Data digitized using Grab It!™, Datatrend Software.
[f]Male and female data were pooled for comparisons; no differences between sexes were noted.
[g]Average seconds estimated from points along the fitted linear regression curves presented by Pitten et al. (2000).

Summary of Animal Evidence Synthesis Judgments

Neurobehavioral Tests

The following factors were influential to the synthesis judgment that the animal studies provide *slight* evidence of formaldehyde exposure-induced neurobehavioral effects, including effects on neural sensitization, motor-related behaviors, and learning and memory.

Neural Sensitization

- *Consistency and Study Confidence*: One medium confidence and five low confidence studies reported effects in rats and mice; however, the possible influence of indirect effects from altered olfaction, irritation, or stress responses specific to the animal exposure scenarios cannot be ruled out.
- *Strength and Precision:* Effects persisted weeks after exposure in several studies.
- *Dose-Response*: Some studies reported increased effects with increasing exposure duration.

- *Biological Plausibility*: Although no MOA was identified, several well-conducted studies show molecular and neurochemical changes in the brain, and changes to circulating stress hormones, at formaldehyde levels lower than those causing sensitization, providing some plausibility for the observed apical effects.

Motor-related Behaviors

- *Consistency and Study Confidence*: Eight *low* confidence studies in rats and mice were consistent in showing some change in motor-related behaviors; however, all studies had exposure deficiencies or were complicated by potential irritation-related confounding and one *medium* confidence study did not observe effects.
- *Strength and Precision:* Effects persisted weeks after exposure in one study.
- *Dose-Response*: Most responses were dose-dependent.
- *Biological Plausibility*: Although no MOA was identified, several well-conducted studies show molecular and neurochemical changes in the brain at formaldehyde levels lower than those affecting these behaviors, providing some plausibility for the observed apical effects.

Learning and Memory

- *Consistency and Study Confidence*: Effects were consistently observed across five *low* confidence studies in rats and mice; however, all studies had exposure deficiencies, and most did not evaluate effects on motor activity as a potential contributing factor.
- *Strength and Precision:* Effects persisted weeks after exposure in one study.
- *Dose-Response*: Responses were dose-dependent in two studies.
- *Biological Plausibility*: Although no MOA was identified, several well-conducted studies show molecular and neurochemical changes in the brain at formaldehyde levels lower than those affecting these behaviors, providing some plausibility for the observed apical effects.

Nervous System Disease

No informative animal studies related to nervous system disease were identified (*indeterminate* animal evidence).

Developmental Neurotoxicity

The following factors were influential to the synthesis judgment that the animal neuropathology studies provide *slight* evidence of formaldehyde exposure-induced developmental neurotoxicity.

- *Consistency and Study Confidence*: One *medium* confidence study (in two publications) and one *low* confidence study reported developmental neuropathology. Certainty is reduced as all studies were conducted in the same laboratory and only at high formaldehyde levels (>7 mg/m^3). Small sample size and risk of bias from potential litter effects increase uncertainty.
- *Strength and Precision*: Toxicity persisted well after exposure, suggesting severe effects.
- *Dose-Response*: Magnitude generally increased with formaldehyde exposure level.

- *Biological Plausibility*: Although no MOA was identified, several well-conducted studies show molecular and neurochemical changes in relevant brain regions, providing some plausibility for the observed apical effects.

Evidence on Mode of Action

Little mode of action (MOA) information regarding potential nervous system effects following formaldehyde inhalation is available. To date, there are no definitive data supporting a specific mechanism for effects on nervous system structure or function. As appreciable amounts of formaldehyde are not expected to reach the systemic circulation or CNS to elicit direct effects, any potential mechanisms would need to be indirect. Thus, this section focuses on mechanisms that might secondarily result from alterations to the respiratory system (see Appendix C.7). As such, only data from formaldehyde inhalation studies are discussed, and confidence in the findings based on individual study evaluations is emphasized (see Appendix B.3.7). Although none has been confirmed experimentally, several biologically plausible, but speculative sequences of mechanistic changes that might support indirect effects can be hypothesized based on the available formaldehyde-specific data, including:

1) Repeated activation of sensory nerves (e.g., trigeminal, vagal) causing sensitization or neurogenic inflammation leading secondarily to effects on neuronal populations unrelated to pain and irritation pathways—based primarily on three *medium* (Kulle and Cooper, 1975; Fujimaki et al., 2004b; Ahmed et al., 2007) and one *low* confidence (Tsukahara et al., 2006) studies.

Repeated stimulation of sensory nerve fibers relaying information related to formaldehyde exposure to neuronal nuclei might eventually lead, indirectly, to lasting changes in centrally located neurons or soluble factors; however, specific data assessing this possibility, and the downstream consequences of such potential changes, remain unexamined. Formaldehyde inhalation has been shown to increase the electrical activity of trigeminal nasal afferents at concentrations below 1 mg/m^3 (Kulle and Cooper, 1975), which appears to cause neurogenic inflammation, a process whereby stimulation of sensory nerve endings causes localized (e.g., into airway tissue) release of neuropeptides (e.g., the tachykinin, substance P) that elicit local inflammatory responses (see discussion in Section 3.2.1). In addition to the "axon reflex" that can be induced upon sensory nerve stimulation (causing a localized release of factors), if the stimulus is of sufficient intensity or duration, signaling along ascending pathways from these afferents can continue, and eventually might lead to central sensitization where the excitability or responsiveness of afferent nerve fibers is enhanced (Woolf and Salter, 2000).

While changes in neuronal nuclei associated with ascending pathways related to pain and irritation signals seems likely following formaldehyde inhalation, there are no data or hypotheses available to inform how this might indirectly affect other neuronal nuclei. Regardless of the unexplainable connection between sensory nerve stimulation and changes in presumably unrelated

neuronal nuclei, hippocampal neurochemical changes which appear to be related to neurogenic inflammation, were observed in the absence of neuronal injury in a series of subchronic formaldehyde inhalation studies by Fujimaki and colleagues at formaldehyde levels as low as 0.1 mg/m^3 (Tsukahara et al., 2006; Fujimaki et al., 2004a; Ahmed et al., 2007). Importantly, these effects were generally only observed after stimulation with foreign materials known to cause an allergic response. Although the evidence related to potential neurogenic inflammation has been primarily observed in the airways, some factors released as a result of this process can be long-lived, and receptors for these upregulated cytokines and neuropeptides, including substance P, are prevalent throughout the CNS (Douglas et al., 2008). These data suggest the possibility that sensory nerve stimulation of sufficient duration and intensity, perhaps particularly in allergic individuals, might eventually result in lasting changes in CNS regions that regulate behaviors unrelated to pain or irritation responses. However, dose-response relationships for the observed mechanistic changes were unclear and data are not available to inform some of the essential logical connections that would be necessary to connect peripheral stimulation to these central changes. An additional uncertainty with this hypothesized relationship is a lack of understanding whether and to what extend this potential mechanism might be involved following chronic exposure. For example, although another respiratory irritant, capsaicin, also causes neurogenic inflammation, no neurogenic inflammatory response to subsequent stimuli is observed following long-term exposure to capsaicin because tachykinins become depleted from sensory neurons (Kashiba et al., 1997; Cadieux et al., 1986). Further, no data are available to inform human relevance, and some suggest responses might differ across species (e.g., distribution of substance P receptors in the brain can differ across species (Rigby et al., 2005)).

2) Neuronal activation following stimulation of the olfactory epithelium leading, indirectly, to alterations in neuronal targets unrelated to olfaction or, directly, to alterations in olfactory-dependent behaviors—based primarily on two *medium* (Hayashi et al., 2004; Boja et al., 1985) and one *low* confidence (Zhang et al., 2014) study.

Formaldehyde is not only a chemical irritant, but also an odorant, and its odor is typically detectable at lower levels than those causing irritation. Repeated and prolonged stimulation of neuronal olfactory receptors in the nasal epithelium at posterior regions of the upper respiratory tract (URT) might affect neurons along ascending pathways related to olfaction; however, similar to the hypothesis presented above, no data exist to describe how such changes could indirectly affect neurons or neuronal regions unassociated with olfaction. Hayashi et al. (2004) reported that subchronic, but not acute, formaldehyde exposure increases the activity of periglomerular (PG) cells in the main olfactory bulb (OB). Increases in the number of tyrosine hydroxylase (TH)$^+$ PG cells were observed at ≥0.1mg/m^3, with no differences in PG cell number or size of the OB (indicating increased TH synthesis in TH$^-$ PG cells rather than new cell formation). These changes might be related to observed decreases in the synapse protein, SNAP25, in the OB after periodic exposure (twice daily 30-minute exposures for 14 days) to high levels of formaldehyde (Zhang et al., 2014),

although these latter results are interpreted with *low* confidence. The results in Hayashi et al. (2004) appear to highlight sensory-induced adaptive properties of the OB in relation to dopaminergic function (TH is an essential enzyme for dopamine synthesis). OB dopamine affects odor detection and can affect odor-related behaviors (e.g., impaired learning was observed with increased dopamine D2 receptor signaling by Escanilla et al. (2009)). Thus, it is considered plausible that formaldehyde exposure could modify rodent behaviors with an olfactory component (e.g., motor-related behaviors; learning and memory in land maze tests); however, the potential for human behaviors, which are far less reliant on odorant signals, to be significantly impacted is unlikely.

It is unknown whether the adaptive changes observed in OB neurons result in alterations in neural circuitry. To date, no electrophysiological experiments have been conducted to specifically address the potential for an association between formaldehyde exposure and CNS electrophysiological changes. From the OB, olfactory signals are typically conveyed to higher order neurons, including those in the amygdala, hypothalamus, and olfactory areas of the entorhinal and piriform cortex. Possibly in relation to this, there is some suggestion of altered dopaminergic or serotonergic signaling in the hypothalamus with high-level formaldehyde exposures [6.15 mg/m^3; (Boja et al., 1985)], but these changes (increased dopamine and 5-HIAA, a serotonin metabolite) were only evaluated acutely following exposure, have not been linked to behavioral changes, and contrast somewhat with *s*uggestive observations of decreases in TH-positive cells across several brain regions at lower levels (Li et al., 2016). In addition, it remains speculative to infer that changes in olfaction-related ascending pathways after formaldehyde exposure might modify neural cell populations that are likely to be unrelated to those specific olfactory neuronal circuits. Overall, the cascade of events surrounding these adaptive changes remains unknown.

3) Altered hypothalamus-pituitary-adrenal gland (HPA) axis signaling (possibly linked to events above) causing persistent, stress-induced changes in behaviors—based primarily on two *medium* confidence studies (Sorg et al., 2001a; Sari et al., 2004).

Stress can be a strong modifier of behavior, particularly at early lifestages. (Sorg et al., 1996; Sorg et al., 2001a) have suggested that behavioral sensitization to formaldehyde may be linked to alterations in HPA axis control of corticosterone or sensitization of limbic circuitry following repeated exposure. In support of this hypothesis, elevated numbers of corticotropin-releasing hormone $(CRH)^+$ neurons in the hypothalamus (at 0.49 mg/m^3) and adrenocorticotropic hormone $(ACTH)^+$ cells in the pituitary gland (at 0.1 mg/m^3) were observed after subchronic formaldehyde exposure (Sari et al., 2004), while increased serum corticosterone (at 0.86 mg/m^3) was evident after exposure for only 4 weeks (Sorg et al., 2001a). These findings may be related to evidence suggesting depressed hippocampal glucocorticoid responses at 2.46 mg/m^3 from a single short-term (7 day), *low* confidence study (Li et al., 2016). CRH and ACTH represent precursor steps in the release of glucocorticoids into the circulation following HPA axis stimulation, and corticosterone is the rodent glucocorticoid equivalent of cortisol in humans. Reported disruptions

in sleep behavior [observed at 2.46 mg/m^3 formaldehyde by (Sorg et al., 2001b)] may also be linked to HPA axis dysfunction (Buckley and Schatzberg, 2005). In addition to highlighting the potential for formaldehyde-induced effects on allergy-related responses to impact the HPA axis, Sari et al. (2004) hypothesized that these stress-related responses might have resulted from neural sensitization via amplification of CNS circuits with repeated exposure; however, as previously mentioned, no well-conducted formaldehyde inhalation studies assessing electrophysiological endpoints were identified. Although formaldehyde exposure appears to be correlated with HPA axis-associated changes, no studies describe exactly how these CNS-regulated HPA responses could be modified by formaldehyde, highlighting a critical information gap. Importantly, the available studies are unable to rule out the possibility that the stress responses might be caused by the animal exposure-specific phenomenon of "inescapable stress" highlighted in Sorg et al. (1996). The available studies have not fully examined the temporal profile of these changes (acute stress responses are not necessarily adverse), and no studies have demonstrated that formaldehyde-induced stress leads to persistent neurobehavioral changes, functional alterations (e.g., through impaired neurogenesis), or neuroanatomical changes.

4) Changes in neuronal health and function due to indirect CNS oxidative stress or excitatory changes (possibly linked to events described above)—based primarily on two *medium* (Songur et al., 2008; Ahmed et al., 2007) and three *low* confidence (Songur et al., 2003; Mei et al., 2016; LICM, 2008) studies.

Markers of oxidative stress in the CNS are commonly associated with altered neuronal health and behavior. Songur et al. (2008) hypothesized that formaldehyde exposure may cause persistent brain changes via oxidative damage. Although a linkage between altered redox balance and hippocampal neuropathology was not tested in the stereological studies from this laboratory (Sarsilmaz et al., 2007; Aslan et al., 2006), an earlier study (Songur et al., 2003) observed reversible upregulation of hippocampal heat shock protein 70, an oxidative stress-responsive protein. Several other studies using molecular endpoints also support that formaldehyde inhalation may disrupt brain oxidative stress responses (i.e., increased malondialdehyde and nitric oxide levels; decreased superoxide dismutase activity and glutathione levels), particularly in the cerebellum, following high-level formaldehyde exposures in juvenile rats [at 7.36–14.7 mg/m^3 in (Songur et al., 2008)] and adult mice [at ~3 mg/m^3 in Mei et al. (2016)]. Songur et al. (2008) observed effects that persisted up to 60 days post-exposure. Lower-level exposures (e.g., 0.123 mg/m^3) for up to 24 hours did not cause changes in brain 8-OHdG to dG ratios (Matsuoka et al., 2010). The evidence for oxidative stress in the brain could be related to prolonged increases in inflammatory mediators in the blood after formaldehyde exposure, including reactive oxygen species, hormones, or other factors (see Appendix C.7); however, this potential linkage has not been tested. Relatedly, changes in oxidative stress markers might reflect effects on excitatory neurotransmission. Specifically, acute formaldehyde inhalation has been shown to increase expression of NMDA receptor subunits (e.g., NR2B) in nasal tissue (Hester et al., 2003) and forebrain regions (LICM, 2008), while

subchronic exposure in rats sensitized to allergen increased NMDA receptor expression (Ahmed et al., 2007) but not protein levels (Tsukahara et al., 2006). However, the cause(s) and functional consequences of these reported molecular increases have not been examined. In general, an explanation for oxidative stress-related changes in the absence of systemic distribution of formaldehyde or very high formaldehyde exposure levels is unavailable, limiting the feasibility of this potential mechanism.

Overall, no MOA for potential formaldehyde-induced nervous system effects is available.

Summary of Inferences Regarding Mode of Action

No verified MOA exists for how formaldehyde could elicit CNS effects without systemic distribution; however, several lines of evidence exist to support the potential for indirect effects on the CNS.

Evidence Integration Summary

Numerous human and animal studies were available and, although multiple lines of evidence suggest that some concern for nervous system effects following formaldehyde inhalation is warranted, major deficiencies in study conduct were identified and the database is considered incomplete. No experimentally supported MOA is available to explain how formaldehyde inhalation could cause nervous system effects, although some potentially relevant mechanistic changes in the brain have been observed in well-conducted studies. Summary evaluations of the evidence for potential nervous system effects of formaldehyde inhalation exposure are provided in Table 3-50.

In human studies, evidence of an association between formaldehyde exposure and ALS was suggested across four studies in different populations by two separate groups of researchers. Positive associations observed in a large prospective study were somewhat corroborated by a few (but not most) comparisons in the other studies, noting that some associations were based on a very small number of cases or secondary analyses. However, three of the studies had uncertainties in the assignment of individual exposure to formaldehyde and two of the four did not observe a dose-response relationship when the data were stratified by estimated formaldehyde levels. In addition, the results were not corroborated in another study in a different population, which had greater certainty in individual exposure assessments. Based on these uncertainties, the currently available human evidence is interpreted as *slight*. Importantly, however, the unexpected nature of the observed associations between formaldehyde exposure and this rare and fatal disease across a growing number of studies (the first association was reported in 2009, with some corroborating evidence in 2015 and 2016) identifies an urgent need for additional research. As no experimental animal or mechanistic studies specific to this effect were identified (i.e., *indeterminate*), overall, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause the fatal human disease, ALS, but additional study is needed for a stronger judgment. This is primarily based on epidemiological studies in occupational settings (presumably higher levels of exposure); however, there were notable uncertainties in the studies' exposure assessments.

Although numerous studies reported changes in behavior following formaldehyde exposure, the evidence was not considered adequate to support a causal hazard conclusion, as it was primarily based on rodent studies with notable methodological limitations, with more limited supporting data from studies in humans. Effects in learning and memory tests, and performance in tests of motor-related behaviors, were relatively consistent across the available animal data, and several human studies reported coherent, but more marginal, changes in related tests. However, the available experiments had significant methodological deficiencies and, overall, the data were not attributable to formaldehyde alone. Based on the methodological limitations of the available studies, both the human and animal evidence for effects in learning and memory tests, and on motor-related behaviors, is considered *slight*. Although no established MOA exists for changes in these behaviors, several well-conducted studies reporting molecular and structural effects in relevant brain regions (e.g., limbic structures and cerebellum) provide some biological plausibility for these effects. Taken together, it was judged that the **evidence suggests**, but is not sufficient to infer, that formaldehyde exposure might cause these potential behavioral effects.

Somewhat separate from the other reported behavioral effects, formaldehyde inhalation in rodents was also reported to be associated with sensitization-related changes in behavior. While several animal studies of varying quality observed amplified behavioral responses after formaldehyde exposure, interpretation of the results is unclear. Additional data are needed to rule out any potential influence from factors other than formaldehyde exposure. No human studies were available to inform this endpoint (i.e., *indeterminate*). In addition, although some biological plausibility is provided by neurochemical and hormonal changes that may be consistent with such effects, without mechanistic information to verify that formaldehyde exposure alone resulted in these effects (e.g., supporting a reasonable MOA or ruling out alternative explanations), the animal findings are considered *slight***.** As uncertainties also exist regarding the relevance of these tests to human exposure scenarios, based on the data overall, it was judged that the **evidence suggests** that formaldehyde might cause neural sensitization-related behavioral changes.

Thus, based on the available database of studies, it was concluded that the available **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause behavioral effects. The primary support for this conclusion is from *low* confidence studies in experimental animals, many of which reported effects at ≤1 mg/m^3. Given that this judgment relates to multiple manifestations of potential behavioral toxicity (i.e., learning and memory; motor- or anxiety-related activity; and neural sensitization), with some findings reported at low-exposure levels, this represents a significant data gap.

Data from experimental animal studies also suggest that excessive formaldehyde inhalation (levels >7 mg/m^3) may cause developmental neurotoxicity. The evidence most informative to this potential health effect was a *medium* confidence study (i.e., two publications on the same experiment) examining neuropathological changes in rats; a few *low* confidence studies reporting somewhat equivocal evidence for developmental effects other than neuropathology did not

contribute. While the methods used in this study to evaluate developmental neuropathology were sensitive and designed to minimize bias, and the endpoint (persistently decreased neuron number) is adverse, relevant to humans, and without contradictory data, there were notable uncertainties introduced by the study design that warrant replication of the results. These include a very small sample size (n = 3 litters), as well as lack of control for potential litter effects. As some mechanistic changes in the hippocampus and related brain regions after developmental exposure have been reported in well-conducted studies, indirect effects of formaldehyde exposure on the CNS have some demonstrated plausibility. In the absence of confirmatory studies (e.g., in other species; by other laboratories; using more informative study designs), the evidence for effects in animals is considered *slight*. No studies in humans were available to inform developmental neurotoxicity (i.e., *indeterminate*). Overall, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause effects on the developing nervous system, primarily based on a set of neuropathology studies from the same laboratory. The primary support for this judgment is from animal studies of neuropathology following developmental exposure to >7 mg/m^3 of formaldehyde. Given the potential for children to be exposed to formaldehyde, this area represents a research need.

Overall, conclusive evidence of a nervous system health hazard in humans exposed to formaldehyde was not identified. Given that, across a number of studies, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple nervous system health effects in humans given sufficient exposure conditions[33] (see Table 3-50), and the general lack of comprehensive and rigorous experiments across the database, additional study is warranted.

[33] In addition, a single, cursory animal experiment on nociception was identified; this evidence was considered *indeterminate*.

Table 3-50. Evidence integration summary for effects of formaldehyde inhalation on nervous system disease, specifically amyotrophic lateral sclerosis

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Nervous System Disease: Amyotrophic Lateral Sclerosis					
Human	*Consistency and Study Confidence*	• Strong effects in one *medium* confidence study, with more limited support from three other *medium* confidence studies (two studies from the same researchers). • Effects were from large, well-conducted longitudinal or retrospective studies.	• No association in one *medium* confidence study. • Uncertainty in individual exposure assessments and effect estimates based on a very small number of exposed cases.	*Slight* Some mixed but strong evidence for effects from a few occupational studies, but no dose- or duration-dependence was observed, plausibility for this effect is lacking, and important aspects of the studies' design introduce significant uncertainty.	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause increases in ALS incidence or mortality, given sufficient exposure conditions.[a] Primarily based on *slight* human evidence from occupational studies (presumably higher levels of exposure than in residential scenarios), generally with uncertain exposure assessments. *Potential susceptibility*: ALS disproportionately affects males, the focus of most of the available formaldehyde studies. (Note: Confirmatory effects in a *medium* confidence human study with a reasonable number of exposed cases and more certain measures of exposure
	Strength and Precision	• Large and precise association in one study.			
	Dose-Response		• Lack of exposure-response trends in studies with adequate data to examine the potential for such trends. • Inconsistency in associations with duration.		
	Coherence	N/A, no biologically related outcomes were identified			
	Biological Plausibility		• No MOA or relevant mechanistic studies in humans were identified, and this effect is surprising (i.e., plausibility is lacking) without systemic distribution.		
Animal	No available animal studies address this outcome.			*Indeterminate* No studies.	

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Other inferences	• *Relevance to humans*: The effect was observed in humans. • *MOA*: No verified MOA exists for how formaldehyde could elicit effects in motor neuron-related systems without systemic distribution. Additional study into the potential involvement of systemic oxidative stress (see also Appendix C.7) is warranted, given research interest in associations between elevated oxidative stress and ALS progression.				would be expected to adjust this to **evidence indicates** [likely]).

Abbreviations: ALS = amyotrophic lateral sclerosis; MOA = mode of action; CNS = central nervous system. N/A = indicates the factor was not applicable to (i.e., did not influence) the judgment drawn.

[a]Given the uncertainty in this judgment and the available evidence, this assessment does not attempt to define what might be the "sufficient exposure conditions" for developing this outcome.

Table 3-51. Evidence integration summary for effects of formaldehyde inhalation on developmental neurotoxicity

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Developmental Neurotoxicity					
Human	No available human studies address this outcome			*Indeterminate* No studies	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause developmental neurotoxicity, given sufficient exposure conditions.[a] Based primarily on *slight* animal evidence from one laboratory that exposed postnatal rats to >7 mg/m^3 formaldehyde. *Potential susceptibility*: The available data relate to postnatal exposure
Animal	*Consistency and Study Confidence*	• Effects in one *medium* confidence study (reported in two papers) and one *low* confidence study of the male rat hippocampus (less convincing evidence on other endpoints from other *low* confidence studies did not contribute). • No conflicting evidence (i.e., no comparable evaluations). • The outcome methods used minimize bias.	• The studies were conducted by a single laboratory, • Low sample size and analyses on a pup (not litter) basis complicate the interpretation of the results without independent replication. • Only tested formaldehyde levels >7 mg/m^3 (which complicates interpretation of human relevance).	*Slight* Concerning findings from a single study with methodological limitations that complicate interpretation	
	Strength and Precision	• Multiple indications of toxicity persisted 60 days after exposure,			

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
		suggesting the effect may be pronounced or permanent.			(other untested lifestages might exhibit even greater sensitivity). (Note: confirmatory effects in a *medium* confidence animal study from another laboratory or in another species, particularly one testing lower exposure levels, would be expected to adjust this to **evidence indicates** [likely].)
	Dose-Response	• Studies were not well-designed to inform dose-response patterns, but magnitude generally increased with exposure.			
	Coherence	N/A, narrow scope of evaluated outcome			
	Biological Plausibility	• Several animal studies with well-conducted exposures (including developmental exposure) demonstrate molecular and neurochemical changes in relevant (i.e., limbic) brain regions at formaldehyde levels lower than those causing pathology, providing plausibility.			
Other inferences	• *Relevance to humans*: Uncertainty regarding the relevance of the animal evidence exists, as the studies only tested high levels of formaldehyde expected to cause strong irritant effects that may not occur in humans; otherwise, rodent neuropathology is relevant to humans and is adverse. • *MOA*: No verified MOA exists for how formaldehyde could elicit CNS effects without systemic distribution, although evidence related to several indirect mechanisms of potential relevance was identified.				

Abbreviations: MOA = mode of action; CNS = central nervous system. N/A = indicates the factor was not applicable to (i.e., did not influence) the judgment drawn.
[a]Given the uncertainty in this judgment and the available evidence, this assessment does not attempt to define what might be the "sufficient exposure conditions" for developing this outcome.

Table 3-52. Evidence integration summary for effects of formaldehyde inhalation on neurobehavior

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Neural Sensitization					The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple manifestations of potential behavioral toxicity, given sufficient exposure conditions.[a] Primarily based on a number of *low* confidence studies in rats and mice, many of which observed effects after formaldehyde exposure ≤1 mg/m^3. (Notes: Confirmatory effects supporting neural sensitization in one *medium* confidence study from another laboratory alongside mechanistic confirmation of the human relevance and adversity of the animal findings would be expected to adjust this to **evidence indicates** [likely]; as the data for other types of behavioral effects are only based on
Human evidence	No available human studies address this outcome.			*Indeterminate* No studies	
Animal evidence	*Consistency and Study Confidence*	• Consistent effects in one *medium* confidence and five *low* confidence studies across two species (rats and mice). • No contrary results.	• Behaviors may be complicated by possible olfaction, irritation, and stress responses specific to animal exposure scenarios that were untested. • Primarily *low* confidence studies.	*Slight* Effects were observed in several, primarily low confidence, studies; however, nonspecific contributors to the responses cannot be reasonably ruled out.	
	Strength and Precision	• Some studies show that responses persist weeks after exposure, suggesting the effect might be pronounced.			
	Dose-Response	• Some studies show that responses increase with increasing exposure duration.			
	Coherence	N/A			
	Biological Plausibility	• Several studies with well-conducted exposures demonstrate molecular and neurochemical changes in the brain, and changes to circulating stress hormones, at formaldehyde levels comparable or lower than the levels causing sensitization; this provides support for plausibility.			

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Other inferences	• *Relevance to humans*: Translatability to human exposure scenarios and adversity in humans remains unclear, requiring further study. • *MOA*: No verified mechanism exists for how formaldehyde could elicit CNS effects without systemic distribution; however, several lines of evidence exist to support the potential for indirect effects on the CNS.				*low* confidence studies, it is expected that confirmatory effects of behavioral changes other than neural sensitization in multiple *medium* confidence studies would be needed to adjust this to **evidence indicates** [likely].) *Potential susceptibility*: Unknown, as well-conducted developmental studies of these effects were not identified.
Tests of Motor-related Behaviors					
Human evidence	*Consistency and Study Confidence*	• Effects in two *low* confidence studies and weak (near equivocal) effects in one *medium* confidence study. • Effects were observed across demographics and behavioral tests.	• Likely co-exposures were not well-evaluated, and data are primarily based on acute exposure. • No effect in one *low* confidence study.	*Slight*	
	Strength and Precision	N/A			
	Dose-Response		• Lack of dose-dependence.		
	Coherence	N/A			
	Biological Plausibility	No relevant human studies identified			
Animal evidence	*Consistency and Study Confidence*	• Effects in eight *low* confidence studies across laboratories in both sexes of rats and mice (multiple strains).	• No effect in one *medium* confidence study • All studies observing effects had test article deficiencies and/or were complicated by irritation-related responses, and few tests assessed a discrete function (e.g., motor activity).	*Slight*	

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
	Strength and Precision	• One study reported effects persisting for weeks, suggesting a pronounced effect.			
	Dose-Response	• Most responses were dose-dependent.			
	Coherence	N/A			
	Biological Plausibility	• Several studies with well-conducted exposures demonstrate molecular and neurochemical changes in the brain at formaldehyde levels comparable or lower than the levels causing the apical effects; this provides some support for plausibility.			
Other inferences	• *Relevance to humans*: The commonly used tests and the changes observed at levels not expected to induce irritation are considered relevant to humans and potentially are adverse. • *MOA*: No verified mechanism exists for how formaldehyde could elicit CNS effects without systemic distribution; however, several lines of evidence exist to support the potential for indirect effects on the CNS. • *Other*: The duration- and timing-dependence of these potential effects is unknown, as most data are from acute and short-term exposure of formaldehyde levels >7 mg/m^3 (high levels which further complicate interpretation).				
Tests of Learning or Memory					
Human evidence	*Consistency and Study Confidence*	• Effects in three *low* confidence, independent studies.	• All were low confidence studies that had significant coexposures or poorly comparable groups • No effect in one *low* confidence study.	*Slight*	

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
	Strength and Precision	N/A			
	Dose-Response	• Effects were related to duration of exposure across studies.	• No dose-dependent effects were observed with controlled exposure.		
	Coherence	N/A			
	Biological Plausibility	No relevant human studies identified			
Animal evidence	*Consistency and Study Confidence*	• Effects in five *low* confidence studies from multiple research laboratories across various durations of exposure and in both sexes of rats and mice • No contrary results.	• All were *low* confidence studies that had test article deficiencies, and most did not evaluate motor activity as a contributing factor.	*Slight*	
	Strength and Precision	• Effect magnitude increased with repeated exposure and effects persisted weeks after exposure (in one subchronic study).			
	Dose-Response	• Effects were dose-dependent in two studies.			
	Coherence	N/A			
	Biological Plausibility	• Several studies with well-conducted exposures demonstrate molecular and neurochemical changes in the brain at formaldehyde levels comparable or lower than the levels causing the apical effects; this			

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
		provides some support for plausibility.			
Other inferences	• *Relevance to humans*: The commonly used tests and the changes observed at levels not expected to induce irritation are considered relevant to humans and potentially are adverse. • *MOA*: No verified mechanism exists for how formaldehyde could elicit CNS effects without systemic distribution; however, several lines of evidence exist to support the potential for indirect effects on the CNS. • *Other*: The duration- and timing-dependence of these potential effects is unknown, as most data are from acute and short-term exposure of formaldehyde levels >7 mg/m^3 (high levels which further complicate interpretation).				

Abbreviations: MOA = mode of action; CNS = central nervous system. N/A = indicates the factor was not applicable to (i.e., did not influence) the judgment drawn.

[a]Given the uncertainty in this judgment and the available evidence, this assessment does not attempt to define what might be the "sufficient exposure conditions" for developing this outcome. (i.e., neural sensitization, tests of motor-related behaviors, and tests of learning and memory), either individually or as encompassed by the broader category of neurobehavioral tests.

3.3.2. Developmental and Reproductive Toxicity

Studies in humans, and a number of animal studies have reported effects of inhaled formaldehyde on pre- and postnatal development and on the female and male reproductive systems. Three studies evaluated residential exposure during pregnancy and fetal and infant growth measures, including ultrasonographic biometric measures, birth weight and head circumference, and postnatal growth. The most common outcome reported by occupational epidemiology studies was an elevated spontaneous abortion risk in different industries, with strong associations seen in the highest exposure categories. Further, maternal, and paternal formaldehyde exposure was associated with decreased fecundity,[34] indicated by a longer time to achieve a pregnancy, in two studies of employees in the woodworking industry (out of a total set of three studies). The associations among female workers may reflect either toxicity to the reproductive system of the mother (ability to achieve and support the pregnancy) or the developing fetus. Together, the findings among women provide *moderate* evidence of developmental or female reproductive toxicity. In animal studies, there is *indeterminate* evidence for manifestations of developmental toxicity (i.e., decreased survival, decreased growth, or increased evidence of structural anomalies) or female reproductive toxicity (ovarian and uterine pathology, ovarian weight, and hormonal changes). All available studies were of *low* confidence, primarily due to exposure-quality concerns (i.e., the use of formalin, or an uncharacterized test substance).

Two studies of exposure to male workers from one research group provide *slight* evidence that formaldehyde exposure is associated with lower total and progressive sperm motility, and delayed fertility and spontaneous abortion. The epidemiological observations are supported by *robust* evidence from experimental studies in animals that used paraformaldehyde to expose the animals. Across this set of studies, coherent evidence for a range of effects on the male reproductive system was demonstrated, including quantitative histopathological effects in the testes and epididymides, decreased serum testosterone (T), decreased sperm count and motility, and increased sperm morphological abnormalities. However, limitations in the animal study database for male reproductive toxicity include a general lack of functional measures in the available studies and no studies that tested formaldehyde levels below 6 mg/m^3, warranting additional study.

Overall, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of developmental or female reproductive toxicity in humans, given sufficient exposure conditions. This conclusion is based on *moderate* evidence in observational studies finding increases in time-to-pregnancy (TTP) and spontaneous abortion risk among women with occupational formaldehyde exposures. The evidence in animals is *indeterminate*, and a plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde is lacking. Likewise, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of reproductive toxicity in men, given sufficient exposure conditions, based on *robust* evidence in animals that

[34]The capacity to conceive and deliver a baby.

presents a coherent array of adverse effects in two species testing formaldehyde concentrations >6 mg/g^3, and *slight* evidence from observational studies of occupational exposure, and no plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde. However, some support for indirect effects in rodents is provided by relevant mechanistic changes in male reproductive organs.

Human Studies

The observational studies of reproductive toxicity or pregnancy outcomes evaluated associations with exposure during pregnancy in three studies and with occupational exposure among cosmetologists, woodworkers, laboratory workers, and hospital staff. The evidence regarding TTP, spontaneous abortion, pre- and post-natal growth and other birth outcomes, and male reproductive toxicity was synthesized, and the studies summarized in Tables 3-53 through 3-56, ordered by the level of confidence in the study result (i.e., *high*, *medium,* or *low*) and then by publication date. Six of the studies that met the PECO criteria were considered *not informative* after evaluation (Stücker et al., 1993; Shumilina, 1975; Seitz and Baron, 1990; Saurel-Cubizolles et al., 1994; Ericson et al., 1984; Axelsson et al., 1984). The study evaluations are included in Appendix B.3.8.

Female Reproductive or Developmental Toxicity

Time to pregnancy and subfertility

TTP is a measure of fertility and has been characterized in terms of number of menstrual cycles that occurred prior to conception. TTP of greater than 12 months of unprotected intercourse is indicative of infertility ((Wilcox, 2010), p. 123). Increased TTP might result from potential effects on gametogenesis, transport, fertilization, migration, implantation, or survival of the embryo (Baird et al., 1986). Thus, the measure reflects a potential impact on multiple biological processes, possibly in both partners, and can be sensitive to the detection of events early during pregnancy that usually cannot be easily detected in population-based studies. Because it is evaluated in number of months or menstrual cycles, TTP is informative regarding exposures with impacts over shorter time periods (e.g., <1 year). TTP is not a measure of infertility as these studies only include women who became pregnant and had a live birth.

One *medium* confidence study (Taskinen et al., 1999) and one *low* confidence study (Zhu et al., 2005) were identified that evaluated effects on TTP in relation to maternal exposure to formaldehyde (see Table 3-53). TTP was retrospectively ascertained using self-completed questionnaires (Taskinen et al., 1999). Taskinen et al. (1999) used an appropriate analytical approach, involving the comparison of fecundability[35] among four exposure groups. The association of maternal formaldehyde exposure with TTP became significantly increased in the highest

[35]Fecundability is the probability of a couple conceiving in 1 month, calculated as the average number of menstrual cycles to achieve a pregnancy for a group divided by the total number of cycles experienced in the group.

exposure group with an 8-hour TWA (TWA8) exposure of 0.27 mg/m^3. The fecundability density ratio (FDR) for individuals in the highest formaldehyde exposure category compared to nonexposed individuals, adjusting for potential confounders and phenol exposure was 0.57 (95% CI 0.37, 0.85). The FDRs for organic solvents, dusts, wood dusts, and phenols in models that adjusted for potential confounders, including formaldehyde as a coexposure, were all greater than 0.90 (p > 0.05). Therefore, the observed association with formaldehyde was not explained by these other exposures because they were not associated with longer TTP. FDR was lowest among 17 women who did not wear gloves, out of 39 women in the highly exposed group (FDR = 0.51; 95% CI 0.28, 0.92), suggesting that dermal exposure contributed to increased risk of increased TTP. In addition to the detailed exposure assignments, (Taskinen et al., 1999) reduced the potential for selection bias by recruiting from female members of a wood workers union who had been employed at least six months prior to their pregnancy. Thus, selection into the study was not conditional on being currently employed in the industry at the time of the study. Zhu et al. (2005) did not observe an association with reduced TTP in a study of lab technicians that assigned exposures based on broad task categories.

Table 3-53. Epidemiology studies describing effects on time to pregnancy in relation to maternal formaldehyde exposure

Study and design	Results
Reference: Taskinen et al. (1999) Retrospective cohort study, Finland **Population:** Women (n = 3,772), recruited from a woodworkers' union and other businesses involving wood processing, 1,094 women eligible (born between 1946 and 1975, had a live birth at age 20–40 years during 1985–1995, had worked in the wood processing industry for at least 1 month, and had first employment in the wood processing industry beginning at least 6 months before the index pregnancy). The first eligible pregnancy was the index pregnancy. Information about personal characteristics, pregnancies, and exposures was collected from mailed questionnaires; response rate 64%. After other exclusions (primarily infertility history, unknown TTP, and contraceptive failure), the final sample included 602 women. Period of recall of TTP period: 1–11 years. **Exposure:** Questionnaire on exposure to specific agents including hours/week during TTP period. Mean daily exposure to formaldehyde was based on measurements taken at the factories where the women worked during the early 1990s or, if measurements unavailable, from comparable industries. Sampling protocol was not described. Formaldehyde concentrations were obtained from comparable industries for 46, 31, and 61% of women in low, medium, and high exposure categories, respectively. Formaldehyde concentration in factories by exposure category: Low mean 0.07 ppm (0.086 mg/m^3)*, range 0.01 to 0.3 ppm (0.012 to 0.37 mg/m^3);	TTP by formaldehyde category N / FDR[a] / 95% CI Not Exposed: 367 / 1.00 / – Low: 119 / 1.09 / 0.86, 1.37 Medium: 77 / 0.96 / 0.72, 1.26 High: 39 / 0.64 / 0.43, 0.92 [a] Fecundability density ratio adjusted for employment, smoking, alcohol consumption, irregular menstrual cycles, and number of children (recent contraceptive use not found to be a confounder). TTP among women with high formaldehyde exposure, by glove use N / FDR[a] / 95% CI Gloves: 22 / 0.79 / 0.47, 1.23 No gloves: 17 / 0.51 / 0.28, 0.92 [a]Fecundability density ratio adjusted for employment, smoking, alcohol consumption, irregular menstrual cycles, and # children.

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Medium mean 0.14 ppm (0.17 mg/m^3), range 0.05 to 0.4 ppm (0.062 to 0.49 mg/m^3);
High mean 0.33 ppm (0.41 mg/m^3), range 0.15 to 1.0 ppm (0.18 to 1.2 mg/m^3)
Other chemicals with measurements: phenol, organic solvents, wood dust, other dusts.
Methods: Analysis: discrete proportional hazards regression; outcome, FDR, ratio of average incidence density of pregnancies in exposed compared to employed, unexposed women); for covariates in model, see results; significance assessed by likelihood ratio test.
Evaluation:[a]
Medium confidence
Expect some error in individual exposure assignments.</td><td>TTP among women with high formaldehyde exposure and phenol (when included in same model)[a]
<table><tr><th></th><th>N</th><th>FDR[b]</th><th>95% CI</th></tr><tr><td>Phenol</td><td>68</td><td>1.56</td><td>0.93, 2.53</td></tr><tr><td>Formaldehyde</td><td>NR[c]</td><td>0.57</td><td>0.37, 0.85</td></tr></table>[a]All women exposed to phenols were also exposed to formaldehyde, but not vice versa.
Fecundability density ratio adjusted for employment, smoking, alcohol consumption, irregular menstrual cycles, and # children.
[c]Not reported.</td></tr>
<tr><td>Reference: Zhu et al. (2005)
Cohort study, Denmark
Population: Exposed were female laboratory technicians, identified through the Danish National Birth Cohort, who had only held one job (n = 1,069); 1st interview in June 1997–February 2003 (at week 12–25 of gestation); excluded women with endometriosis, ovarian or cervical cancer, unplanned or partly planned pregnancies, and included only 1st pregnancy in study period for each woman (final n = 829, 77.5% of initial study cohort); 8.6% ≥35 years old, 13.9% smoker during 1st trimester; 29.3% previous spontaneous abortion. Referents were teachers identified in same manner; n = 6,250 (73.9% of initial cohort of 8,461); 12.7% ≥35 years old, 20.1% smoker during 1st trimester; 31.1% previous SA
Exposure: Queried at gestation week 12–25 (median week 17). Self-report on laboratory work processes during pregnancy and 3 months before, including frequency and use of protective measures.
Exposure index (EI) calculated as exposure level × frequency of work contact, using scores for exposure level and frequency:
Formaldehyde exposure level (low = 1, medium = 2), assigned by study researchers as follows:
Low: human blood and tissue processing, work with experimental animals, work with microorganisms; medium: preparation of slides for microscopy. No work processes were identified considered to involve high exposure to formaldehyde.
Frequency: everyday = 4, several times per week = 3, several days per month = 2, and rarely = 1.
Exposure Index categories: 1–5 and ≥6
Methods: Self-report of TTP (4 categories: 0–2 months, 3–5 months, 6–12 months, and >12 months); Fecundability ratios analyzed using discrete-time survival analysis (complementary log-log link); comparisons between laboratory technicians and referents (teachers) and among laboratory technicians; covariates in model see results.
Evaluation:[a]
Low confidence</td><td>Fecundability ratio for 1st pregnancies among 829 laboratory technicians, by formaldehyde exposure index
<table><tr><th>EI</th><th>N</th><th>cFR</th><th>aFR[a]</th><th>95% CI</th></tr><tr><td>1–5</td><td>112</td><td>1.0</td><td>0.92</td><td>0.69, 1.22</td></tr><tr><td>≥6</td><td>74</td><td>1.18</td><td>1.03</td><td>0.74, 1.43</td></tr></table>[a]aFR: adjusted for maternal age, gravidity, smoking, prepregnancy BMI, and paternal job (also evaluated history of spontaneous abortion and alcohol consumption).

Fecundability ratios for 1st pregnancies: laboratory technicians compared to teachers
<table><tr><th></th><th>N</th><th>cFR</th><th>aFRb</th><th>95% CI</th></tr><tr><td>Teacher</td><td>6,250</td><td>1.00</td><td>1.00</td><td></td></tr><tr><td>Lab technician</td><td>829</td><td>1.01</td><td>0.98</td><td>0.86, 1.13</td></tr></table>[b]FRa: adjusted for maternal age, gravidity, smoking, prepregnancy BMI, and paternal job (also evaluated history of spontaneous abortion and alcohol consumption).</td></tr>
</table>

Study and design	Results
Categorized TTP (decreased precision), missed pregnancies that ended before 1st interview. Variation in probability or intensity of formaldehyde exposure possible for work processes across different types of labs and high likelihood of exposure misclassification (likely underestimating the effect estimate), did not account for large proportion of participants who used protective measures to prevent inhalation exposure. JEM was not validated for formaldehyde.	

Organized by study confidence, then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.
[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.8).
Abbreviations: TTP = time to pregnancy; CI = confidence interval; EI = exposure index; JEM = job-exposure matrix; FDR = fecundability density ratio; BMI = body mass index.
[*]Converted study exposure values are presented in [italics]. Conversion factors for formaldehyde in air (at 25°C): 1 ppm = 1.23 mg/m^3.

Spontaneous abortion

Two *medium* confidence studies provide evidence (see Table 3-54) that formaldehyde exposure to female workers is associated with an increased risk of spontaneous abortion. A third *low* confidence study contributed information about exposure-response patterns, which was included as a consideration in the synthesis. These studies examined diverse occupational groups exposed to different combinations of chemical exposures and products containing formaldehyde (wood working, cosmetology, research laboratories). Relatively high odds ratios (ORs) of 2–3.5 in the highest exposure categories were observed (Taskinen et al., 1994; Taskinen et al., 1999; John et al., 1994). Studies of hospital, nursing, or medical employees generally did not report an association with formaldehyde exposure, although these *low* confidence studies tended to use less precise exposure assessment methods, a major limitation that reduced the sensitivity of these studies.

All of the studies defined spontaneous abortion, also called miscarriage, as a pregnancy loss before the 20th week of gestation. Spontaneous abortions were ascertained retrospectively, primarily using questionnaires, and in several studies these self-reports were included for analysis only if they could be verified using additional information. Some studies included all eligible spontaneous abortions recalled by participants (Taskinen et al., 1999; Steele and Wilkins, 1996). These studies had greater sensitivity (ascertained early pregnancies prior to clinical recognition). Other studies identified spontaneous abortions directly from a hospital discharge register (Lindbohm et al., 1991; Hemminki et al., 1985), an approach that avoids the limitations of recall bias but is prone to under ascertainment of early recognized losses that do not merit medical attention (Wilcox, 2010).

All of the studies focused their exposure assessments on the first trimester of pregnancy (women). The assignment of formaldehyde exposure during this period of susceptibility for spontaneous abortion (Wilcox and Horney, 1984) was less certain for two *low* confidence studies, possibly resulting in misclassification and reduced study sensitivity (Steele and Wilkins, 1996; Lindbohm et al., 1991).

Two *medium* confidence studies conducted analyses or provided details to evaluate potential confounding by coexposures and found that formaldehyde exposure posed an independent risk. One study adjusted for other coexposures in the workplace that also posed a possible risk of spontaneous abortion (John et al., 1994). In this evaluation of cosmetologists, an adjusted OR of 2.1 was reported for use of formaldehyde-based disinfectants (95% CI 1.0, 4.3). Taskinen et al. (1999) evaluated previous spontaneous abortions reported by female woodworkers, all of whom had a live birth, using unconditional logistic regression, and adjusted for age, employment, smoking, and alcohol consumption. No associations were observed for exposure to phenol, organic solvents, wood, and other dusts. Because formaldehyde was the only exposure associated with spontaneous abortion, these other work exposures were not confounders in this analysis. Potential confounding was identified to be a limitation for a study of laboratory technicians (Taskinen et al., 1994). This study observed a strong association between formalin exposure at a frequency of 3–5 days per week and spontaneous abortion (OR = 3.5; 95% CI 1.3, 7.5), but most of the participants exposed to formalin also reported exposure to xylene, which also was strongly associated with spontaneous abortion (OR = 3.1; 95% CI 1.3, 7.5). Although potentially confounded by xylene, the results of this study were compared to those of John et al. (1994) and Taskinen et al. (1999) to assess a potential bias away from the null. Other studies did not provide information to evaluate confounding by coexposures and did not provide risk estimates adjusted for coexposures.

ORs for spontaneous abortion risk in relation to maternal formaldehyde exposure are plotted in Figure 3–30 and are grouped by industry. The three studies indicate that maternal formaldehyde exposure is associated with risk of spontaneous abortion among woodworkers, laboratory workers, and cosmetologists (Taskinen et al., 1994; Taskinen et al., 1999; John et al., 1994). Two studies evaluated multiple exposure groups and found that stronger associations were observed among women in the highest exposure groups (OR range 3.2–3.5). Although, Taskinen et al. (1994) did not control for xylene exposure, which also was associated with spontaneous abortion risk, the magnitude of the OR among laboratory workers with the most frequent exposure was comparable to the two higher confidence studies.

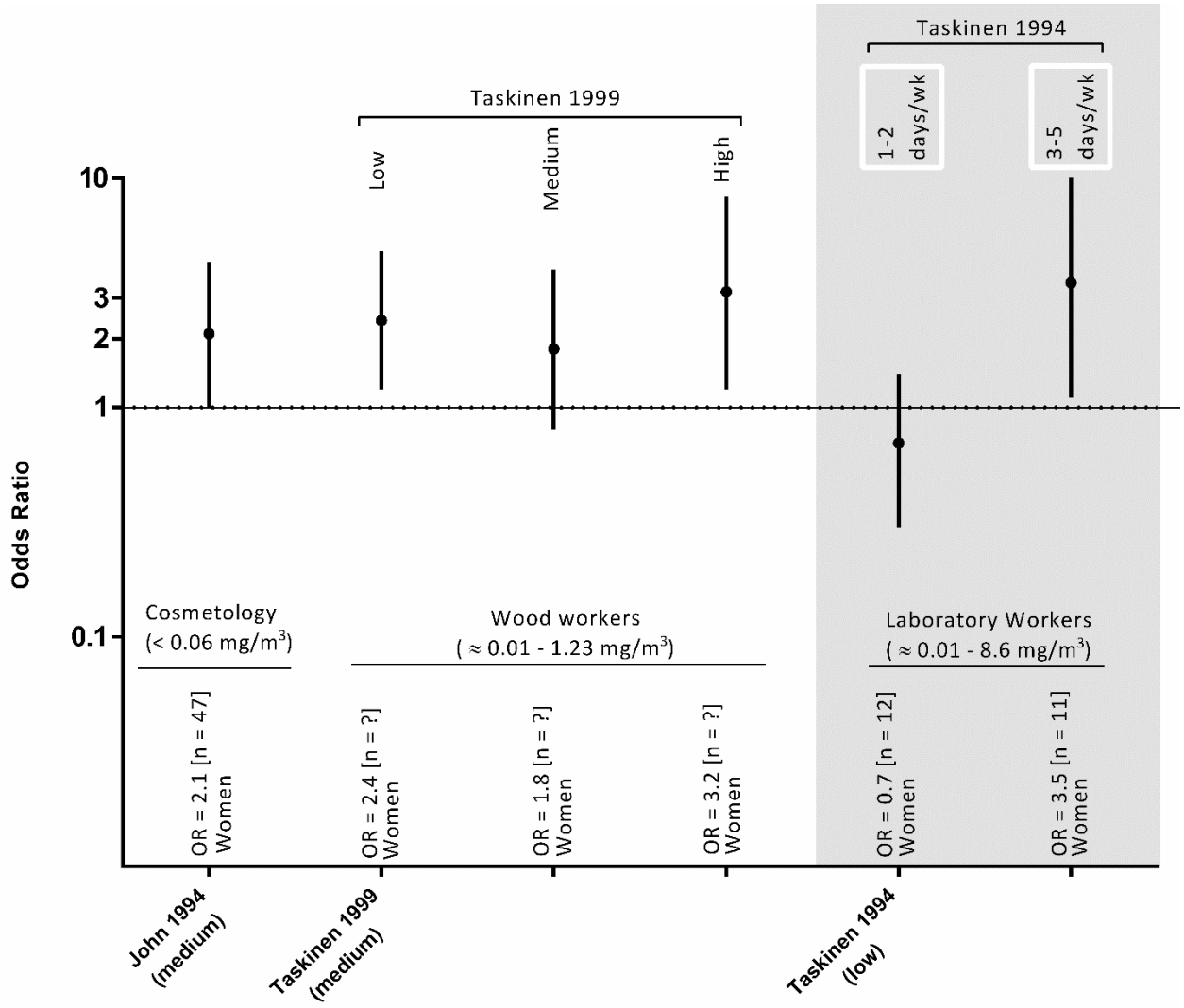


Figure 3-30. Risk of spontaneous abortion associated with maternal occupational formaldehyde exposure.

OR and number of exposed cases are presented for each study. Taskinen et al. (1999) and John et al. (1994) were *medium* confidence studies, and Taskinen et al. (1994) was a *low* confidence study due to potential confounding possibly resulting in bias away from the null (shaded). The number of exposed cases was not reported by Taskinen et al. (1999). A range of formaldehyde exposure concentrations experienced in specific industries is presented. Formaldehyde concentration ranges reported or cited by the authors are presented (Taskinen et al., 1994; Taskinen et al., 1999), or were obtained from the literature for cosmetology (Tsigonia et al., 2010; Labrèche et al., 2003).

Table 3-54. Epidemiology studies describing effects on spontaneous abortion in relation to formaldehyde exposure

Study and design	Results
Reference: John et al. (1994) United States Case-control study **Population:** 6,202 of 8,356 women (74%) in North Carolina cosmetology license registry responded to screening questionnaire; 1,249 of 1,696 women (74%) with eligible pregnancy (most recent pregnancy for which last menstrual period occurred between April 1983 and March 1988) completed detailed questionnaire. Data obtained on 191 of 267 eligible spontaneous abortions, and 1,058 of 1,429 eligible live births (1,696 total abortions and live births); 87% white, 92% high school education, 65% income <$20,000, mean age 25.9 years. **Exposure:** Self-reported exposure through mailed questionnaire to formaldehyde-based disinfectant products during first trimester. Other measures of exposure intensity: number of customers, number and type of chemical services performed per week, number of hours per day spent standing, disinfection products used, and glove use. **Methods:** Three spontaneous abortions were excluded because no positive pregnancy test or subsequent medical care was reported. Women working ≥35 hrs/week as cosmetologists, with or without use of formaldehyde disinfectants, were compared to women working in other jobs (referent) during first trimester, and cosmetologists working with formaldehyde disinfectants were compared with those who did not. Multivariate unconditional logistic regression. **Evaluation:**[a] *Medium* confidence Selection of most recent eligible pregnancy (potential underascertainment); no ambient measurements; adjustment for previous pregnancy loss may introduce bias.	Spontaneous abortions in 7.8% of most recent pregnancies; mean gestational age for spontaneous abortion: 9.8 weeks. Spontaneous abortion among women working full-time (≥35 hr/week) during 1st trimester {# SA, OR[a], 95% CI} Other jobs: 26, 1.0, Referent Cosmetology work, no formaldehyde-based disinfectant use: 16, 0.8, 0.4, 1.6 Cosmetology work, use of formaldehyde-based disinfectant: 51, 1.7, 1.0, 3.0 [a]Adjusted for mother's age at conception, previous pregnancy loss, and cigarette smoking. Spontaneous abortion among women working full-time (≥35 hr/week) as cosmetologists during 1st trimester {formaldehyde disinfectant use, # SA, OR[a], 95% CI} No: 14, 1.0 Yes: 47, 2.1, 1.0, 4.3 [a]Adjusted for variables listed above and other work exposures (hours worked, hours standing, chemical services, formaldehyde-based disinfectant, alcohol-based disinfectant, and nail sculpturing). ORs increased with standing ≥8 hours a day and the number of chemical services/week. Previous pregnancy loss, ≥3 pregnancies, and cigarette smoking were more prevalent among women with spontaneous abortion.
Reference: Taskinen et al. (1999) Retrospective cohort study, Finland **Population:** Women (*n* = 3,772), recruited from a woodworkers' union and other businesses involving wood processing. 1,094 women eligible (born between 1946 and 1975, had a live birth at age 20–40 years during 1985–1995, had worked in the wood processing industry for at least 1 month, and had first employment in the wood processing industry beginning at least 6 months before the index pregnancy). The first eligible pregnancy was the index pregnancy. Information about personal characteristics, pregnancies, and exposures was collected from mailed questionnaires;	For 52 pregnancies with report of previous spontaneous abortion and same place of employment for both events (95% CI) {Exposure, OR, 95% CI} Low: 2.4, 1.2, 4.8 Medium: 1.8, 0.8, 4.0 High: 3.2, 1.2, 8.3 Organic solvents, dusts, wood dusts, and phenols were not associated with spontaneous abortions.

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>response rate 64%. After other exclusions (primarily infertility history, unknown TTP, and contraceptive failure), the final sample included 602 women.
Exposure: Questionnaire on exposure to specific agents including hours/week during the period pertaining to TTP. Exposures during critical exposure period(s) for spontaneous abortion were not estimated. Mean daily exposure to formaldehyde was based on measurements taken at the factories where the women worked during the early 1990s or, if measurements unavailable, from comparable industries. Sampling protocol was not described.
Formaldehyde concentrations were obtained from comparable industries for 46, 31, and 61% of women in low, medium, and high exposure categories, respectively.
Formaldehyde concentration in factories by exposure category:
Low mean 0.07 ppm (0.086 mg/m^3)[a], range 0.01 to 0.03 ppm (0.012 to 0.37 mg/m^3);
Medium mean 0.14 ppm (0.17 mg/m^3), range 0.05 to 0.4 ppm (0.062 to 0.49 mg/m^3);
High mean 0.33 ppm (0.41 mg/m^3), range 0.15 to 1.0 ppm (0.18 to 1.2 mg/m^3)
Other chemicals with measurements: phenol, organic solvents, wood dust, other dusts.
Methods: Self-reported spontaneous abortions occurring prior to the index pregnancy and at the same workplace were evaluated.
Unconditional logistic regression, ORs, adjusted for age, employment, smoking, and alcohol; # exposed cases not reported.
Evaluation:[a]
Medium confidence
Uncertainty regarding exposure measurements with regard to critical exposure period(s) for spontaneous abortion; excluded women with no live birth (missing spontaneous abortions to women with no live births).</td><td></td></tr>
<tr><td>**Reference:** Taskinen et al. (1994)
Finland, Retrospective case-referent
Population: Sampled from payroll of state lab personnel (1970, 1975–1986), Finnish Union of Laboratory Assistants (1987), and Register of Employees Occupationally Exposed to Carcinogens (1979–1986)
Exposure: Self-reported exposure from mailed questionnaire.
Substances listed in questionnaire or open-ended question
Frequency:
Rare: 1–2 days/week
Frequent: 3+ days/week
Reviewed by two occupational hygienists blinded to case status; 8/10 cases and 5/7 referents exposed to formalin were also exposed to xylene.
Methods: Participants responded to mailed questionnaire regarding occupational exposure, health status, medications, contraception use, smoking, and alcohol consumption during 1st trimester (824 returned/1,000 mailed (82.4%)). Sample linked to Hospital Discharge</td><td>Spontaneous abortion risk by frequency of formaldehyde exposure
<table><tr><th>Exposure</th><th>Cases/ Referent</th><th>OR</th><th>95% CI</th></tr><tr><td>Employed</td><td></td><td>0.9</td><td>0.5, 1.7</td></tr><tr><td>Laboratory</td><td></td><td>1.4</td><td>0.9, 2.2</td></tr><tr><td>Formalin</td><td></td><td></td><td></td></tr><tr><td>1–2 days/week</td><td>12/28</td><td>0.7</td><td>0.3, 1.4</td></tr><tr><td>3–5 days/week</td><td>11/8</td><td>3.5[a]</td><td>1.1, 11.2</td></tr></table>[a] $p < 0.05$

Other substances also were associated with spontaneous abortion during 1st trimester; xylene</td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Register and database of spontaneous abortions treated at hospital outpatient clinics, 1973−1986. Cases: 206 women aged 20−34 years with one spontaneous abortion during study period; 329 referents: 2/case selected from registered births and not a case, matched on age (24 months) and year of end of pregnancy. Logistic regression for matched data adjusting for parity, previous miscarriage, febrile diseases during pregnancy, used contraception at beginning of pregnancy, alcohol consumption, and employment status.
Evaluation:[a]
Low confidence (↑)
Adjustment for parity and previous miscarriage may introduce bias; lack of adjustment for xylene, an exposure associated with the spontaneous abortion and formalin exposure. Evaluation of increasing frequency of use a strength.</td><td>3−5 days/week (OR 3.1; 95% CI 1.3, 7.5), toluene 3−5 days/week (OR 4.7; 95% CI 1.4, 15.9).</td></tr>
<tr><td>Reference: Steele and Wilkins (1996) United States
Population: 85% of 2,978 eligible women graduating from U.S. colleges of veterinary medicine during 1970−1980, mean age 36.1 years, 96.2% White; 1,444 women reported 3,098 pregnancies, 2,375 after graduation.
Exposure: Self-reported job exposure to specific listed chemical or physical agents (yes, no, don’t know). Exposed pregnancy defined if estimated time of conception was during the reported years of a job for which exposure also was reported.
Definitions of exposure:
1. Job classification associated with the index pregnancy (type of clinical practice). Referent pregnancies: women unemployed when pregnancies began.
2. Specific chemical and physical agents. Referent: employed women reporting no exposure to that agent or unemployed while pregnant. Thirteen exposure categories examined: disinfectants, antibiotics, animal insecticides, formaldehyde, non-DES hormones, solvents, radiation, diethylstilbestrol, nonhalothane anesthetics, halothane, antineoplastics, heavy metals, and ethylene oxide.
Methods: Self-reported (via mailed questionnaire in 1987) pregnancy and employment history. Evaluated eligible pregnancies (live births, induced abortions, spontaneous abortions) in relation to postgraduate employment. Spontaneous abortion defined as fetal death prior to 20 weeks. Unconditional multiple logistic regression of spontaneous abortion in relation to clinical practice type or self-reported exposures adjusting for maternal age, gravidity, history of spontaneous abortion, history of smoking, and alcohol use.
Evaluation:[a]
Low confidence
No information on intensity and frequency of formaldehyde exposure, which would likely be variable among veterinarians (exposure misclassification–decreased sensitivity). Adjustment for gravidity and previous spontaneous abortion may introduce bias.</td><td>264 (11.1%) spontaneous abortions.
Analysis limited to women holding only one job at the time of conception (1,813 pregnancies).

Spontaneous abortions in veterinarians with self-reported exposure to formaldehyde, adjusted[a] OR (95% CI)
<table><tr><th>Clinical practice</th><th>Exposed pregnancies (N)</th><th>OR</th><th>95% CI</th></tr><tr><td>All types</td><td>172</td><td>0.9</td><td>0.6, 1.5</td></tr><tr><td>All small animal</td><td>115</td><td>1.1</td><td>0.6, 2.0</td></tr></table>[a]adjusted for age, history of spontaneous abortion, gravidity, smoker, drinker.</td></tr>
<tr><td>Reference: Hemminki et al. (1982) Finland
Retrospective cohort</td><td>Adjusted spontaneous abortion rate (total pregnancies (N) and adjusted rate) among</td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Population: Female nursing staff working in sterilizing units (exposed) or auxiliary units (referent) in all (approx. 80) general hospitals; 50 exposed pregnancies, 1,100 unexposed pregnancies.
Exposure: Exposure to sterilizing agents (formaldehyde, ethylene oxide, glutaraldehyde) at beginning of pregnancy (1960–1980) assigned by supervising nurse. Blind to case status; 50 formaldehyde-exposed pregnancies out of 545 total exposed group (9%).
No air monitoring conducted.
Methods: Questionnaire mailed to current supervising nurses to identify nurses exposed to chemical sterilizing agents and nurses not exposed to sterilizing agents, X-rays, or anesthetic gases; response in exposed 91.6%; referent 90.6%.
Spontaneous abortions, 1960–1980, identified via questionnaire sent to nurses (self-report); compared to Finland hospital discharge register, 1973–1979.
Spontaneous abortion rate (compared to total pregnancies, live births, induced abortions, spontaneous abortions), logistic regression adjusting for age, parity, decade of pregnancy, smoking habits, alcohol, and coffee consumption.
Evaluation:[a]
Low confidence
Adjustment for parity may introduce bias. Assumed sterilant use was same throughout period; no information on intensity and frequency of formaldehyde exposure (exposure misclassification–decreased sensitivity); no adjustment for other sterilants. Small number of exposed cases.</td><td>women not exposed and exposed to formaldehyde during pregnancy
<table><tr><th></th><th colspan="2">Not Exposed</th><th colspan="2">Exposed</th></tr><tr><th>Agent</th><th>N</th><th>Rate</th><th>N</th><th>Rate</th></tr><tr><td>HCHO[a]</td><td>1,100</td><td>8.3</td><td>50</td><td>8.4</td></tr></table>[a] Some individuals used more than one sterilizing agent

Adjusted rates among women exposed to ethylene oxide were higher 16.1% versus 7.8%, $p < 0.01$.</td></tr>
<tr><td>Reference: Hemminki et al. (1985) Finland
Case-control study
Population: Pregnancies during 1973–1979 among women who worked in anesthesia surgery, intensive care, operating room, or internal medicine departments of a general hospital.
Exposure: Exposure assessment via questionnaire sent to head nurses at all general hospitals in Finland. For each study subject, requested occupation and exposure (yes, no) to any of the listed substances during a stated 3-month period (1st trimester); blind to case status.
Listed substances were anesthetic gases (nitrous acid, halothane, other), sterilizing agents (ethylene oxide, glutaraldehyde, formaldehyde), disinfectant soaps (requested names), cytostatic drugs, and X-rays. Included information about job: shift work, night shift, rotating etc.
Occupation identified during 1st trimester for 87.1% cases and 87.8% controls. Information on employment and exposure obtained for 81% of case:control sets.
No air monitoring conducted.
Methods: Spontaneous abortions identified by linking Finnish Hospital Discharge Register with Central Register of Health Care Personnel; 217 cases identified from register as treated for spontaneous abortion 1973–1979 (ICD8 643 & 645).
Controls (n = 571) were nurses who gave birth to a healthy infant 1973–1979 and other pregnancies who were not cases. Selected three</td><td>Spontaneous abortion
Crude rate (# cases/# all pregnancies): 8.3%; not different from Finnish rate: 8.4%

Exposed pregnancies (#) (at least once per week) among cases and controls (unadjusted OR)
<table><tr><th>Agent</th><th colspan="2">Cases</th><th colspan="2">Controls</th><th>OR</th></tr><tr><th></th><th>#</th><th>%</th><th>#</th><th>%</th><th></th></tr><tr><td>HCHO</td><td>6</td><td>3.7</td><td>24</td><td>5.2</td><td>0.6</td></tr></table>Exposure defined as whether subject used sterilizing agent or sterilized instruments</td></tr>
</table>

Study and design	Results
controls per case, matched on age (± 1.5 years), among nurses from same hospital as case. Relationships between spontaneous abortion and formaldehyde analyzed using an unmatched crude analysis. **Evaluation:**[a] *Low* confidence No information on intensity or frequency (exposure misclassification–decreased sensitivity); very small number of exposed cases.	

Organized by study confidence, then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.8). Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Abbreviations: SA = spontaneous abortion; OR = odds ratio; CI = confidence interval; HCHO = formaldehyde.

Birth outcomes

The epidemiology literature is very limited regarding formaldehyde exposure and birth outcomes (see Table 3-55). One birth cohort study reported decreases of 0.044 and 0.056 in the z-scores for birth weight and head circumference, respectively, with each 1 μg/m^3 unit increase in formaldehyde concentration measured in the mother's homes at 34 weeks gestation (Franklin et al., 2019). Gestational age was not associated with exposure. The median concentration in the homes was 0.0028 mg/m^3 and 23.3% of samples were below the LOD in this relatively small study. Another pregnancy cohort study in South Korea observed lower birth weights associated with increasing formaldehyde concentration measured at mid to late pregnancy (mean concentrations were 0.08 mg/m^3), although the association for formaldehyde was not strong while the association for total volatile organic compounds (VOCs) was of greater magnitude. Total VOCs were correlated with formaldehyde levels (Chang et al., 2017). Another study of pregnant women in the southeastern United States, rated as *low* confidence, reported an association of biparietal diameter, suggestive of intrauterine growth retardation, with personal formaldehyde exposure >0.037 mg/m^3, both measured in the second trimester (Amiri and Turner-Henson, 2017). Preterm birth and low birth weight were not associated with exposure to high formaldehyde concentrations among a cohort of male woodworkers in China (Wang et al., 2012).

An elevated association with congenital malformations and maternal exposure was reported by a limited set of *low* confidence studies among female hospital or laboratory workers (Zhu et al., 2006; Hemminki et al., 1985). The precision of the ORs was low, as indicated by the wide CIs generally overlapping 1.0. In addition, the studies evaluated associations for all, or major malformations grouped together. These outcomes may be etiologically distinct, so this lack of specificity limits the ability to interpret these results. The probability or frequency of exposure to formaldehyde likely was low in these studies, which would have limited the ability to detect differences across various exposure groups for these rare outcomes (Hemminki et al., 1985; Ericson et al., 1984).

Table 3-55. Epidemiology studies describing effects on prenatal growth and births outcomes in relation to formaldehyde exposure

Study and design	Results
Reference: Franklin et al. (2019) Birth cohort study, Australia **Population:** Pregnant women, all nonsmokers, recruited prior to 18 weeks gestation. 305 of 373 recruited, 81.7% participation; Birth data available for 262 live births. N=129 males and N=133 females, gestational age 38.97 weeks (6 infants born at 36–37 weeks). **Exposure:** Air monitoring in homes at 34 weeks gestation, 7-day sampling duration using validated passive samplers in bedroom and living room. LOD 2.4 µg/m^3; used LOD/2 for values <LOD. House Median (range) 2.81 (LOD–17.33) µg/m^3; 23.3% < LOD. **Methods:** Gestational age (untransformed), birth weight, birth length and head circumference (all z-scores) obtained from birth records. **Evaluation:**[a] *Medium* confidence Uncertainties in exposure distribution due to proportion < LOD, and analysis as continuous variable.	**Prenatal growth** Regression coefficients (95% CI) per µg/m^3 Birth weight (z-score) -0.044 (-0.085, -0.004; p =0.033) Head circumference (z-score) -0.056 (p = 0.06) General linear models adjusted for maternal age, parity, maternal asthma, maternal diabetes, maternal hypertension, and season of birth. ETS and distance to roads evaluated but not included in final model. No associations with gestational age or birth length (results not reported)
Reference: Chang et al. (2017) (Pregnancy cohort) South Korea **Population:** Women were selected from hospital-based pregnancy cohort (n = 383), Mother and Childrens Environmental Health Study. Infants followed at 6 (n=262), 12 (n=234), 24 (n=199), and 36 months (n=92). **Exposure:** Personal formaldehyde measurements during mid- or late pregnancy, 3 days. Categorized into two groups below and above the 75th percentile and also continuous variable with log transformation. Mean (SD) 0.082 (0.052) mg/m^3, geometric mean 0.067, 75th percentile 0.106 mg/m^3. Correlation between TVOCs and formaldehyde 0.22, p<0.01. **Methods:** Birth weight from medical records; Age-specific postnatal weight at 6, 12, 24, and 36 months by gender using growth standard for Korean children. **Evaluation:**[a] *Medium* confidence Hospital-based cohort, notable attrition over time	**Birth weight** Regression coefficient (SE) -37.98 (39.55) per 1 log unit change in formaldehyde (p value = 0.34) Multiple linear regression adjusted for maternal age, body mass index, education level, parity, infant's gender, and gestational age at delivery. Postnatal weight Mean difference by exposure group, p value, at 6 months -0.09, 0.529 12 months -0.25, 0.149 24 months -0.04, 0.860 36 months 0.22, 0.702 Multiple linear regression adjusted for birth weight with maternal age, gestational age at delivery, pre-pregnancy BMI, educational level, parity, and infant's gender plus, air cleaner use and house age. Association with greater magnitude observed for TVOCs for birth weight and postnatal weight Prevalence LBW 2.5% Prevalence gestational age <37 weeks, 3.6%
Reference: Amiri and Turner-Henson (2017) Cross-sectional study (Southeastern United States) **Population:** Pregnant women in 2nd trimester (n = 140) recruited from obstetrics and gynecology clinics with no history of chronic	**Ultrasonographic biometry** BPD percentile lower by 0.271% among infants with maternal exposure >0.03 ppm (0.037 mg/m^3), (p < 0.013).

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>disease or high-risk pregnancy, 19 - 40 years old, 46% White, 37% African American, 16% other race. Participation 63% (n = 88).
Exposure: Personal exposure during 2nd trimester, vapor monitor badges, 24-hour period, detection limit 0.003 ppm.
Mean (SD) 0.04 (0.06) ppm; 0.049 (0.074) mg/m^3
Methods: Ultrasonographic biometry during 2nd trimester for head circumference, abdominal circumference, femur length, biparietal diameter, estimated fetal weight, and ratio of abdominal circumference to femur length. Measurements in mm converted to percentiles using gestational age and the Hadlock formulas.
Evaluation:[a]
Low confidence
Convenience sample, sampling frame not described. Lower participation rate. Small sample size. Reference population for BPD measure was not appropriate for >50% of participants.</td><td>Multiple linear regression adjusted for race. Maternal age and fetal sex were not associated.

Other biometric measures were not associated with formaldehyde exposure.</td></tr>
<tr><td>**Reference:** Hemminki et al. (1985)
Case-control study, Finland
Population: Pregnancies during 1973−1979 among women who worked in anesthesia surgery, intensive care, operating room, or internal medicine departments of a general hospital.
Exposure: Exposure assessment via questionnaire sent to head nurses at all general hospitals in Finland. Reported occupation for each name and whether exposed to listed substance during a stated 3-month period (1st trimester); blind to case status.
Substances were anesthetic gases (nitrous acid, halothane, other), sterilizing agents (ethylene oxide, glutaraldehyde, formaldehyde), disinfectant soaps (requested names), cytostatic drugs, and X-rays. Included information about job: shift work, night shift, rotating etc. Occupation identified during 1st trimester for 87.1% cases and 87.8% controls. No air monitoring conducted.
Methods: Congenital malformations identified by linking with Register of Congenital Malformations; 46 cases 1973−1979.
Controls were nurses who gave birth to a healthy infant 1973−1979 and other pregnancies were not cases. Selected three controls per case, matched on age (± 1.5 years), among nurses from same hospital as case. Congenital malformation controls: 128.
Evaluation:[a]
Low confidence
No information on intensity or frequency (exposure misclassification–decreased sensitivity); very small number of exposed cases.</td><td>**Congenital Malformations**
Exposed pregnancies (E) (at least once per week) and total pregnancies (T) among cases and controls (unadjusted OR)
<table><tr><th>Agent</th><th>Cases</th><th></th><th>Controls</th><th></th><th>OR</th></tr><tr><td></td><td>E/T</td><td>%</td><td>E/T</td><td>%</td><td></td></tr><tr><td>HCHO</td><td>3/34</td><td>8.8</td><td>5/95</td><td>5.3</td><td>1.8</td></tr></table>Exposure defined as whether subject used sterilizing agent or used sterilized instruments (only one nurse sterilized instruments)</td></tr>
<tr><td>**Reference:** Zhu et al. (2006)
Cohort study, Denmark
Population: Source: Danish National Birth Cohort; 30−40% of all pregnant women in Denmark, 1st interview June 1997−February 2003; 1,025 of 1,069 pregnancies of laboratory technicians with one job at interview and 1st pregnancy; excluded induced abortions, hydatidiform mole, or unknown outcomes of pregnancy (95.9% of eligible); 9.7% ≥35 years old, 14.9% smoker during 1st trimester; 27.7% previous spontaneous abortion. Referent: 8,037 of 8,461</td><td>ORs for 1st pregnancies among 991 laboratory technicians by formaldehyde exposure category (N, adjusted OR, [95% CI]).
<table><tr><th></th><th>Exposure Index</th><th></th></tr><tr><td>0</td><td>1–5</td><td>≥6</td></tr><tr><td>**“Major” malformation**</td><td></td><td></td></tr><tr><td>20, 1.0</td><td>20, 1.2 (0.6, 2.1)</td><td>16, 1.5 (0.8, 2.9)</td></tr></table></td></tr>
</table>

Study and design	Results
teachers; 14.6% ≥35 years old, 22.1% smoker during 1st trimester; 29.6% previous spontaneous abortion. **Exposure**: Queried at gestation week 11–25 (median week 16). Self-report on laboratory work processes during pregnancy and 3 months before including frequency and use of protective measures. JEM: EI = Exposure level times Frequency of work contact **Exposure level**: low (1), medium (2), and high (3); assigned by study researchers For formaldehyde: low: human blood and tissue processing, work with experimental animals, work with microorganisms; medium: preparation of slides for microscopy. No work processes were identified with high exposure to formaldehyde. Frequency: everyday (4), several times per week (3), several days per month (2), and rarely (1); EI categorized into two levels: 1–5 and ≥6. **Methods**: Cohort linked to National Hospital Register and Medical Birth Register, Cox regression and hazard ratios for late fetal loss and congenital malformations; laboratory technicians compared to teachers and comparisons within laboratory technicians. Adjusted for maternal age, history of spontaneous abortion, gravidity, prepregnancy BMI, smoking, paternal laboratory job, alcohol consumption, child's sex (some models). **Evaluation**:[a] *Low* confidence (↓) Variation in probability or intensity of formaldehyde exposure possible for work processes across different types of labs, did not account for large proportion of participants who used protective measures to prevent inhalation exposure. JEM was not validated for formaldehyde.	Unexposed technicians were exposed to other work processes.

Organized by study confidence, then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.8). Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Abbreviations: OR = odds ratio; EI = exposure index; BMI = body mass index; JEM = job-exposure matrix.

Male reproductive toxicity

Four epidemiology studies were available regarding formaldehyde exposure and male reproductive toxicity (see Table 3-56). Two studies (*medium* confidence) of male woodworkers in China from one research group reported associations with lower sperm motility (total and progressive) (Wang et al., 2015), delayed fertility and spontaneous abortion (Wang et al., 2012). Eligible participants were of Han Chinese ethnicity and were occupationally exposed for at least 24 months. A detailed exposure assessment involved formaldehyde measurements and individual information regarding workplace, work tasks, time spent at work tasks, and duration of employment. Progressive motility and total motility were inversely associated with formaldehyde exposure index, a cumulative measure of exposure, and a strong association with this exposure metric also was observed in logistic models of below-normal values of these motility measures. For example, ORs of 2.58 and 3.41 were found for progressive motility less than 32% in the low and high exposure groups, respectively, compared to the community-based referent group. In another

study, no statistically significant differences in sperm counts or percentage of abnormal sperm were observed in an underpowered, *low* confidence study of autopsy workers (Ward et al., 1984).

Wang et al (2012) reported odds ratios of 2.83 for a TTP > 12 months (95% CI:1.08, 7.41) and 1.92 (95% CI:1.10, 3.33) for spontaneous abortion associated with formaldehyde exposure among male woodworkers in China. Elevated odds ratios also were observed for preterm birth, low birth weight and birth defects although these risk estimates were imprecise. Lindbohm et al. (1991) reported no association with spontaneous abortion identified from a nationwide hospital discharge register in relation to male formaldehyde exposure assessed using census data. There was a high likelihood of exposure misclassification using this assessment method, which reduced the sensitivity of the study (i.e., judged as *low* confidence) to identify an association with developmental endpoints.

Table 3-56. Epidemiology studies describing male reproductive toxicity in relation to formaldehyde exposure

Study and design	Results
Reference: Wang et al. (2015) China Prevalence **Population:** Woodworkers; *N* = 124 participated (62.3%), *N* = 10 with missing semen data, aged 23–40, Chinese Han ethnicity, occupational exposure at least 24 months; excluded men living in newly built or recently remodeled house, men with genital malformations or other chronic disease; *N* = 81 (40.5%) recruited referent group age-matched, male Han volunteers from same area (salesmen and clerks), *N* = 5 with missing semen data. **Exposure:** Sampling: 25-minute samples at three times on one workday, same day as questionnaire. Exposure information based on workplace, work tasks, work duration, and time (referenced (Wang et al., 2012)). Exposure index based on formaldehyde concentration (mean of three samples) multiplied by exposed work time during workday and exposure duration (years). Two categories with cutpoint at median. Concentrations: Exposed 0.22–2.91 mg/m^3, exposure index 4.54–195.08, median 56.55; referent 0–0.02 mg/m^3. Measurement and adjustment for other contaminants was not described (e.g., phenols). **Methods:** Semistructured interview questionnaire, genital examination, semen collection (2–7 days after abstinence), and analysis (within 2 weeks of formaldehyde sampling); parameters were semen volume, sperm concentration, total sperm count, sperm progressive motility, total sperm motility, and kinematic parameters (WHO, 2010). Linear regression Ln-transformed semen parameters and formaldehyde exposure and logistic regression of abnormal semen parameters. Models adjusted for age, BMI, education, income, smoking, alcohol, and abstinence duration. **Evaluation:**[a] *Medium* confidence	Regression analysis of sperm parameters and formaldehyde exposure index Volume (mL)[a]: β −0.02; 95% CI −0.08, 0.03 Concentration (10^6/mL)[a]: β −0.02; 95% CI −0.19, 0.14 Total sperm count[a]: β −0.20; 95% CI −0.68, 0.29 Sperm progressive motility (%)[b]: β −0.19; 95% CI −0.25, −0.12 Total motility[b,c]: β −0.23; 95% CI −0.30, −0.16 [a]Relative percentage change [b]Absolute change [c]Progressive motility plus nonprogressive motility No association with kinematic parameters Logistic regression of below-normal values of sperm parameters and formaldehyde exposure index (below and above median, compared to referent (*N* = 76) Semen volume (<1.5 mL): Low (*N* = 57) 1.83 (0.63, 5.36); High (*N* = 57) 2.28 (0.75, 6.91) Concentration (<15 × 106/mL): Low 1.67 (0.33, 8.43); High 1.25 (0.21, 7.35) Total sperm count (<39 × 10^6): Low 1.59 (0.45, 5.61); High 1.73 (0.49, 6.15)

Study and design	Results
Other workplace exposures in woodworking industry (solvents) have been associated with sperm motility but not accounted for; however, otherwise strong design and analysis, including evaluation of increasing exposure-response relationship.	Progressive motility (<32%): 2.58 (1.11, 5.97); 3.41 (1.45, 7.92) Total motility (<40%): 3.21 (1.24, 8.28); 4.84 (1.83, 12.81)
Reference: Wang et al. (2012), Retrospective cohort, 2007–2009 China **Population:** Woodworkers; 302 eligible of 1,035 married men, aged 23–40, Chinese Han ethnicity, occupational exposure at least 24 months; excluded 733 couples living in newly built or recently remodeled house before and during pregnancy, couples who never tried to conceive, couples with genital malformations or other chronic disease, wives with occupational exposure to reproductive toxicants, pregnancies before husband's formaldehyde exposure and data incomplete; 305 of 816 recruited referent group age-matched, married male Han volunteers from same area (salesmen and clerks) **Exposure:** Mean daily exposure for each worker: Reported workplace, work tasks, and hour per day exposed to formaldehyde; concentration monitored three times during different periods. Daily exposure index: Mean formaldehyde concentration times proportion of exposed work time during work day multiplied by 100 [cited exposure assessment by Taskinen et al. (1999)]. Daily mean concentration categorized in low (n = 151) and high (n = 151), equal number in each group. Formaldehyde sampling details not provided (concentrations, sampling protocols, sampling locations, etc.). TWA formaldehyde concentrations were not reported. Measurement and adjustment for other contaminants was not described (e.g., dust, phenols) **Methods:** Semistructured interview questionnaire. Most recent pregnancy; TTP: # months of unprotected intercourse leading to pregnancy; spontaneous abortion defined as termination of pregnancy prior to 20th week gestation; preterm: <37 weeks; low birth weight: 2,500 g; major structural birth defects. **Evaluation:**[a] Spontaneous abortion *Medium* confidence Other workplace exposures in woodworking industry (solvents) have been associated with spontaneous abortion but not accounted for; Analysis of most recent pregnancy: possible selection for live births (time-lapse bias) and impact of gravidity on spontaneous abortion Time-to-pregnancy *Medium* confidence Exposure levels not reported (but robust assessment method). Dichotomized TTP in analysis (low sensitivity).	OR (95% CI) associated with paternal formaldehyde exposure Exposed: Referent; High: Low TTP >12 months: 2.83[a] (1.08, 7.41); 2.29 (0.78, 6.77) Spontaneous abortion: 1.92[b] (1.10, 3.33); 1.78 (0.88, 3.62) Preterm birth: 1.25[c] (0.55, 2.84); 0.85 (0.28, 2.60) Low birth weight: 1.26 (0.59, 2.66); 1.0 (0.37, 2.74) Birth defects: 2.61[d] (0.79, 8.65); 1.26 (0.33, 4.78) [a]Adjusted for: BMI, alcohol [b]Adjusted for: Cigarette smoking [c]Adjusted for: Education [d]Adjusted for: Alcohol No confounders were identified for low birth weight Logistic regression model adjusted for confounders identified through univariate analyses. Confounders considered: age, BMI, education, income, smoking, alcohol, and frequency of intercourse. The numbers of exposed and referent cases were not presented.
Reference: Lindbohm et al. (1991) Finland; Registry linkage **Population:** All Finnish women with diagnosis of spontaneous abortion (ICD–8 643, 645), induced abortion (ICD–8 640–642), or birth (ICD–8	Spontaneous abortion rate 8.8% (including induced abortions in denominator).

Study and design	Results
650−662) between 1973 and 1982 were identified using the nationwide Hospital Discharge Register and hospital outpatient records. Information on occupation and industry of women and their husbands, and SES (women only), was obtained from Finnish national censuses from 1975 to 1980. Excluded pregnancies among women <12 years or >50 years of age, and those lacking data on occupation, industry, or SES. Final study population included 99,186 pregnancies ending Jan. 1–Dec. 31, 1976 or May 1, 1980−Apr. 30, 1981. **Exposure:** Job-exposure classification developed by two industrial hygienists using combinations of occupation and industry with similar type of exposure. Identified jobs held during census period close to period of susceptibility. List of toxic agents associated with job groups developed using air sampling data from Finnish occupational health agency and register of employees occupationally exposed to carcinogens. Exposure categories: 1. Not exposed 2. Potential, low: jobs with low levels but high prevalence of exposure, jobs without exposure data but in register of occupational exposure to carcinogens, or jobs with high level but unknown prevalence of exposure 3. Moderate or high: jobs with levels ≥TLV, or periodically ≥TLV and high prevalence Paternal exposure to any mutagenic agent: Not exposed: 87,616 Potential, low: 9,930 Moderate/high: 1,640 **Methods:** Logistic regression models were used to evaluate association between spontaneous abortion and paternal occupation or industry during period of susceptibility (spermatogenesis 80 days prior to conception, or 1st trimester). **Evaluation:**[a] *Low* confidence Industry/occupation coding has low specificity; potential exposure misclassification and imprecise assignment of exposure period to period of spermatogenesis relevant to identified pregnancy.	Spontaneous abortion risk by paternal exposure to formaldehyde[a] Group — *N* — Cases — OR[b] — 95% CI Not exposed — 87,616 — 7,772 — 1.0 — Potential, low — 1,212 — 110 — 1.1 — 0.9, 1.4 Mod/High — 596 — 54 — 1.0 — 0.8, 1.4 [a]Among 25 evaluated exposures. [b]Adjusted for maternal age, socioeconomic status, and maternal exposure to potential reproductive hazards. Paternal exposures to solvents (petroleum refineries), rubber production solvents, rubber chemicals, and ethylene oxide were associated with increased odds of spontaneous abortion ($p < 0.05$).
Reference: Ward et al. (1984) Texas **Population:** Exposed: 11 male pathologists and coworkers at university autopsy service. Matched referent: 11 staff and students in medical branch; matched on sex, age, tobacco, alcohol, and recreational drug use. **Exposure:** Area and personal breathing zone samples; exposures episodic, maximum 5.8 ppm (*7.13 mg/m³*),* LOD = *0.12 mg/m³* TWA 0.61–1.32 ppm (*0.75–1.62 mg/m³*) **Methods:** Morning semen samples every 2−3 months. Sperm counts and morphology (percentage abnormal); three samples per subject at 2- to 3-month intervals; mean value analyzed; Pearson correlation coefficients.	Sperm abnormalities (mean [SD]) by exposure group — Exposed — Referent Count[a] — 62.9 (49.9) — 87.4 (75.0) percentage abnormal — 44.5 (13.4) — 53.5 (16.2) [a] millions/cc of semen Differences between exposed and referent were reported to be not statistically significant.

Study and design	Results
Evaluation:[a] *Low* confidence Small sample size; uncertainty regarding reliability of morphology scoring.	

Organized by study confidence, then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.
[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.8).
Abbreviations: BMI = body mass index; TWA = time-weighted average; SD = standard deviation.
Converted study exposure values are presented in (*italics*). Conversion factors for formaldehyde in air (at 25°C): 1 ppm = 1.23 mg/m^3.

Summary of Human Evidence Synthesis Judgments on Developmental and Reproductive Toxicity

Female Reproductive or Developmental Toxicity

The following factors, in particular the consistent effects in the available *medium* confidence studies, were influential to the synthesis judgment that the human studies on female reproductive or developmental toxicity provide *moderate* evidence of formaldehyde exposure-induced effects.

- *Consistency and Study Confidence*: Decreased fecundability among a working population with maternal exposure in a *medium* confidence study. Increased spontaneous abortion risk among working populations with maternal exposure in two *medium* confidence studies and one low confidence study. Decreased birth weight and head circumferences in two *medium* confidence studies. *Low* confidence studies were mixed, but most were null; the *low* confidence null findings did not reduce certainty.
- *Dose-Response*: Evidence of dose-dependence in effects on fecundability and spontaneous abortion risk was shown by a *medium* confidence study and one *low* confidence study.

Male Reproductive Toxicity

The following factors led to the synthesis judgment that the human studies on male reproductive toxicity provide *slight* evidence of formaldehyde exposure-induced effects.

- *Consistency and Study Confidence*: Two *medium* confidence studies from the same research group observed effects on several sperm parameters, time-to-pregnancy longer than 12 months, increased risk of spontaneous abortion, and an indication of postnatal effects.
- *Coherence*: Several biologically related endpoints were unchanged, reducing certainty.

Animal Studies

This section provides a separate discussion of the available experimental animal studies on developmental toxicity, female reproductive toxicity, and male reproductive toxicity, which are separately summarized in Tables 3-57, 3-58, and 3-59, respectively. For each of these three categories of health effects, the discussion is organized based on the types of endpoints evaluated, and the evidence tables are organized by endpoint, study confidence (if applicable; see Appendix B.3.8 for details), species, and descending publication year.

Two of the studies that assessed developmental toxicity evaluated a standard battery of developmental endpoints following inhalation exposure of formaldehyde to rats on gestation days (GDs) 6–15 (Martin, 1990) or GD 6–20 (Saillenfait et al., 1989) (i.e., during [at a minimum] the period of major organogenesis in the rat). Both of these studies had limitations. Martin (1990) employed robust exposure methods but failed to report methodological details and quantitative results. In contrast, Saillenfait et al. (1989) was well reported, but rodents were exposed to formalin (including 10% methanol), which introduces substantial uncertainty regarding the role of formaldehyde in the observed effects. Importantly, of these two studies, only Saillenfait et al. (1989) identified adverse developmental outcomes. There are also reports identifying developmental effects resulting from formaldehyde exposures administered throughout gestation to rats (Sheveleva, 1971; Senichenkova, 1991a; Senichenkova and Chebotar, 1996a; Pushkina et al., 1968; Monfared, 2012; Kum et al., 2007; Kitaev et al., 1984; Gofmekler et al., 1968). Evidence that inhalation exposures to formaldehyde might affect the female reproductive system in rats is limited to three studies that are considered to be *low* confidence (Wang et al., 2013; Maronpot et al., 1986; Kitaev et al., 1984). However, all of the available animal studies of female reproductive toxicity and developmental toxicity had serious methodological limitations, most notably poor methods used in conducting formaldehyde exposures, and are all interpreted with *low* confidence.

Additionally, studies in rodents reported that formaldehyde adversely affects the male reproductive system after inhalation exposures of varied durations. Some of the studies were considered as *high* to *medium* confidence (Vosoughi et al., 2012; Vosoughi et al., 2013; Sarsilmaz et al., 1999; Ozen et al., 2002; Ozen et al., 2005); however, all of the available *medium* and *high* confidence studies exposed animals to high formaldehyde concentrations (>5 mg/m^3). The other available studies, including many testing lower formaldehyde levels, had methodological limitations that resulted in their consideration as *low* confidence studies (Zhou et al., 2006; Zhou et al., 2011a; Zhou et al., 2011b; Xing et al., 2007a; Han et al., 2015; Golalipour et al., 2007; Appelman et al., 1988). Studies examining developmental immunotoxicity following gestational exposure and developmental neuropathology following postnatal exposure were discussed previously (see Sections 3.2.3 and 3.3.1, respectively).

Developmental toxicity

The formaldehyde database contains results of studies that evaluated effects on pre- or postnatal development following inhalation exposures (see Table 3-57). The evidence table is organized by several major manifestations of developmental toxicity (U.S. EPA, 1991): survival, growth, and morphological development. (Functional developmental toxicity is not addressed here.) Because all of the developmental toxicology studies have limitations that result in *low* confidence ratings, studies within each category are presented in alphabetical order by author in the table. The results of these studies are presented in Figure 3-31.

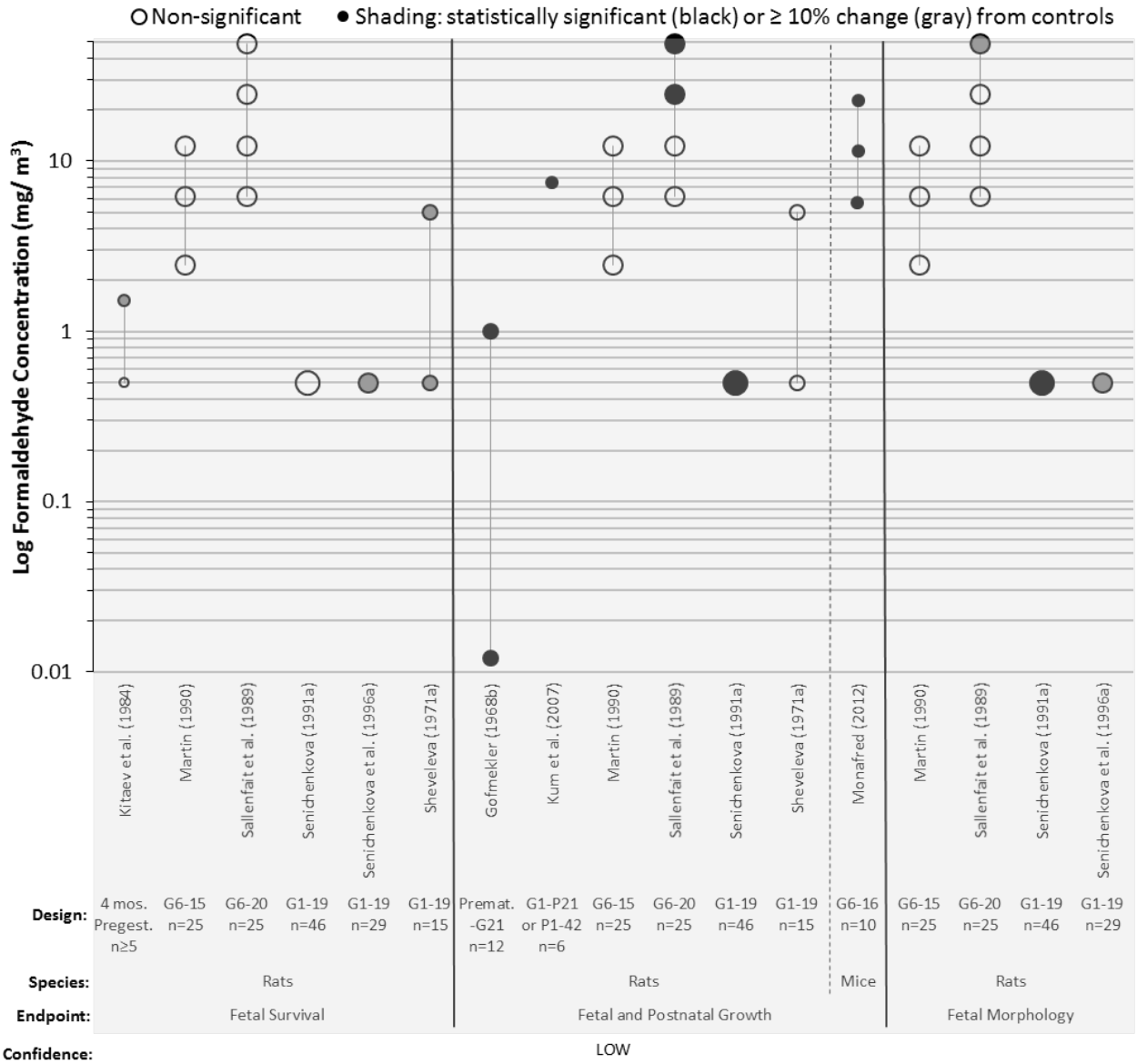


Figure 3-31. Animal studies evaluating the effects of formaldehyde inhalation exposure on developmental toxicity.

Low confidence animal studies of developmental toxicity are presented. As no *high* or *medium* confidence experimental animal studies were identified (see Appendix B.3.8), the available studies are organized by endpoint, then species, then by timing of exposure (e.g., premating [premat.] or pregestational [pregest.]; gestational [g= gestational day]; or postnatal [p = postnatal day] exposure). Filled shapes indicate statistical significance, as indicated by the study author (black), or ≥10% change from control groups (gray). The size of the points reflecting the sample size for that particular exposure group (larger size = larger *n*). The *low* confidence experiments are shown on a gray background, as the identified study limitations substantially reduce confidence in the reliability of the results; these low confidence experiments contribute very little to the weight of evidence for developmental toxicity.

Fetal survival

Decreased prenatal survival following developmental exposures was observed as increased preimplantation loss by Kitaev et al. (1984) at 1.5 mg/m^3 and by (Sheveleva, 1971) at 0.5 mg/m^3 or increased postimplantation loss at 0.5 mg/m^3 by Senichenkova and Chebotar (Senichenkova and Chebotar, 1996b). The evidence for these outcomes across the available studies is inconsistent (see Table 3-57). For example, only Kitaev et al. (1984), Senichenkova et al. (1991b), and Sheveleva et al. (1971) treated the dams during the preimplantation period (i.e., GD 0–6 in rats) and specifically indicated that preimplantation loss was examined. Kitaev et al. (1984) found degenerated embryos on GD 3, but not GD 2 (which could reasonably have been the result of continued exposure of the embryos to stressors resulting from formaldehyde exposure and may not have been an inconsistency in response); however, increased preimplantation loss was not observed by (Senichenkova, 1991b). The increased postimplantation loss reported by Senichenkova and Chebotar (1996a) was not observed by Senichenkova et al. (1991b), in spite of the fact that these two studies used the same procedures and exposure levels, nor was it reported by Sheveleva et al. (1971), Saillenfait et al. (1989), or Martin et al. (1990). The reason for these varied responses is unknown, although they might have been influenced by differences in study protocols or study conduct that are not transparently elucidated in the publications. Because of limitations in the description of methods or results for most of these studies, it is not possible to conduct an in-depth evaluation of this issue.

Fetal and postnatal growth

Evidence of decreased or delayed fetal or early postnatal growth was noted in a number of studies, but a consistent pattern of response was difficult to identify due to differences in study protocols and study quality. Following gestational formaldehyde exposure, significant 24–32% decreases in fetal body weight (accompanied by alterations in placental weight and ultrastructural conformation of the placenta) were observed in mice at exposure levels of ≥5.68 mg/m^3 by Monfared et al. (2012). Saillenfait et al. (1989) reported significant fetal weight decreases in rats of 5% at 24.6 mg/m^3 and of 19–21% at 49.2 mg/m^3. However, fetal weight deficits were not noted by Martin et al. (1990) at exposure levels up to 12.3 mg/m^3 or by Sheveleva (1971) at 5 mg/m^3. Conversely, significantly increased fetal body weight was noted in some studies following gestational exposure to comparatively lower exposure levels of formaldehyde, e.g., Gofmekler et al. (1968) (7% and 13% increased fetal weight at 0.012 and 1 mg/m^3, respectively) and Senichenkova et al. (1991b) (a 5% increase at 0.5 mg/m^3). It is possible that such findings might be more subtle signals for developmental disruption of metabolic regulation and function. At 7.38 mg/m^3, Kum et al. (2007) found significant 31% decreases in rat pup weights at 3 weeks of age following in utero and lactational exposures and significant 14% decreases at 6 weeks of age (i.e., around the time of puberty) following 6 weeks of exposure starting at birth. Body weight decreases (9%) in young adult rats after 6 weeks of exposure starting at 4 weeks of age did not reach statistical significance.

Notably, the same outcome did not occur when adult rats on the study were treated for 6 weeks. These findings suggest the possibility of a life stage-related susceptibility to formaldehyde exposures. Gofmekler et al. (1968) reported significantly decreased neonatal relative liver and lung weights (~5 and 20%, respectively) following gestational exposures to ≥0.012 mg/m^3. A 2–3-day increase in the mean postnatal day on which incisor eruption occurred, another indicator of delayed postnatal growth, was reported in rat pups that had been exposed in utero to 0.5 mg/m^3 (Senichenkova, 1991a).

Fetal morphological development

Morphological alterations of fetuses exposed in utero were reported in three studies (Senichenkova, 1991a; Senichenkova and Chebotar, 1996a; Saillenfait et al., 1989). Senichenkova et al. (1991b) and Saillenfait et al. (1989) observed delayed skeletal ossification of various bones, some of which are generally consistent with developmental delays, at 0.5 and 49.2 mg/m^3, respectively. However, Senichenkova et al. (1991b) noted significantly increased metatarsal and metacarpal ossification centers; this finding suggests more advanced ossification states rather than a delay in development and is consistent with the finding of increased fetal weights in that study. Senichenkova et al. (1991b) also reported an increase in litters with uncharacterized internal organ anomalies at 0.5 mg/m^3. The only outcome specific to reproductive system development was a reported ~20% increase in "cryptorchidism" by Senichenkova and Chebotar (Senichenkova and Chebotar, 1996a) and Senichenkovae et al. (1991b) at 0.5 mg/m^3; this was interpreted as evidence of a delay in fetal (i.e., 1st stage) testes descent. No study in the available database specifically examined the second stage of postnatal testes descent in pups. Thus, there is no evidence to determine if the observed effect represented a developmental delay or if it was related to disruptions in male reproductive tract ontogeny, which is dependent on normal levels of fetal testicular testosterone and on the expression of insulin-like hormone-3 (*insl3*) in fetal Leydig cells (Klonisch et al., 2004). This abnormality was not observed in any other study in the formaldehyde database; however, no single or multigeneration reproduction studies were available, and it is with this type of protocol that such a finding would more likely be detected. Martin et al. (1990) did not report any structural anomalies resulting from inhalation exposures during gestation up to exposure levels of 12.3 mg/m^3.

The potential influence of maternal toxicity on developmental findings was considered in the review of the available data. For several studies, information on maternal toxicity was not reported (Senichenkova, 1991a; Senichenkova and Chebotar, 1996b; Monfared, 2012) although for these studies, it is not known whether (1) maternal toxicity was not assessed or (2) maternal toxicity was assessed, but results were not reported. Kum et al. (2007) measured maternal body and liver weight but found no treatment-related effects. In Kitaev et al. (1984), increased luteinizing hormone (LH) or follicle-stimulating hormone (FSH) levels were observed in dams at 0.5 and 1.5 mg/m^3, with compromised preimplantation survival noted at the highest exposure level. Although the maternal hormonal alterations could have been related to the embryo loss, there was

no confirmation in other studies. Gofmekler et al. (1968) noted increased gestation duration at 0.012 and 1 mg/m^3, with corollary evidence of increased newborn body and organ weights at those exposure levels. Sheveleva et al. (1971) reported evidence suggesting maternal toxicity at 5 mg/m^3, including a decreased threshold of neuromuscular excitability, increased rectal temperature, and increased hemoglobin in dams; however, developmental toxicity (i.e., increased preimplantation loss) was observed at both 0.5 and 5 mg/m^3. Martin et al. (1990) reported significantly decreased maternal weight gain and food consumption only at the highest exposure level (12.3 mg/m^3), but no developmental toxicity was observed in the study. In the Saillenfait et al. (1989) study, significantly decreased maternal body-weight gain was observed only at the highest exposure level (49.2 mg/m^3); however, significantly decreased fetal weight was observed at both 24.6 and 49.2 mg/m^3. Thus, in the limited developmental toxicity database available for evaluation, there was little evidence that maternal toxicity was a major contributing factor to observations of developmental toxicity.

Overall, the database for the evaluation of developmental toxicity (survival, growth, and morphological alterations) consisted of weak (*low* confidence) studies that had methodological limitations, primarily lack of information about the test substance or the described use of formalin, with known or presumed methanol coexposures. Effects on fetal survival, pre- or postnatal growth, or morphological alterations were observed in several studies and sometimes more than one rodent species, and maternal toxicity did not appear to be a confounding influence. However, inconsistencies in response were also observed, and clear dose-response relationships were not discernable. Additional animal experiments using stronger study designs are needed to thoroughly assess the effect of formaldehyde exposure on development.

Table 3-57. Summary of developmental effects observed in animal studies following inhalation exposure to formaldehyde

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)		
Low confidence (all animal studies of developmental toxicity)			
Fetal survival			
Reference: Senichenkova and Chebotar (1996a) Rats (mongrel, strain not reported), 29/group 4 hr/day, GD 1–19 (C-section GD 20) 0 or 0.5 mg/m^3 Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article, exposure generation, animal strain/source, # dams/group, maternal tox NR; limited description of methods.		**0**	**0.5**
	Mean postimplantation loss[c]	-	29%
Reference: Senichenkova (1991b) Rats (white mongrel), 137 dams total, ≈46 dams/group 4 hr/day, GD 1–19 (C-section GD 20) 0 or 0.5 mg/m^3		**0**	**0.5**
	Number (%) preimplantation loss	38/381 (10.0)	25/304 (8.2)
	Number (%) postimplantation loss	26/343 (7.6)	12/279 (7.3)

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)
Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article NC; exposure generation, animal strain/source, # dams/group, maternal tox NR; limited description of methods.	Mean preimplantation loss – –3% Mean postimplantation loss – –15%
Reference: Martin (1990) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–15 0, 2.46, 6.15, 12.3 mg/m^3 Test article: Paraformaldehyde Maternal tox: Significantly decreased maternal body-weight gain and food consumption at 12.3 mg/m^3 **Main limitations**: Inadequate reporting of methods and quantitative results.	Report states that there was no evidence of decreased fetal survival; no data were presented.
Reference: Saillenfait et al. (1989) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–20 0, 6.15, 12.3, 24.6, or 49.2 mg/m^3 Test article: Formalin Maternal tox: Significantly decreased maternal body-weight gain at 49.2 mg/m^3 **Main limitation**: Formalin.	**0** / **6.15** / **12.3** / **24.6** / **49.2** Mean total fetal loss/litter[c]: – / –33 / 0 / 0 / 0%
Reference: Kitaev et al. (1984) Rats (Wistar), 200 females total 4 hr/day, 5 days/week, for 4 months 0, 0.5 or 1.5 mg/m^3 Test article: Not characterized Maternal tox: Altered LH and FSH levels in treated dams **Main limitations**: Test article NC; limited description of methods.	**0** / **0.5** / **1.5** Number (percentage) degenerated embryos GD 2 (n = 5–8): 2 (5.1) / 3 (3.8) / 5 (10.2) Number (percentage) degenerated embryos GD 3 (n = 5–9): 3 (4.4) / 4 (9.1) / 10 (14.9)
Reference: Sheveleva (1971) Rats (mongrel, strain not reported), 15/group terminated GD 20, 6/group littered 4 hr/day, GD 1–19 0, 0.5, or 5 mg/m^3 Test article: Not characterized Maternal tox: Decreased threshold of neuromuscular excitability, rectal temperature, and hemoglobin in dams at 5 mg/m^3 **Main limitations**: Test article NC; exposure generation, animal strain/source NR; limited description of methods.	**0** / **0.5** / **5** Mean preimplantation loss[c]: - / 50 / 70% Mean postimplantation loss[c]: - / 0 / 0%
Fetal and postnatal growth	
Reference: Monfared (2012) Mice (Balb/C), 10/group 8 hr/day, GD 6–16 (C-section GD 17) 0, 5.68, 11.38, or 22.76 mg/m^3	**0** / **5.68** / **11.38** / **22.76** Mean fetal weight (g): - / -24* / -27* / -32%* Mean placental weight (g): - / 35* / 57* / 39%*

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)			
Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article NC; maternal tox: NR.	Thickness of placental tropho-blastic basement membrane (nm)	-	148*	177*	203%*
	Thickness of placental labyrinth interhemal membrane (µm)	-	45*	42*	49%*
Reference: Kum et al. (2007) Rats (Sprague Dawley), 6/group 8 hr/day, 7 days/week, for 6 weeks starting at GD 1, PND 1, Week-4, or Adult 0 or 7.38 mg/m^3 Test article: Formalin Maternal tox: Not reported **Main limitations**: Formalin; limited description of methods; maternal tox NR.		**0**	**7.38**		
	Decreased pup weight (g) (3-week old pups that were exposed in utero and during lactation)	-	-31%*		
	Decreased pup weight (g) (6-week old pups that were exposed during lactation and for 3 weeks postweaning)	-	-14%*		
	Decreased young adult weight (g) (10-week old young adults that were exposed starting at 4-weeks of age)	-	-9%		
	Mature adult weight (g) (6-week exposure to adult rats)	-	7%		
Reference: Senichenkova (1991b) Rats (white mongrel), 137 dams total, ≈46 dams/group 4 hr/day, GD 1-19 (C-section GD 20) 0 or 0.5 mg/m^3 Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article NC; exposure generation, animal strain/source, # dams/group, maternal tox NR; limited description of methods.		**0**	**0.5**		
	Mean fetal body weight (g)	-	5%*		
	Mean fetal length (mm)	-	0%		
	Mean day of upper incisor eruption	-	17%*		
	Mean day of lower incisor eruption	-	25%*		
Reference: Martin (1990) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–15 0, 2.46, 6.15, 12.3 mg/m^3 Test article: Paraformaldehyde Maternal tox: Significantly decreased maternal body-weight gain and food consumption at 12.3 mg/m^3 **Main limitations**: Inadequate reporting of methods and quantitative results.	Report states that fetal weights were not affected by treatment; no data were presented.				
Reference: Saillenfait et al. (1989) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–20 0, 6.15, 12.3, 24.6, or 49.2 mg/m^3 Test article: Formalin Maternal tox: Significantly decreased maternal body-weight gain at 49.2 mg/m^3 **Main limitation**: Formalin.		**0**	**6.15**	**12.3**	**24.6**	**49.2**
	Mean fetal body weight/litter – male	-	-1	-2	-5*	-21%*
	Mean fetal body weight/litter – female	-	1	0	-3	-19%*
Reference: Sheveleva (1971) Rats (mongrel, strain not reported), 15/group terminated GD 20, 6/group littered 4 hr/day, GD 1–19 0, 0.5, or 5 mg/m^3 Test article: Not characterized		**0**	**0.5**	**5**		
	Mean fetal weight (g)	-	0	3%		
	Mean fetal length (mm)	-	0	0%		

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)		
Maternal tox: Decreased threshold of neuromuscular excitability, rectal temperature, and hemoglobin in dams at 5 mg/m^3 **Main limitations**: Test article NC; exposure generation, animal strain/source NR; limited description of methods.			
Reference: Gofmekler et al. (1968) Rats (strain not specified), 12 females/group Continuous exposure 10–15 days prior to mating and throughout gestation 0, 0.012, or 1 mg/m^3 Test article: Not characterized Maternal tox: Increased duration of gestation at both dose levels **Main limitations**: Test article NC, exposure generation, animal strain/source NR; limited description of methods; limited reporting.		**0**	**0.012**	**1**
	Mean newborn weight (g)	-	7*	13%*
	Mean relative neonatal lung weight (mg/10 g BW)	-	-20*	-19%*
	Mean relative neonatal liver weight (mg/10 g BW)	-	-5*	-6%*
Fetal morphological development				
Reference: Senichenkova and Chebotar (1996a) Rats (mongrel, strain not reported), 29/group 4 hr/day, GD 1–19 (C-section GD 20) 0 or 0.5 mg/m^3 Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article NC; exposure generation, animal strain/source, # dams/group, maternal tox NR; limited description of methods.		**0**	**0.5**	
	Mean percentage litters with hydronephrosis	-	5%	
	Mean percentage litters with cryptorchidism	-	21%	
Reference: Senichenkova (1991b) Rats (white mongrel), 137 dams total, ≈46 dams/group 4 hr/day, GD 1–19 (C-section GD 20) 0 or 0.5 mg/m^3 Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article NC; exposure generation, animal strain/source, # dams/group, maternal tox NR; limited description of methods.		**0**	**0.5**	
	Mean percentage fetuses with cryptorchidism	-	20%*	
	Number of litters with internal organ anomalies	2	8%	
	Mean number of litters with internal organ anomalies	-	914%*	
	Number (percentage) embryos with ossification centers in the hyoid bone	145(100)	61(91)*	
	Mean number of metacarpal bone centers	-	13%*	
	Mean number of metatarsal bone centers	-	9%*	
Reference: Martin (1990) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–15 0, 2.46, 6.15, 12.3 mg/m^3 Test article: Paraformaldehyde Maternal tox: Significantly decreased maternal body-weight gain and food consumption at 12.3 mg/m^3 **Main limitations**: Inadequate reporting of methods and quantitative results.	Report states that fetal incidences of major malformations, minor external and visceral anomalies, or minor skeletal anomalies were not affected by treatment; no data presented.			

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)				
Reference: Saillenfait et al. (1989) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–20 0, 6.15, 12.3, 24.6, or 49.2 mg/m^3 Test article: Formalin Maternal tox: Significantly decreased maternal body-weight gain at 49.2 mg/m^3 **Main limitation**: Formalin.		**0**	**6.15**	**12.3**	**24.6**	**49.2**
	Unossified sternebrae [fetal(litter) incidence]	3(3)	1(1)	6(3)	6(3)	15(7)
	Unossified sternebrae [fetal percentage]	0.9	0.4	1.9	2	4.4%
	Unossified sternebrae [litter percentage]	12.5	4.8	13	14.3	29.2%

Within each category of effect, organized by study confidence then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: GD = gestational day; LH = luteinizing hormone; FSH = follicle-stimulating hormone; NC = not characterized; NR = not reported.
[a]Studies with gestational or lactational exposures and evaluation of pre- or postnatal developmental outcomes are included in this table.
[b]Response relative to control for mean data, or incidence data.
[c]Incidence data not reported.
*Statistically significant difference from control value ($p < 0.05$), as reported by the study author.
Study exposure levels converted from ppm to mg/m^3 are presented in italics (1 ppm = 1.23 mg/m^3).

Female reproductive toxicity

Information on female reproductive toxicity in the formaldehyde database of animal studies is minimal (see Table 3-58; Figure 3-32). For the three *low* confidence studies that noted effects on the female reproductive system, the test substance was either not characterized (Wang et al., 2013; Kitaev et al., 1984) or was reported to be formalin (Maronpot et al., 1986).

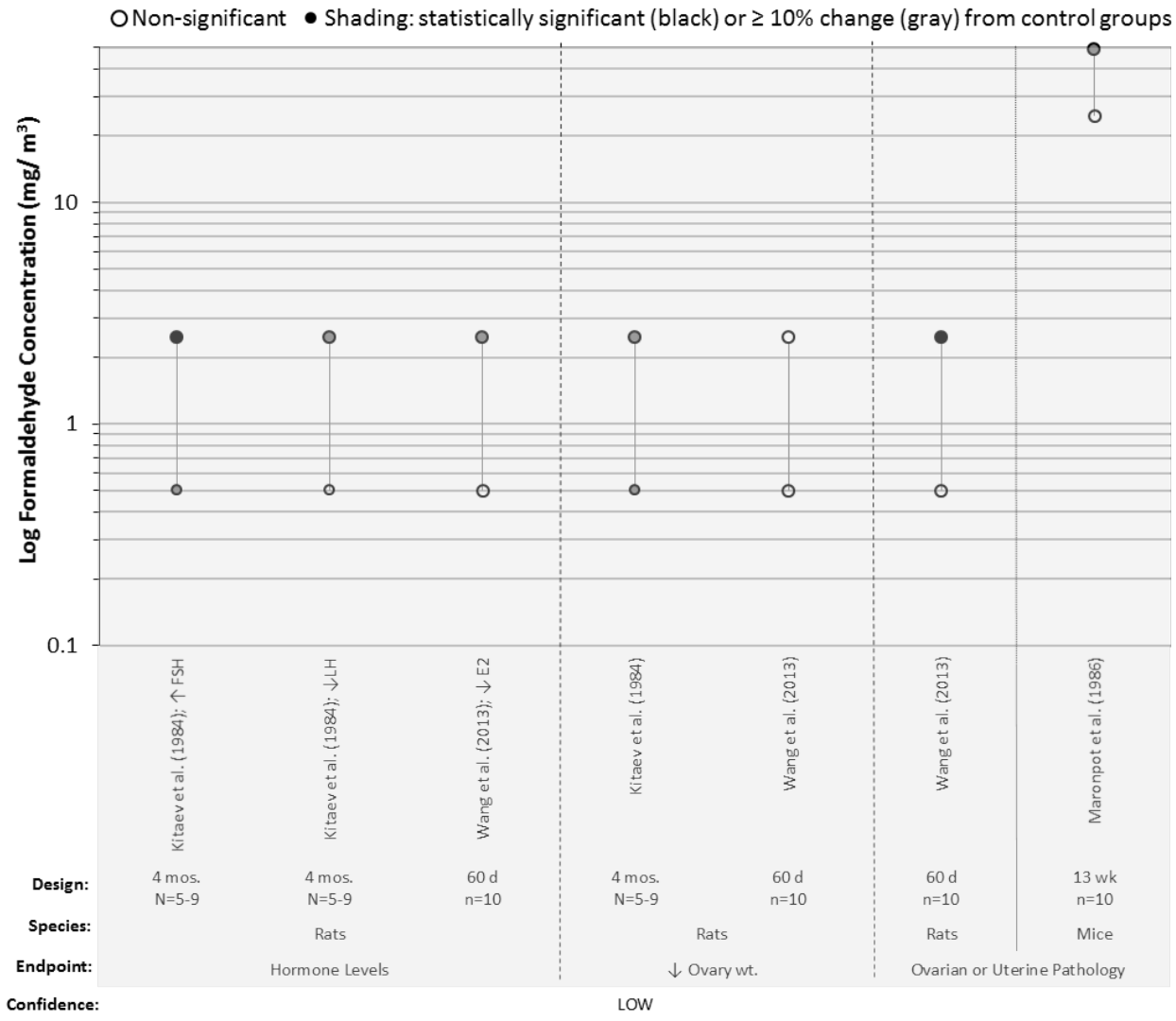


Figure 3-32. Animal studies evaluating female reproductive toxicity.

As no *high* or *medium* confidence experimental animal studies were identified (see Appendix B.3.8), the available studies are organized by endpoint, species, and then by duration of exposure. Symbol shading indicates statistically significant (black) or ≥10% change (gray) from controls, and the size of the points reflects the sample size for that exposure group (larger size = larger *n*). The *low* confidence experiments are shown on a gray background, as the identified study limitations substantially reduce confidence in the reliability of the results; these *low* confidence experiments contribute very little to the weight of evidence judgments for female reproductive toxicity.

Uterine and ovarian hypoplasia was observed by Maronpot et al. (1986) in 100% of the mice on study at 49.2 mg/m^3 following 13 weeks of inhalation exposure; the incidence of these findings was zero at the next lower exposure level of 24.6 mg/m^3. Histopathological evaluation conducted by Wang et al. (2013) did not confirm these findings, but identified a significant decrease in the number and size of mature ovarian follicles with a concomitant increase in the number of atretic follicles, and disruptions in structural integrity of the ovary in rats after 8 weeks of

formaldehyde exposure. Kitaev et al. (1984) reported a 56% increase in relative ovarian weight, accompanied by increased blood LH and FSH levels (11 and 36%, respectively) and significantly increased ovulation (not shown in evidence table), at the lowest dose tested (0.5 mg/m^3) in rats following 4 months of inhalation exposure; these findings are suggestive of a treatment-related disruption of the hypothalamic-pituitary-ovarian (HPO) axis. At the highest dose tested in the same study (1.5 mg/m^3), ovarian weights and LH levels were decreased by 33 and 17%, respectively, as compared to control, and FSH levels were statistically significantly increased (191%); these findings might represent evidence of direct ovarian toxicity and the consequences of disturbed early embryo development in addition to effects on the HPO axis. However, a lack of information about sample collection and analytical methods render it difficult to interpret these data with confidence. The nonmonotonic effect on ovarian weight observed by Kitaev et al. (1984) was not corroborated by Wang et al. (2013). The hormonal alterations observed by Kitaev et al. (1984) could have been related to increased preimplantation loss observed in that study or indicative of an adverse effect on female reproductive system integrity. Other evidence of hormonal disruption, such as 12% decreased estradiol (E2) levels observed by Wang et al. (2013), might have been related to the ovarian histopathology observed in that study.

Overall, as only *low* confidence animal studies of female reproductive toxicity were available, this points to the need for further evaluation of the female reproductive system following formaldehyde inhalation exposure, including an assessment of overall female reproductive function.

Table 3-58. Summary of female reproductive effects observed in animal studies following inhalation exposure to formaldehyde

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)
Low confidence (all animal studies of female reproductive toxicity)	
Reference: Wang et al. (2013) Rats (SD), 10 females/group 8 hr/day, 7 days/week, for 60 days 0, 0.5, 2.46 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC	**0** / **0.5** / **2.46** Mean serum E2 (ng/L)[c]: 0 / −2 / −12 Mean ovarian weight (g)[c]: 0 / −2 / −8 Ovarian histopathological findings at 2.46 mg/m^3 [d]: • Number and size of mature follicles significantly decreased • Number of atretic follicles increased • Vascular congestion, interstitial edema, structure disorder
Reference: Maronpot et al. (1986) Mice (B6C3F1), 10/sex/group 6 hr/day, 5 days/week, for 13 weeks 0, 2.46, 4.92, 12.3, 24.6 or 49.2 mg/m^3 Test article: formalin **Main limitations**: Formalin; limited reporting of methods and results.	**0** / **2.46** / **4.92** / **12.3** / **24.6** / **49.2** Ovarian hypoplasia: 0/10 / NE / NE / NE / 0/10 / 10/10 Uterine hypoplasia: 0/10 / NE / NE / NE / 0/9 / 9/9
Reference: Kitaev et al. (1984) Rats (Wistar), 200 females total 4 hr/day, 5 days/week, for 4 months 0, 0.5 or 1.5 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; limited description of methods.	**0** / **0.5** / **2.46** Mean relative ovary weight[c]: 0 / 56 / −33 Mean blood LH (mg/mL)[c]: 0 / 11 / −17 Mean blood FSH (mg/mL)[c]: 0 / 36 / 191* Number (%) degenerated embryos GD 2 (n = 5–7): 2 (5.1) / 3 (3.8) / 5 (10.2) Number (%) degenerated embryos GD 3 (n = 5–9): 3 (4.4) / 4 (9.1) / 10 (14.9)

Organized by study confidence then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: NE = not evaluated.
[a]Studies that evaluated female reproductive system toxicity are included in this table. Studies are organized by endpoint, species, and lowest dose tested.
[b]Response relative to control for mean data, or incidence data.
[c]Data digitized using Grab It!™, Datatrend Software.
[d]Incidence data not reported.
*Statistically significant difference from control value ($p < 0.05$), as reported by the study author.
Study exposure levels converted from ppm to mg/m^3 are presented in italics (1 ppm = 1.23 mg/m^3).

Male reproductive toxicity

Fourteen studies in rodents assessed effects on the male reproductive system following inhalation formaldehyde exposure (see Table 3-59; Figure 3-33); although eight of the studies had substantial methodological limitations, 13 of the 14 studies demonstrated treatment-related effects. Of the available studies, only those by (Vosoughi et al., 2012; Vosoughi et al., 2013) (both of which reported data from the same cohort of mice; see footnote in Table 3-59), (Ozen et al., 2002; Ozen et

al., 2005), Appelman et al. (1988), Sapmaz et al. (2018), and Sarsilmaz et al. (1999) administered paraformaldehyde to the test animals and provided adequate characterization of the exposure paradigm (note: Appelman et al. (1988) was classified as *low* confidence due to reporting concerns). The results of these paraformaldehyde studies are interpreted with *high* (Vosoughi et al., 2012; Vosoughi et al., 2013) and *medium* (Sarsilmaz et al., 1999; Sapmaz et al., 2018; Ozen et al., 2002; Ozen et al., 2005) confidence; however, the results of the remaining studies in this section are considered much less reliable (i.e., *low* confidence), based in part upon deficient exposure criteria (see Appendix B.3.8). Evaluations of male reproductive toxicity in the more reliable (e.g., *medium,* and *high* confidence) studies are constrained by a complete lack of testing at lower formaldehyde concentrations. Specifically, one *medium* confidence study (Sapmaz et al., 2018) tested a single concentration of 6.15 mg/m^3 and one *medium* confidence study (Ozen et al., 2005) tested concentrations >6 mg/m^3, while the remainder of the *medium* (Sarsilmaz et al., 1999; Ozen et al., 2002) and *high* (Vosoughi et al., 2012; Vosoughi et al., 2013) confidence studies only examined concentrations >12 mg/m^3. These high levels of formaldehyde could introduce additional complications to interpretation, including potential reflex bradypnea. In this regard, Ozen et al. (2005) and Sarsilmaz et al. (1999) noted clinical signs of respiratory irritation or altered breathing rate, while Ozen et al. (2002) and (Vosoughi et al., 2012; Vosoughi et al., 2013) did not report such observations. Sapmaz et al. (2018) did not report observations consistent with reflex bradypnea at 6.15 mg/m^3.

The evidence table is organized by outcomes of male reproductive toxicity, in order of the strength of the evidence: histopathology, sperm measures, gonadotropic hormone measures, organ weights, and reproductive function. Within each category, the studies are organized by *high* to *low* confidence, and then alphabetically within a confidence category. The available animal studies of male reproductive toxicity are illustrated in Figures 3-33 and 3-34, with Figure 3-33 presenting all of the studies and Figure 3-34 presenting in greater detail the studies interpreted with *medium* or *high* confidence.

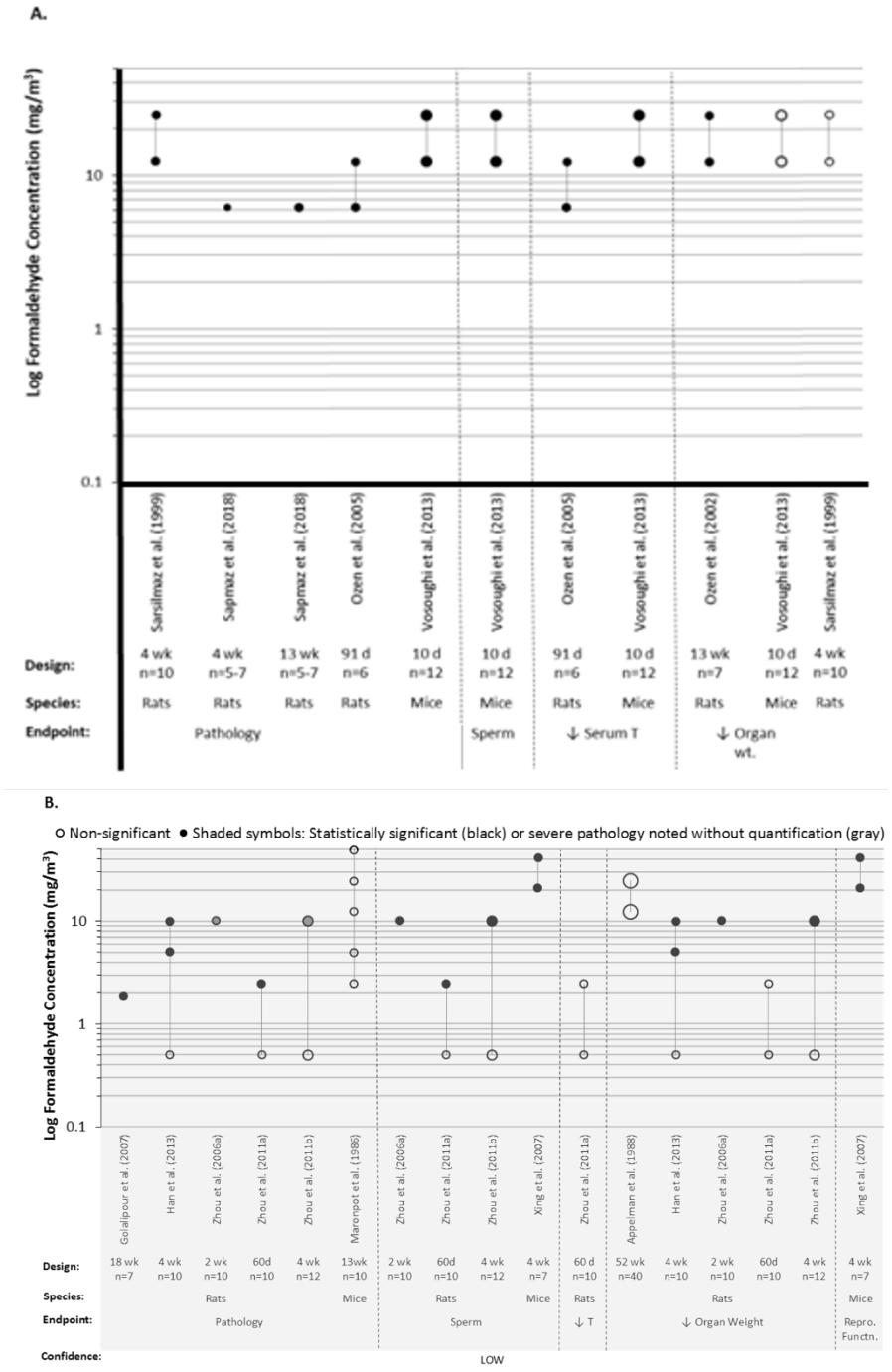


Figure 3-33. Animal studies evaluating male reproductive toxicity.

The available studies are organized into high (i.e., only Vosoughi et al., 2013) and medium confidence studies (panel A) and low confidence studies (panel B), then by endpoint, and then by species. Shaded symbols indicate statistically significant effects ($p < 0.05$ as reported by the study authors) unless otherwise noted, and the size of the points reflects the sample size for that exposure group (larger size = larger n). The low confidence experiments (panel B) are shown on a gray background, as the study limitations substantially reduce confidence in the reliability of the results; these low confidence experiments contribute very little to the weight of evidence judgments for male reproductive toxicity.

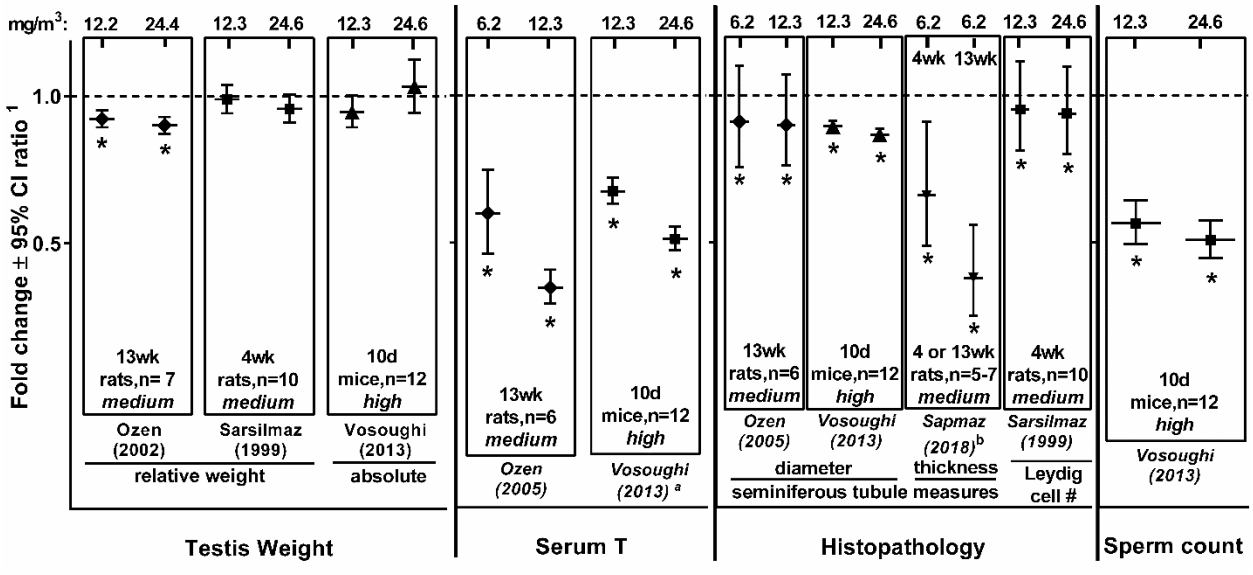


Figure 3-34. *Medium* and *high* confidence animal studies evaluating male reproductive toxicity.

The available *high* and *medium* confidence studies are arrayed and organized by endpoint. [1]Results are displayed as fold change from control animals (control responses at 1 are illustrated as a dashed line), with variability in both the controls and treatment groups represented by the quotient (ratio) of the 95% confidence intervals (CI), as calculated based on the method originally described by E.C. Fieller (Cox and Ruhl, 1966), which assumes Gaussian distributions. [a]The serum T measure at 24 hr is presented from Vosoughi et al. (2013). [b]Seminiferous tubule diameter was not significantly affected by formaldehyde exposure ($p > 0.05$) in Sapmaz et al. (2018), although in addition to the reduced thickness shown above, the authors also reported a significantly reduced percentage of intact tubules at both formaldehyde exposure timepoints (i.e., 71.1% in controls; 42.2% with 6.2 mg/m^3 at 4 weeks; and 17.2% with 6.2 mg/m^3 at 13 weeks). Notes: * = author-reported statistical significance ($p \leq 0.05$). Vosoughi et al. (2013) reflects results from both the 2012 and 2013 studies (Vosoughi et al., 2012; Vosoughi et al., 2013), which report data from the same cohort of mice; (Ozen et al., 2002; Ozen et al., 2005) and Sarsilmaz et al. (1999) are studies from the same research group.

Testes and epididymides histopathology

Quantitative and qualitative histopathological findings in the testes of adult male rodents following from 10 days to 18 weeks of inhalation exposure were reported in one *high* confidence studies (Vosoughi et al., 2012; Vosoughi et al., 2013) and three *medium* confidence studies (Sarsilmaz et al., 1999; Sapmaz et al., 2018; Ozen et al., 2005) that used paraformaldehyde, and in five *low* confidence studies that used formalin (Zhou et al., 2006; Zhou et al., 2011a; Zhou et al., 2011b; Han et al., 2013; Golalipour et al., 2007). Alterations in germ cell number and integrity, statistically significant reductions in germinal epithelium thickness or seminiferous tubule diameter (5–30%), tubular atrophy, markers of disrupted spermatogenic process, and Leydig cell damage were observed. Epididymal findings (e.g., decreased tubule diameters or atrophy, epithelial alterations, or absence of sperm) in Zhou et al. (2011b) also indicated a disruption of

spermatogenesis. One *low* confidence study in mice treated for 13 weeks (Maronpot et al., 1986) did not report any lesions of the male reproductive tract. Notably, while this study used formalin as the test article, this limitation would be expected to bias the study toward observing an effect; thus, there is no credible rationale for this negative outcome. However, evidence of treatment-related testicular pathology in the *high* confidence mouse study by (Vosoughi et al., 2012; Vosoughi et al., 2013) suggests that the absence of effects in Maronpot et al. (1986) is probably not attributable to a difference in species response, although any potential influence of animal strain on response is unknown.

Sperm measures

A significantly decreased sperm count of 44–49% was observed at 35 days post-treatment in a *high* confidence study of mice exposed to ≥12.2 mg/m^3 paraformaldehyde for 10 days (Vosoughi et al., 2012; Vosoughi et al., 2013). In a *low* confidence study in rats, 10 mg/m^3 formalin exposure significantly decreased sperm count by 38% with a 2-week exposure (Zhou et al., 2011a) and 77% with a 4-week exposure (Zhou et al., 2011b), demonstrating an increase in the magnitude of the response as the duration of exposure increased, with the exposure concentration level remaining constant. In a second *low* confidence study, Zhou et al. (2011a) reported a significant 13% reduction in sperm count at 2.46 mg/m^3 after 60 days of formalin exposure, consistent with the interrelationship among concentration, exposure duration, and magnitude of response. These data provide evidence of the downstream effects of disruptions to spermatogenesis that are observed histopathologically.

In the same studies, sperm motility was significantly decreased (by 40–46%) in mice (Vosoughi et al., 2012; Vosoughi et al., 2013) and by 13–17% in rats (Zhou et al., 2011a; Zhou et al., 2011b) at exposure levels ≥10 mg/m^3 paraformaldehyde or formalin, respectively, and significant abnormal sperm morphology was observed at the same exposure levels (Zhou et al., 2006; Vosoughi et al., 2012; Vosoughi et al., 2013). Statistically significant increases in abnormal sperm were also observed in the *low* confidence study by (Xing Sy, 2007; Xing et al., 2007b) after 4 weeks of formalin exposure at exposure levels >20 mg/m^3. The alterations in sperm count, motility, and morphology reported by (Vosoughi et al., 2012; Vosoughi et al., 2013) achieved statistical significance at 35 days (but not at 24 hours) postexposure, demonstrating a biologically plausible temporal delay in the outcomes associated with disruption of spermatogenesis. Altered sperm measures are considered biomarkers of reduced fertility; however, with the exception of the high exposure study by (Xing Sy, 2007; Xing et al., 2007b) that identified a male-mediated reduction in viable conceptuses, the formaldehyde database does not include any studies that specifically assessed fertility measures.

Hormone measures

One *high* confidence study (Vosoughi et al., 2012; Vosoughi et al., 2013) and one *medium* confidence study (Ozen et al., 2005) that exposed rodents to paraformaldehyde found significant,

dose-dependent decreases in serum testosterone (T). Vosoughi et al. (2012); Vosoughi et al. (2013) exposed mice to paraformaldehyde for 10 consecutive days and reported 32–49% decreases at 24 hours post-exposure and 10–15% decreases at 35 days postexposure. While this might suggest postexposure recovery or a compensatory process, there are no other studies that tested this possibility. Ozen et al. (2005) noted similar 40-65% decreases in serum T after exposing rats for 91 days to paraformaldehyde. Zhou et al. (2011a), a *low* confidence formalin study in rats, demonstrated nonsignificant decreases (up to 6%) in serum T after 60 days of exposure. The decreased serum testosterone levels observed by Ozen et al. (2005); (Vosoughi et al., 2012; 2013), and Zhou et al. (2011a) are biologically consistent with the Leydig cell pathology observed by (Vosoughi et al., 2012; 2013) and Sarsilmaz et al. (1999) because Leydig cells are the primary source of testosterone production in the testes. No other studies evaluated alterations in serum T levels following formaldehyde exposure.

Vosoughi et al. (2012); (2013) also reported a significant 15% decrease in serum LH at 24 hours postexposure but not at 35 days postexposure. In the same study, FSH levels were not affected at the 24-hour and 35-day assessment times.

Testes and epididymides weights

A treatment-related effect on testes weight is suggested by the available data. However, even though a number of studies examined testes and epididymides weights, the findings were neither consistent nor easily interpretable. Statistically significant decreased mean testes or epididymal weight of ≥ 20% magnitude was reported in three *low* confidence rat studies with inhalation exposures to 5–10 mg/m^3 formalin for 2- or 4- weeks duration (Zhou et al., 2006; Zhou et al., 2011b; Han et al., 2013). Conversely, testis or epididymal weights were not decreased in two studies: one *high* confidence study that exposed mice to paraformaldehyde for 10 days at up to 24.4 mg/m^3 (Vosoughi et al., 2012; 2013) and one *low* confidence study that exposed rats for 60 days to 2.46 mg/m^3 formalin (Zhou et al., 2011a). It is possible that these two studies did not detect effects on testes weight due to either the short exposure duration or the low-exposure level used, respectively.

Slight decreases in relative (to body weight) testes weight data in rats resulting from 12.2 or 24.4 mg/m^3 paraformaldehyde exposures were reported by Ozen et al. (2002) and Sarsilmaz et al. (1999), *medium* confidence studies in rats. Findings at 4 weeks of exposure in each study were similar, with ≤3% decreases in relative testes weights (although statistical significance was reported by Ozen et al. (2002). Notably, following 13 weeks of exposure, Ozen et al. (2002) reported significant relative testes weight decreases compared to control of up to 10%, suggesting that there was a duration-related component to the response. A significant increase in mean relative (to body weight) testes weight following 53 weeks of paraformaldehyde exposure was reported for a *low* confidence study by Appelman et al. (1988); however, no quantitative data were presented in the study report. Appelman et al. (1988) attributed the relative testes weight increase to decreased body weights. Due to the absence of data on body weight, the veracity of this

interpretation could not be assessed. The use of relative testes weights is typically not preferred for assessment of reproductive toxicity because testes weight has been shown to be generally conserved across 5–30% decreases in body weight (OECD, 2013). Insufficient information (on either the mean testes or body weights used in deriving the relative weight values) was provided in Ozen et al. (2002), Sarsilmaz et al. (1999), and Appelman et al. (1988) to fully evaluate the magnitude of the absolute testes weight effects.

Coherence of the animal evidence

Overall, the database for the evaluation of male reproductive toxicity (histopathology, sperm measures, gonadotropic hormone measures, organ weights, and reproductive function) included multiple *high* or *medium* confidence studies that provided coherent evidence of toxicity spanning biochemical, cellular, tissue, and functional levels. These findings were supported by evidence of male reproductive system toxicity in seven of eight of the remaining *low* confidence studies, although the interpretability of these findings is questionable, primarily due to a lack of information about the test substance or the described use of formalin. Specifically, effects on testes and epididymides histopathology were observed in a *high* confidence study in mice (Vosoughi et al., 2012; Vosoughi et al., 2013), two *medium* confidence studies in rats (Sarsilmaz et al., 1999; Ozen et al., 2005), and five *low* confidence studies in rats. The histopathological outcomes were supported by evidence of reduced serum testosterone in the *high* confidence mouse study (Vosoughi et al., 2012; Vosoughi et al., 2013) and a *medium* confidence rat study (Ozen et al., 2005), and alterations in sperm measures (count, motility, and morphology) in the *high* confidence study in mice (Vosoughi et al., 2012; Vosoughi et al., 2013) and four other *low* confidence studies in rodents, together demonstrating downstream consequences of the testes and epididymides histopathological lesions. Data on testes and epididymides weights provided some support, primarily from a *medium* confidence rat study (Ozen et al., 2002) and several *low* confidence studies, although the results overall were more mixed and difficult to interpret. Uncertainties remain due to a complete lack of *high* or *medium* confidence studies testing exposure levels <6 mg/m^3, and observations potentially consistent with the occurrence of reflex bradypnea at >6 mg/m^3 in two of the studies. However, the observed responses to high levels of formaldehyde provided a coherent pattern of effects in well-conducted studies performed across two international laboratories, using two rodent species, and varied durations, and, in some cases, demonstrating clear concentration-dependent responses of exposure. None of the studies in the database conducted an in-depth assessment of male reproductive function (e.g., including mating or fertility) or evaluated outcomes attributable to early-life exposures (such as would be assessed in a multigeneration reproduction study).

Table 3-59. Summary of male reproductive effects observed in animal studies following inhalation exposure to formaldehyde

Reference and study design[a]	Results[b] and exposure levels (mg/m³)
Testes and epididymides histopathology	
High confidence	
Reference: Vosoughi et al. (2012); Vosoughi et al. (2013)[c] Mice (NMRI), 12 males/group 8 hr/day, 10 days 0, 12.3, or 24.6 mg/m³ Test article: Paraformaldehyde	Histopathological findings in treated males at 35 days postexposure[d]: Testes: seminiferous tubule atrophy Testes: increased space between germ cells Testes: degeneration of Leydig cells Testes: disintegration of seminiferous epithelial cells Testes: degeneration of a number of seminiferous tubules **0** / **12.2** / **24.4** Mean seminiferous tubule diameter (µm)–24 hr postexposure: - / -6 / -7%* Mean seminiferous tubule diameter (µm)–35 days postexposure: - / -11* / -13%*
Medium confidence	
Reference: Sapmaz et al. (2018) Rats (Sprague-Dawley), 7 males/group 8 hr/day, 5 days/week, for 4 or 13 weeks 0 or 6.15 mg/m³ Test article: Paraformaldehyde **Main limitations**: Lack of detailed reporting on quantitative analyses of histopathology; small sample size.	**0** / **6.15 (4wk)** / **6.15 (13wk)** Mean germinal epithelial thickness (% change): - / -33.7%* / -62%* Mean seminiferous tubule diameter (% change): - / -5.2% / -2.2% Percent intact tubules: 71.7% / 42.2%* / 17.2%*
Reference: Ozen et al. (2005) Rats (Wistar), 6 males/group 8 hr/day, 5 days/week, for 91 days 0, 6.15, or 12.3 mg/m³ Test article: Paraformaldehyde **Main limitations**: Limited and incomplete reporting; small sample size.	**0** / **6.15** / **12.3** Mean seminiferous tubule diameters (µm) (*n* = 100 randomly selected tubules/group): - / -23* / -26%*
Reference: Sarsilmaz et al. (1999) Rats (Wistar), 10 males/group 8 hr/day, 5 days/week, for 4 weeks 0, 12.3, or 24.6 mg/m³ Test article: Paraformaldehyde **Main limitations**: Inadequate information for quantitative analysis of histopathology data,	**0** / **12.3** / **24.6** Mean Leydig cell quantity (100 sections total): - / -5* / -6%* Leydig cell nuclear damage (picnotic, karyoretic, karyolitic) (% normal): - / -6 / -22%

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)
Low confidence	
Reference: Zhou et al. (2011b) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/week, for 4 weeks 0, 0.5, 5, or 10 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; exposure generation NR; static chamber used; limited reporting of study results and group data.	Histopathological findings at 5 and 10 mg/m^3 [d]: Testes: seminiferous tubule atrophy Testes: decreased spermatogenic cells Testes: oligospermic lumina **0** / **0.5** / **5** / **10** Mean seminiferous tubule diameter: - / -4 / -28* / -30%*
Reference: Zhou et al. (2011a) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/week, for 60 days 0, 0.5, or 2.46 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	Histopathological findings[d]: Testes: seminiferous tubule atrophy Testes: spermatogenic cells decreased Testes: oligozoospermic lumina Epididymis: oligozoospermic lumina **0** / **0.5** / **2.46** Mean seminiferous tubule diameter (µm): - / -2 / -7%* Mean epididymal tubular diameter (caput): - / -1 / 0% Mean epididymal tubular diameter (cauda): - / 1 / -2%
Reference: Zhou et al. (2011b) Rats (Sprague Dawley), 12 males/group 8 hr/day, 7 days/week, for 4 weeks 0, 0.5, or 10 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	Histopathological findings [d]: Atrophy of epididymal tubules Disintegration of epididymal epithelium Disorganization and denaturalization of epididymal epithelial cells Epididymis: hyperemia of interstitial vasculature Epididymis: oligozoospermic lumina
Reference: Golalipour et al. (2007) Rats (Wistar), 7 males/group 18 weeks formaldehyde exposure (1) 4 hr/day, 4 days/week (2) 2 hr/day, 4 days/week (3) 2 hr/day, 2 days/week 0 or 1.85 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; open air exposures; *N* = 4/group.	Histopathological findings in group (3)[d]: Increased spaces between germ cells in seminiferous tubules Disrupted association between Sertoli and germinal cells Histopathological findings in group (2)[d]: Decreased germ cells and increased thickness of basal membrane in 75% of seminiferous tubules Histopathological findings in group (1)[d]: Severe decrease in germ cells in >85% of seminiferous tubules Arrested spermatogenesis (C) / (1) / (2) / (3) Mean seminiferous tubule diameter: - / -19* / -8* / -5%* Mean seminiferous tubule height: - / -21* / -16* / -12%*

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)			
Reference: Zhou et al. (2006) Rats (Sprague Dawley), 10 males/group (1) 0 (gavage saline) (2) 10 mg/m^3, 12 hr/day, 2 weeks (3) 10 mg/m^3, 12 hr/day, 2 weeks, plus 30 mg/kg-day oral vitamin E Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	Histopathological findings observed in formaldehyde exposure group (2)[d]: Atrophy of seminiferous tubules Decreased spermatogenic cells Disintegrated and sloughed seminiferous epithelial cells Edematous interstitial tissue with vascular dilation and hyperemia Azoospermic seminiferous tubule lumina			
Reference: Maronpot et al. (1986) Mice (B6C3F1), 10/sex/group 6 hr/day, 5 days/week, for 13 weeks 0, 2.46, 4.92, 12.3, 24.6 or 49.2 mg/m^3 Test article: Formalin **Main limitations**: Formalin; limited reporting of methods and results.	No observed effect of treatment on testes histopathology			
Sperm measures				
High confidence				
Reference: Vosoughi et al. (2012); Vosoughi et al. (2013)[c] Mice (NMRI), 12 males/group 8 hr/day for 10 days 0, 12.3, or 24.6 mg/m^3 Test article: Paraformaldehyde	**24-hours Post-exposure:**	**0**	**12.2**	**24.4**
	Mean epididymal sperm count (10^6/mL)	-	-18	-22%
	Mean progressive motility (%)	-	-7	-18%
	Mean immotile sperm (%)	-	33	56%*
	Sperm viability (%)	-	-8	-14%*
	Mean normal morphology (%)	-	-7	-7%
	35-days Post-exposure:			
	Mean sperm count (10^6/mL)	-	-44*	-49%*
	Mean progressive motility (%)	-	-40*	-46%*
	Mean immotile sperm (%)	-	129*	170%*
	Sperm viability (%)	-	-26*	-34%*
	Mean normal morphology (%)	-	-13*	-16%*
Low confidence				
Reference: Zhou et al. (2011a) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/week, for 60 days 0, 0.5, or 2.46 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.		**0**	**0.5**	**2.46**
	Mean epididymal sperm count (× 10^6)	-	-2	-13%*
	Mean percentage motile sperm	-	-3	-4%
	Mean percentage abnormal sperm	-	1	4%*

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)			
Reference: Zhou et al. (2011b) Rats (Sprague Dawley), 12 males/group 8 hr/day, 7 days/week, for 4 weeks 0, 0.5, or 10 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.		**0**	**0.5**	**10**
	Mean epididymal sperm count (× 10^6)[e]	-	3	-77%*
	Mean percentage motile sperm[e]	-	-1	-14%*
Reference: Xing Sy (2007); (Xing et al., 2007b) Mice (unspecified strain), 7 males/group 2 hr/day, 6 days/week, for 4 weeks 0, 20.79, 41.57, or 83.15 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; exposure generation, strain NR; high exposure levels.		**0**	**20.8**	**41.6**	**83.2**
	Percentage abnormal sperm	6.5	9.5*	14.3*	16.2*
Reference: Zhou et al. (2006) Rats (Sprague Dawley), 10 males/group (1) 0 (gavage saline); (2) 10 mg/m^3, 12 hr/day, 2 weeks; (3) 10 mg/m^3, 12 hr/day, 2 weeks, plus 30 mg/kg-day oral vitamin E Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.		**(1)**	**(2)**	**(3)**
	Mean epididymal sperm count (10^7/g epididymal wt)	-	-38*	-16%
	Mean percentage motile sperm	-	-17*	-11%
	Mean percentage abnormal sperm	-	13*	6%
Hormone measures				
High confidence				
Reference: Vosoughi et al. (2012); Vosoughi et al. (2013)[c] Mice (NMRI), 12 males/group 8 hr/day, 10 days 0, 12.3, or 24.6 mg/m^3 Test article: Paraformaldehyde	**Postexposure assessments:**	**0**	**12.2**	**24.4**
	Mean serum T (ng/mL), 24 hours	-	-32*	-49%*
	Mean serum T (ng/mL), 35 days	-	-10*	-15%*
	Mean serum LH (ng/mL), 24 hours	-	-15*	
	Mean serum LH (ng/mL), 35 days	-	-5	
	Mean serum FSH (ng/mL), 24 hours	-	-5	
	Mean serum FSH (ng/mL), 35 days	-	-5	
Medium confidence				
Reference: Ozen et al. (2005) Rats (Wistar), 6 males/group 8 hr/day, 5 days/week, for 91 days 0, 6.15, or 12.3 mg/m^3 Test article: Paraformaldehyde **Main limitations**: Limited and incomplete reporting; small sample size.		**0**	**6.15**	**12.3**
	Mean (terminal) serum T (nmol/L) (*n* = 6)	-	-40*	-65%*

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)			
Low confidence				
Reference: Zhou et al. (2011a) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/week, for 60 days 0, 0.5, or 2.46 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.		**0**	**0.5**	**2.46**
	Mean (terminal) serum T (nmol/L)	-	-1	-6%
Testes and epididymides weights				
High confidence				
Reference: Vosoughi et al. (2012); Vosoughi et al. (2013)[c] Mice (NMRI), 12 males/group 8 hr/day, 10 days 0, 12.3, or 24.6 mg/m^3 Test article: Paraformaldehyde	**Postexposure assessments:**	**0**	**12.2**	**24.4**
	Mean testes weight (mg), 24 hr[e]	-	2	7%
	Mean testes weight (mg), 35 days[e]	-	-1	0%
Medium Confidence				
Reference: Ozen et al. (2002) Rats (Wistar), 7 males/group 8 hr/day, 5 days/week, for 4 weeks or 13 weeks 0, 12.2, or 24.4 mg/m^3 Test article: Paraformaldehyde **Main limitations:** Non-preferred results reporting; small sample size.		**0**	**12.2**	**24.4**
	Mean relative testes weight (4 weeks)	-	-2*	-3%*
	Mean relative testes weight (13 weeks)	-	-8*	-10%*
Reference: Sarsilmaz et al. (1999) Rats (Wistar), 10 males/group 8 hr/day, 5 days/week, for 4 weeks 0, 12.3, or 24.6 mg/m^3 Test article: Paraformaldehyde **Main limitations**: Inadequate information for quantitative analysis of histopathology data.		**0**	**12.2**	**24.4**
	Mean relative testes weight	-	-1	-4%
Low confidence				
Reference: Zhou et al. (2011b) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/week, for 4 weeks 0, 0.5, 5, or 10 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; exposure generation NR; static chamber used; limited reporting of study results and group data.		**0**	**0.5**	**5**	**10**
	Mean testes weight (g)[e]	-	-3	-24*	-21%*

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)
Reference: Zhou et al. (2011a) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/week, for 60 days 0, 0.5, or 2.46 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	**0** / **0.5** / **2.46** Mean testes weight (g): - / -1 / -3% Mean epididymis weight (g): - / 4 / -2%
Reference: Zhou et al. (2011b) Rats (Sprague Dawley), 12 males/group 8 hr/day, 7 days/week, for 4 weeks 0, 0.5, or 10 mg/m^3 Test article: Not characterized **Main limitations**: test article, exposure generation NR; static chamber used.	**0** / **0.5** / **10** Epididymis weight (g)[e]: - / -2 / -31%*
Reference: Zhou et al. (2006) Rats (Sprague Dawley), 10 males/group (1) 0 (gavage saline); (2) 10 mg/m^3, 12 hr/day, 2 weeks; (3) 10 mg/m^3, 12 hr/day, 2 weeks, plus 30 mg/kg-day oral vitamin E Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	**(1)** / **(2)** / **(3)** Mean testes weight (g)[e]: - / -22* / -3%
Reference: Appelman et al. (1988) Rats (Wistar), 40 males/group 6 hr/day, 5 days/week, for 13 or 52 weeks 0, 0.123, or 12.3 mg/m^3 Test article: Paraformaldehyde **Main limitations**: No indication if histopathology performed on male reproductive organs; quantitative testes weights not presented.	Significant increase in mean relative testes weight at 53 weeks at 10 ppm (12.3 mg/m^3) reported (no data were presented); effect was attributed by study author to decreased body weight.
Reproductive function	
Low confidence	
Reference: Xing Sy (2007); (Xing et al., 2007b) Mice (unspecified strain), 7 males/group, mated with untreated females 2 hr/day, 6 days/week, for 4 weeks 0, 20.79, 41.57, or 83.15 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; exposure generation, strain NR.	**0** / **20.8** / **41.6** / **83.2** Mean live fetuses/litter: - / -3 / -12 / -18%* Mean percentage resorptions[e]: - / 7* / 8* / 10%*

Within each category of effect, organized by study confidence then descending publication year. Results from *low* confidence studies are shaded; these findings are considered less reliable.

Abbreviations: NR = not reported; NC = not characterized; T = testosterone; LH = luteinizing hormone; FSH = follicle-stimulating hormone.

[a]Studies that evaluated male reproductive system toxicity are included in this table. Studies are organized by endpoint, species, and lowest dose tested.
[b]Response relative to control for mean data, or incidence data.
[c][Vosoughi et al., 2012; Vosoughi et al., 2013] reported histopathology and sperm measure data for the same low-exposure group study animals. However, serum LH and FSH data were presented only in Vosoughi et al. (2012) and serum T and testes weight data were presented only in Vosoughi et al. (2013).
[d]Incidence data not reported.
[e]Data digitized using Grab It!™, Datatrend Software.
*Statistically significant difference from control value, as reported by the study author.
Study exposure levels converted from ppm to mg/m^3 are presented in italics (1 ppm = 1.23 mg/m^3).

Summary of Animal Evidence Synthesis Judgments on Developmental and Reproductive Toxicity

Developmental Toxicity

The following factors led to the synthesis judgment that the animal studies on developmental toxicity provide *indeterminate* evidence of formaldehyde exposure-induced effects.

- *Consistency and Study Confidence*: A few *low* confidence studies reported decreased fetal survival, altered fetal or postnatal growth, as well as structural anomalies; however, findings were overall inconsistent across studies and no higher confidence studies were available.

Female Reproductive Toxicity

The following factors led to the synthesis judgment that the animal studies on developmental toxicity provide *indeterminate* evidence of formaldehyde exposure-induced effects. A judgment of *slight* would have been supported if not for the confounding concerns for this nonrespiratory effect.

- *Consistency and Study Confidence*: Three *low* confidence studies reported some female reproductive effects; however, no higher confidence studies were available and there was significant concern for confounding in the available studies which examined only very high formaldehyde levels.
- *Coherence*: Several of the findings in the *low* confidence studies were biologically coherent, including effects on ovarian weights, histopathology and circulating hormones.

Male Reproductive Toxicity

The following factors, in particular the strong consistency and coherence of findings, led to the synthesis judgment that the animal studies on male reproductive toxicity provide *robust* evidence of formaldehyde exposure-induced effects.

- *Consistency and Study Confidence*: One *high* and three *medium* confidence studies consistently observed multiple manifestations of male reproductive effects in both rats and mice, although effects on male reproductive organ weights across studies were inconsistent.
- *Dose-Response:* Dose-dependent effects on some endpoints (serum T; histopathology) were observed in two or more *high* or *medium* confidence studies.

- *Coherence*: Findings from *high* and *medium* confidence studies indicated a constellation of biologically coherent male reproductive effects, including decreased serum testosterone, testes and epididymal histopathology, and effects on sperm.
- *Biological Plausibility*: Multiple biomarkers of oxidative stress, as well as heat shock protein induction, have been observed in the testes or epididymides of exposed rats in well-conducted studies. Heat shock protein immunoreactivity and oxidative stress resulting in hypomethylated sperm (no studies were identified that evaluated sperm methylation changes) have been linked to human male infertility.

Evidence on Mode of Action

Mode of action (MOA) information for potential developmental and reproductive toxicity associated with formaldehyde exposures is limited. No definitive data have been identified that fully support a specific MOA for developmental outcomes, or for alterations in male or female reproductive system conformation or function. Because it is considered unlikely that formaldehyde is distributed via systemic circulation to the reproductive organs, this section discusses potential mechanisms by which formaldehyde exposures might indirectly affect reproductive outcomes following toxic insult at the portal of entry. Mechanistic events associated with respiratory health effects (see Sections 3.2.1–3.2.4 and Appendix C.7) were considered. Biological mechanisms that could plausibly be associated with developmental and reproductive toxicity are discussed, based upon consideration of experimental animal data that included inhalation exposures to formaldehyde. These include: oxidative stress and neuroendocrine-mediated effects (alterations of adrenergic or gonadotropic hormones). Although additional study is needed to better define and verify these potential mechanisms, they could be operant in several primary outcomes that have been noted across toxicology or epidemiology studies with inhalation exposures to formaldehyde: developmental delays, fetal loss, and effects on sperm quality and quantity.

1) Effects on the reproductive system that are due to indirect oxidative stress, possibly linked to inflammatory responses following formaldehyde exposures (evidence from three *medium* and two *low* confidence studies (Zhou et al., 2006; Zhou et al., 2011b; Sapmaz et al., 2018; Ozen et al., 2002; Ozen et al., 2005).

Oxidative stress/damage by reactive oxygen species (ROS) has been hypothesized to play a role in reproductive and developmental toxicity (Wells and Winn, 1996; Juchau et al., 1992; Fantel and Macphail, 1982). Markers of increased oxidative stress have been identified in the blood following formaldehyde inhalation exposures (see Section 3.2.3 and Appendix C.7), and thus, this could also be occurring in peripheral tissues. Plausibly, inflammatory mediators, ROS, or other factors observed in the blood could be operant in reproductive or developmental outcomes by indirectly eliciting responses in the reproductive system or in the developing fetus.

ROS-related outcomes have been detected in cells and tissues distal from the POE, notably in the male reproductive system, where testicular and epididymal toxicity and effects on sperm

have been observed. In a *medium* confidence study in rats, Ozen et al. (2002) investigated the mechanism of oxidative stress associated with testes toxicity by assessing testicular iron, copper, and zinc levels. Zinc and copper levels were reduced in the rat testes, consistent with an increase in testicular ROS. A *medium* confidence study in rats (Sapmaz et al., 2018) identified a statistically significant decrease in glutathione peroxidase (GSH-Px) activities and a statistically significant increase in malondialdehyde (MDA) levels, A *low* confidence study (Zhou et al., 2006) investigated biomarkers of oxidative stress as a potential MOA for testicular toxicity following inhalation exposures of rats to formaldehyde. Significant effects on antioxidants and redox enzymes were observed: decreases in superoxide dismutase (SOD), GSH-Px, and glutathione (GSH), as well as an increase in the oxidative stress biomarker, MDA. The authors also demonstrated the protective effect of coadministration with the antioxidant vitamin E (Zhou et al., 2006) on decreased testes weight, biochemical alterations, histopathological effects, or on sperm count, motility, and morphology. Zhou et al. (2011b), another *low* confidence study from the same research laboratory, demonstrated significantly decreased SOD and GSH-Px activities and significantly increased MDA levels in the epididymides of rats exposed to formaldehyde. No studies have been identified that specifically evaluated the generation of ROS in fetuses following maternal inhalation exposures to formaldehyde, which would be directly informative to this potential relationship.

Chemical or physical stress has been shown to increase the synthesis of heat shock protein 70 (Hsp70), which is involved in protein folding and repair (Craig and Schlesinger, 1985), regulation of apoptosis (Takayama et al., 2003), and it is synthesized during normal spermatogenesis (Dix et al., 1997; Dix, 1997). Additionally, testicular heat shock protein immunoreactivity has been associated with human infertility (Werner et al., 1997). Ozen at al. (2005), a *medium* confidence study, reported the detection of increased Hsp70 in spermatogenic cells from the seminiferous tubules of rats following 13 weeks of inhalation exposure to formaldehyde. The increase in testicular Hsp70 could reflect a response to chemical (formaldehyde) stress to the respiratory system, but no mechanisms exist to explain this potential association. Regardless, the role of heat shock proteins in mammalian fetal development is well-recognized (Walsh et al., 1997).

It has also been proposed that oxidative stress resulting from formaldehyde exposure could result in epigenetic consequences to the male reproductive system (Duong et al., 2011). Tunc and Tremellen (2009) reported that oxidative stress to sperm DNA has resulted in hypomethylation in infertile men. Abnormal methylation of a key spermatogenic gene is associated with defective sperm (Navarro-Costa et al., 2010). This represents a hypothetical indirect mechanism by which formaldehyde could influence methylation in sperm DNA and alter male fertility. None of the studies reporting sperm alterations or related measures (see previous sections) examined the potential role of sperm methylation in these outcomes.

2) Neuroendocrine-mediated mechanisms: disruption of the hypothalamus-pituitary-adrenal gland (HPA) axis or hypothalamic-pituitary-gonadal (HPG) axis (evidence from two *high*,

two *medium*, and one *low* confidence studies—(Vosoughi et al., 2012; Vosoughi et al., 2013; Sorg et al., 2001a; Sari et al., 2004; Ozen et al., 2002; Kitaev et al., 1984).

A stress-induced mechanism might contribute to adverse outcomes on the reproductive system and development in the absence of systemic distribution of formaldehyde.

Disruption of the HPA axis: Stressors such as chemical exposure can cause increased secretion of CRH in the hypothalamus, ACTH in the anterior pituitary gland, and adrenal corticosteroids in the adrenal gland (Smith and Vale, 2006). In support of this hypothesis, a *high* confidence study, Sorg et al. (2001a), demonstrated an increase in blood corticosterone levels after inhalation exposure to formaldehyde. Additionally, Sari et al. (2004), a *medium* confidence study, reported effects of inhalation formaldehyde exposures to mice on CRH neurons in the hypothalamus and ACTH cells in the pituitary gland. The effects of stress on disruptions to reproductive function and outcome in humans are well-recognized (Negro-Vilar, 1993; Mcgrady, 1984; Barnea and Tal, 1991). The preoptic area of the hypothalamus is considered a potential site of integration between the HPA axis and gonadal steroid hormones (Smith and Vale, 2006).

Disruption of the HPG axis: A steroidal endocrine-mediated mechanism would be consistent with outcomes observed in some of the reproductive and developmental epidemiology and toxicology studies. Developmental delays can result from effects on the maternal HPG axis. Hormone levels in pups were not measured in any identified studies; however, there are three studies in adult animals that have directly tested for changes in reproductive hormones after formaldehyde exposure. Kitaev et al. (1984), a *low* confidence study, observed serum FSH increases and LH decreases after inhaled formaldehyde in adult female rats. Alterations in hormone levels could compromise pregnancy maintenance. Another potentially endocrine-mediated outcome, lack of ovarian luteal tissue in females exposed to formaldehyde, was reported in a *low* confidence study by Maronpot et al. (1986). In males, alteration of the HPG axis by formaldehyde exposure could also be theoretically operant. A *high* confidence study in mice (Vosoughi et al., 2012; Vosoughi et al., 2013) and a *medium* confidence study in rats (Ozen et al., 2002), reported significant serum testosterone level decreases, accompanied by histopathological evidence of seminiferous tubule depletion. (Vosoughi et al., 2012; Vosoughi et al., 2013) also reported a significant decrease in serum LH at 24 hours after inhalation formaldehyde exposure. This is notable because the initiation and maintenance of spermatogenesis in rodents and primates require LH stimulation (Plant and Marshall, 2001). Reduced testosterone levels might also contribute to sperm quality and quantity decrements.

These two potential mechanisms are not necessarily mutually exclusive. If verified, they could be shown to be acting alone for certain endpoints (in which case the others may not be operant) or in concert for others. Nevertheless, as stated above, no definitive data have been identified that define an MOA(s) explaining how developmental or reproductive outcomes might occur following inhalation exposure to formaldehyde.

Summary of Inferences Regarding Mode of Action

No verified MOA exists for how formaldehyde could elicit reproductive or developmental effects without systemic distribution; however, several lines of evidence exist to support the potential for effects through indirect mechanisms.

Evidence Integration Summary

Hazard conclusions integrating the evidence of developmental and reproductive hazards in humans and animals were drawn for two categories: female reproductive or developmental toxicity (TTP, spontaneous abortion, birth outcomes, fetal survival, growth, and malformations), and male reproductive toxicity (see Table 3-60). Specifically, for the purposes of this assessment and based on the outcomes reported in the epidemiological literature, female reproductive toxicity and developmental toxicity were considered as a group because it is difficult to distinguish the underlying events that may have resulted in either a delayed recognized pregnancy or fetal loss.

Female reproductive or developmental toxicity

While studies that evaluated physiological measures of reproductive health in females were not available, two *medium* confidence studies reported strong associations of occupational exposure to formaldehyde with decreased fecundability, increased TTP, and spontaneous abortion (Taskinen et al., 1999; John et al., 1994). A third study also reported an elevated risk of spontaneous abortion with higher exposure frequency of similar magnitude, but the effect estimate may have been biased to an unknown degree by confounding from coexposure to xylene (Taskinen et al., 1994). Excluding the study would not change the weight-of-evidence conclusion for the epidemiological evidence. It is recognized that the decreased fecundability and increased TTP might have resulted from early fetal loss or be a consequence of alterations in maternal reproductive function (discussed below). Only one of the occupational studies (in woodworkers) reported the levels of formaldehyde that resulted in the observed associations (0.27 mg/m^3) (Taskinen et al., 1999). Studies of hospital, nursing, or medical employees generally did not report an association with formaldehyde exposure, although these *low* confidence studies tended to use less informative exposure-assessment methods, a major limitation that reduced the sensitivity of these studies. An association of uncharacterized birth defects with maternal exposure (Zhu et al., 2006; Saurel-Cubizolles et al., 1994; Hemminki et al., 1985) was suggested in some occupational epidemiological studies; the precision of the ORs was quite low, as indicated by the wide CIs, which limited the sensitivity of these analyses. Three studies of pregnancy cohorts indicate an association with fetal growth including biparietal diameter in the 2nd trimester and birthweight, although there are questions about the interpretation of the results overall given that stronger associations were observed in a population with very low exposures (Franklin et al., 2019) and a relatively weak association was observed in a population with higher exposure with potential confounding by TVOCs (Chang et al., 2017). Preterm birth and low birth weight were not associated with higher formaldehyde exposure among a cohort of male woodworkers in China (Wang et al., 2012).

Animal studies evaluated several endpoints relevant to developmental toxicity (i.e., decreased survival, decreased growth, or increased evidence of structural anomalies) or female reproductive toxicity (i.e., ovarian and uterine pathology, ovarian weight, or hormonal changes). All available studies were of *low* confidence, primarily due to exposure-quality concerns (i.e., the use of formalin, or an uncharacterized test substance). In addition, there was considerable heterogeneity in both of these data sets, and consistent evidence supporting manifestations of toxicity after formaldehyde exposure was not reported. However, as several of these studies did identify potential findings of concern, these outcomes are deserving of additional study. In addition, several studies examining effects on the nervous system after formaldehyde exposure in rats during development suggest that formaldehyde inhalation might have the potential to affect the developing nervous system (see Section 3.3.1), however, additional studies are needed to clarify these preliminary findings. Studies on developmental immunotoxicity were considered *not informative* (see Section 3.2.3 and Appendix B.3.4) and no epidemiological studies of children were identified.

Overall, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of developmental or female reproductive toxicity in humans, given sufficient exposure conditions. This conclusion is based on *moderate* evidence in observational studies finding increases in TTP and spontaneous abortion risk among women occupationally exposed to formaldehyde; the evidence in animals is *indeterminate*, and a plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde is lacking. The primary basis for this conclusion is from studies of women with occupational exposures to formaldehyde.

Male reproductive toxicity

Few epidemiological studies evaluated effects on the male reproductive system. Two studies of male woodworkers in China from one research group reported associations with lower total and progressive sperm motility, and delayed fertility and spontaneous abortion (Wang et al., 2012; Wang et al., 2015). The investigators used a well-designed exposure assessment to evaluate associations in this highly exposed occupational population (0.22–2.91 mg/m^3). Two other studies with low sensitivity to detect associations (due to concerns with low precision and exposure misclassification) did not observe effects on sperm counts and morphology or spontaneous abortion among exposed men (Ward et al., 1984; Lindbohm et al., 1991).

Animal studies were available that evaluated several effects from formaldehyde inhalation exposure on the male reproductive system. A coherent set of *high* and *medium* confidence studies in mice and rats that tested formaldehyde exposures >6 mg/m^3 reported effects on multiple endpoints, although interpretations could not be drawn regarding the potential for these effects in experimental animals at lower formaldehyde exposure levels. Qualitative and quantitative histopathological effects were observed in the testes and epididymides of a *high* confidence study in mice (Vosoughi et al., 2012; Vosoughi et al., 2013) and in two *medium* confidence rat studies (Sarsilmaz et al., 1999; Ozen et al., 2005). Histopathological findings in testes were also observed by

(Sapmaz et al., 2018), a *medium* confidence study in rats. These observations were supported by similar findings in a number of *low* confidence studies. Decreased serum testosterone (T) was also observed in one *high* and one *medium* confidence studies in mice and rats, respectively (Vosoughi et al., 2012; Vosoughi et al., 2013; Ozen et al., 2005), as well as in a *low* confidence rat study (Zhou et al., 2011b). The decreased serum T is biologically consistent with testicular Leydig cell damage observed in the histopathological evaluations reported in well-conducted studies (Vosoughi et al., 2012; Vosoughi et al., 2013; Sarsilmaz et al., 1999). Downstream effects of disruptions in spermatogenesis observed in the histopathology data included decreased sperm count and motility, and increased sperm morphological abnormalities in a *high* confidence study in mice (Vosoughi et al., 2012; Vosoughi et al., 2013) and several *low* confidence studies in rats. Testes and epididymides weight alterations are often correlated to some degree with histopathology in those organs; however, while significantly decreased dose- and duration-dependent testes weights were observed in the *medium* confidence study in rats by Ozen et al. (2002), organ weight alterations were not observed in the *high* confidence study in mice by (Vosoughi et al., 2012; Vosoughi et al., 2013), were equivocal in the other *medium* confidence study in rats by Sarsilmaz et al. (1999), and results in *low* confidence studies were mixed, preventing clear interpretations.

Overall, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of reproductive toxicity in men, given sufficient exposure conditions, based on *robust* evidence in animals that presents a coherent array of adverse effects in two species, and *slight* evidence from observational studies of occupational formaldehyde exposure. No plausible, experimentally verified MOA exists to explain such effects without systemic distribution of formaldehyde; however, some support for indirect effects in rodents is provided by relevant mechanistic changes in male reproductive organs. The primary basis for this conclusion is based on bioassays in rodents testing formaldehyde concentrations above 6 mg/m^3 (no *medium* or *high* confidence studies tested lower exposure levels).

Data gaps

While reduced fecundity observed in exposed women may be due to reproductive toxicity or toxicity to the developing fetus, no studies are available in exposed humans or animal experiments that provide more complete assessments of reproductive organ endpoints. This also is true for the evaluation of postnatal developmental toxicity. The anthropomorphic findings by a single study of low residential exposures are concerning and additional studies are needed of these endpoints. The findings by Wang et al. (2015) suggesting formaldehyde-related toxicity to sperm and possible resulting effects on fecundity and fetal survival, and which may be supported by a *low* confidence study in mice (Xing et al., 2007a), provide evidence of male-mediated decreases in fetal viability, and should be investigated further. Ideally, such investigations would include additional human studies of different populations using similarly detailed exposure assessments, as well as single or multigeneration reproductive toxicity studies in animals (which were not identified in the current database). Such studies would also assess female reproductive outcomes, which are not

extensively evaluated in the current database. Ideally, any future toxicology experiments would generate formaldehyde exposures using paraformaldehyde to eliminate the uncertainties pertaining to potential confounding by methanol that limit the majority of currently available animal studies on developmental and reproductive toxicity.

Importantly, as the hazard conclusion for male reproductive toxicity is based on animal studies that only tested formaldehyde exposures ≥6 mg/m^3 (one study) or ≥12 mg/m^3, which introduces uncertainties regarding potential irritation-related effects (e.g., reflex bradypnea, which is not experienced by humans and is expected to be operant at these levels; see Appendix C.2), well-conducted, detailed animal studies testing these endpoints at lower formaldehyde concentrations are warranted.

Table 3-60. Evidence integration summary for effects of formaldehyde inhalation on female reproductive or developmental toxicity

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Female Reproductive or Developmental Toxicity					
Human (female reproductive or developmental toxicity)	*Consistency and Study Confidence*	• Two *medium* confidence studies in two independent populations (woodworkers, cosmetologists): decreased fecundability and increased spontaneous abortion risk. Supporting evidence of association with spontaneous abortion from one *low* confidence study among laboratory workers. • Two *medium* confidence studies of pregnancy cohorts indicating decreased birth weight and head circumference. Two low confidence studies report small increased risk of malformations.	• Null evidence on fecundability and spontaneous abortion from five *low* confidence studies with low sensitivity [note: this does not substantially decrease certainty in the findings from the *medium* confidence studies].	*Moderate* Based on consistent observations among *medium* confidence studies, risk estimates of strong magnitude and observed dose dependence.	The **evidence indicates** that inhalation of formaldehyde likely causes increased risk of female reproductive or developmental toxicity in humans, given sufficient exposure conditions.[a] Primarily based on studies of women with occupational exposures to formaldehyde. *Potential susceptibilities*: no specific data were available to inform potential differences in susceptibility.
	Strength and Precision	• Risk estimates of large magnitude were observed in the highest exposure groups for time-to-pregnancy and spontaneous abortion	• Increases in the two *low* confidence studies of malformations were small and imprecise.		
	Dose-Response	• The *medium* confidence studies of fecundability and spontaneous abortion evaluated multiple exposure categories with highest risk at highest exposure level.			
	Coherence	N/A			

	Biological Plausibility	No direct evidence. However, evidence of elevated oxidative stress in the blood of exposed adults (see Section 3.2.3 and Appendix C.7) might provide a potential indirect linkage. This was not interpreted as sufficient to notably increase certainty.			
Animal (developmental toxicity)	*Consistency and Study Confidence*	• Findings from some *low* confidence studies included decreased fetal survival (pre- or postimplantation loss), altered fetal or postnatal growth, and structural anomalies.	• Findings were overall inconsistent (mixed) across studies on these outcomes. Variations in study design and reporting deficiencies inhibit interpretation. • All studies are *low* confidence, with significant concern for confounding.	*Indeterminate for developmental toxicity* Based on inconsistent findings for several developmental endpoints from *low* confidence studies. [Note: developmental neurotoxicity (*slight* evidence in animals) is addressed under nervous system effects (Section 3.3.1) and did not influence this synthesis judgment].	
	Strength and Precision	N/A			
	Dose-Response	N/A			
	Coherence	N/A			
	Biological Plausibility	No direct evidence. However, evidence of elevated oxidative stress and hormonal alterations in the blood of adult rodents (see Section 3.2.3 and Appendix C.7) might provide a potential indirect linkage, as it is recognized that both oxidative stress and the HPG axis have potential roles in developmental toxicity. This was not interpreted as sufficient to increase certainty to a level beyond *indeterminate*.			
Animal (female reproductive toxicity)	*Consistency and Study Confidence*	• Three *low* confidence studies (two in rats, one in mice) observed some effects on the female reproductive system.	• All studies are *low* confidence, with significant concern for confounding (particularly given the very high formaldehyde levels tested and the nonrespiratory outcome) across the small evidence base.	*Indeterminate (near to Slight) for female reproductive toxicity* Based on findings of reproductive toxicity in a few *low* confidence studies.	
	Strength and Precision	N/A			
	Dose-Response	N/A			

	Coherence	• Although findings are sparse, the observed decreased ovarian weight is coherent with some of the histopathology (e.g., hypoplasia). • Some of the observed hormonal changes in rats could reflect ovarian toxicity, although this linkage was not specifically tested.			
	Biological Plausibility	Neuroendocrine-mediated mechanisms, particularly involving disruption of the hypothalamic-pituitary-gonadal axis, are consistent with alterations of female reproductive hormones observed in low confidence rodent studies following formaldehyde exposures. This was not interpreted as sufficient to increase certainty to a level beyond *indeterminate*.			
Other inferences	• *Relevance to humans*: Relevant health effects observed in humans are the primary basis for the hazard determination. Most of the animal studies only tested high levels of formaldehyde expected to cause irritant effects that may not occur in humans. • *MOA*: No experimentally established MOA exists, and any potential mechanisms have not been well studied.				

N/A = indicates the factor was not applicable to (i.e., did not influence) the judgment drawn.
[a]The "sufficient exposure conditions" are more fully evaluated and defined through dose-response analysis in Section 5.1.

Table 3-61. Evidence integration summary for effects of formaldehyde inhalation on male reproductive toxicity

Evidence	Factor	Increasing certainty	Decreasing certainty	Synthesis judgment	Hazard determination
Male Reproductive Toxicity					
Human	*Consistency and Study Confidence*	• Two *medium* confidence studies of exposure among male woodworkers observed an inverse association with sperm motility measures, as well as an increased prevalence of time to	• The two *medium* confidence studies were conducted by the same research group and are presumed to involve overlapping populations (note: certainty was not reduced by null evidence for effects on sperm counts and	*Slight* Based on deficits in sperm motility, fecundity, spontaneous abortion and birth defects in a	The **evidence indicates** that inhalation of formaldehyde likely causes increased risk of reproductive toxicity in men, given sufficient exposure conditions.[a]

		pregnancy, spontaneous abortion, and birth defects.	morphology in two *low* confidence studies).	male occupational population.	Primarily based on bioassays in rats and mice testing formaldehyde concentrations above 6 mg/m^3 (no *medium* or *high* confidence studies tested lower exposure levels). *Potential susceptibilities*: No specific data were available to inform potential differences in susceptibility.
	Strength and Precision	N/A			
	Dose-Response	N/A			
	Coherence		• Some biologically related endpoints (e.g., sperm counts) were unchanged, although adequate power was a concern.		
	Biological Plausibility	No directly relevant studies were identified.			
Animal	*Consistency and Study Confidence*	• Histopathological lesions of the testes or epididymides in one *high* confidence study in mice, three *medium* confidence studies in rats, and five *low* confidence studies in rats. • One *high* confidence study in mice and *four* low confidence studies in rats: dose-related effects on epididymal sperm. • One *high* confidence study in mice, one *medium* confidence study in rats, and one *low* confidence study in rats: dose-related decreased serum testosterone (and decreased serum luteinizing hormone in the *high* confidence study in mice).	• Mixed results for organ weight changes (i.e., testes; epididymis) across studies. • Null evidence for testes histopathology in one *low* confidence study in mice did not reduce certainty.	*Robust* Based on coherent changes to the male reproductive system in a *high* confidence study of mice and three *medium* confidence studies of rats at formaldehyde levels above 6 mg/m^3 (lower levels were not tested in well-conducted studies). [Note: No multigeneration study was conducted].	

		• One *low* confidence study in mice with evidence of male-mediated decreases in fetal survival.			
	Strength and Precision	N/A			
	Dose-Response	• Dose-related qualitative or quantitative histopathological lesions of the testes or epididymides in the available *medium* and *high* confidence studies.			
	Coherence	• Multiple *high* or *medium* confidence studies provided coherent evidence of toxicity spanning biochemical, cellular, tissue, and functional levels.			
	Biological Plausibility	• Multiple biomarkers of oxidative stress, as well as heat shock protein induction, have been observed in the testes or epididymides of exposed rats in well-conducted studies. Heat shock protein immunoreactivity and oxidative stress resulting in hypomethylated sperm (no studies were identified that evaluated sperm methylation changes) have been linked to human male infertility.			

Other inferences	• *Relevance to humans*: Some uncertainty regarding the relevance of the animal evidence exists, as the studies only tested extremely high concentrations expected to cause strong irritant effects that may not occur in humans; however, in light of the concordant findings in a well-conducted study of humans and an absence of other evidence to the contrary, the relevance of animal male reproductive toxicity outcomes to humans is presumed. • *MOA*: No experimentally established MOA exists, and any potential mechanisms have not been well-studied; however, mechanistic data provide some support for indirect effects on the male reproductive system.	

N/A = indicates the factor was not applicable to (i.e., did not influence) the judgment drawn.

[a]The "sufficient exposure conditions" are more fully evaluated and defined through dose-response analysis in Section 5.1.

3.3.3. Lymphohematopoietic Cancers

The specific endpoints considered in this section include diagnoses of Hodgkin lymphoma, multiple myeloma, myeloid leukemia, or lymphatic leukemia in exposed humans (note: diagnosis of non-Hodgkin lymphoma, a nonspecific grouping of dozens of different lymphomas, was not formally evaluated; see Appendix B.3.9), as well as experimental animal and mechanistic studies relevant to the interpretation of potential effects on the lymphohematopoietic (LHP) system.

Human studies provided *robust* evidence for myeloid leukemia and *slight* evidence for multiple myeloma based on epidemiology studies of occupational formaldehyde levels either in specific work settings (e.g., cohort studies) or in case-control studies. Aneuploidy in chromosomes 1, 5, and 7 in circulating myeloid progenitor cells, considered a potential primary target for LHP carcinogenesis, was associated with occupational formaldehyde exposure. The type of aneuploidies observed in the formaldehyde-exposed asymptomatic human workers are also found in patients with leukemia, as well as in other worker cohorts at increased risk of developing leukemias, which provides support for the plausibility of an association between chronic formaldehyde exposure and leukemogenesis. Moreover, the strong and consistent evidence from a large set of studies that observed mutagenicity in circulating leukocytes of formaldehyde-exposed humans, specifically chromosomal aberrations (CA), and micronucleus (MN) formation, provides additional evidence of biological plausibility for these cancer types. Further support is provided by studies that observed perturbations to immune cell populations in peripheral blood associated with formaldehyde exposure. In particular, decreases in red blood cells (RBCs), white blood cells (WBCs), and platelets, along with a 20% decrease in colony-forming units that arose in vitro as descendants from dedicated progenitors of granulocytes and macrophages (CFU-GMs) were observed in the same exposed group, suggesting both a decrease in the circulating numbers of mature RBCs and WBCs as well as possible decreases in the replicative capacity of myeloblasts.

Increased LHP cancers have not been observed in a well-reported chronic rodent bioassay involving inhalation exposure of both rats and mice to formaldehyde, nor in another rat bioassay that failed to report the incidence of non-nasal neoplastic lesions. Further, positive associations with leukemia have not been reported in rodent studies. Thus, there appears to be a lack of concordance between evidence from chronic rodent bioassays and human epidemiological evidence, although such concordance is not necessarily expected (U.S. EPA, 2005a).

Taken together, based on the *robust* human evidence for these cancers from studies that reported increased risk in groups exposed to occupational formaldehyde levels, the **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans. Separately, based on a limited number of epidemiological studies and potentially relevant mechanistic evidence in exposed humans, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple myeloma and Hodgkin lymphoma. While mechanisms for the induction of myeloid leukemia are yet to be elucidated, they do not appear to require direct interactions between formaldehyde and bone marrow constituents, and either are different in animals or the

existing animal models tested thus far do not characterize the complex process leading to cancers in exposed humans.

Overview of Lymphohematopoietic Cancer Biology

LHP neoplasias describe a broad group of cancers of the blood, bone marrow, and lymph nodes, which includes leukemia, lymphoma, and myeloma. The various LHPs originate through a multistep process in different stages of the hematopoietic pathway (the process through which blood cells are formed). In normal human adults, this process occurs primarily in the bone marrow, with the exception of lymphocytes, which continue to mature in the thymus, spleen, and peripheral tissues. Therefore, LHPs may derive from discrete precursor or stem cells, as well as mature lymphoid cells. Figure 3-35 illustrates the hematopoietic pathway, the location of each differentiation (bone marrow or peripheral tissues), and the likely site of occurrence for transformation in each subtype of LHP. Briefly, normal hematopoietic stem cells differentiate into one of two lineages: myeloid or lymphoid progenitor cells. Normal myeloid progenitor cells may then differentiate into mature RBCs, platelets, or granulocytes; lymphoid progenitor cells derive T and B lymphocytes as well as natural killer (NK) cells and dendritic cells (see Figure 3-35).

LHP neoplasias arise from abnormal hematopoietic and lymphoid cells that are unable to differentiate normally to form mature blood cells. Neoplasias following the myeloid lineage are designated as chronic or acute leukemias, depending on the rate of expansion and the dominant stage of cell differentiation. Acute leukemias are characterized by a rapid onset, whereas chronic leukemias develop slower and progress over a period of months or years. Lymphoid neoplasias may either reside in the blood as chronic or acute lymphoblastic leukemias or develop within peripheral lymphoid sites such as the lymph nodes, spleen, or thymus—these are designated as lymphomas. Some rare leukemias exhibit both myeloid and lymphoid characteristics and are known as biphenotypic leukemias (Russell, 1997).

The majority of leukemias originate in the bone marrow at the hematopoietic stem cell stage or at a later, lineage-restricted stage. Specifically, adult leukemias of myeloid origin such as acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and chronic myeloid leukemia (CML) as well as adult acute lymphoblastic leukemia (ALL) are thought to originate at the stem or progenitor cell stage (Warner et al., 2004).

Lymphomas primarily derive from mature lymphoid cells in peripheral tissues such as the spleen, lymph nodes, and thymus, and are generally classified as either Hodgkin or non-Hodgkin lymphomas (NHLs) depending on the appearance of a specific cancer cell type found in Hodgkin lymphomas. Within the larger groupings of NHLs are numerous subtypes with unique characteristics and origins. Myeloma (also called multiple myeloma) is a cancer of the plasma cells that forms a mass or tumor located in the bone marrow. Most lymphomas and all myelomas, as well as some rare leukemias/lymphomas (adult T cell leukemia [TCL], adult chronic lymphocytic leukemia [CLL], prolymphocytic leukemia [PLL], and hairy cell leukemia [HCL]) originate in mature lymphoid cells (Harris et al., 2001; Greaves, 1999).

While hematopoietic stem cells are normally located in the bone marrow, they do spontaneously mobilize into the peripheral blood at low levels, or in response to chemical insult, mobilize in large numbers (Schulz et al., 2009; Lévesque et al., 2007). These mobilized cells remain in circulation for very short periods of time (minutes to hours) and then localize to peripheral tissues or in some cases, return to the bone marrow. Consequently, there may be a recirculation of hematopoietic stem cells between the bone marrow and other peripheral tissues. Therefore, the potential exists for DNA damage or other types of leukemogenic alteration during this mobilization between tissues. Cells confined to the bone marrow are less vulnerable to environmental insult than cells that enter the general circulation. Therefore, knowledge of the location of origin of discrete LHPs is important to understanding the potential targets of carcinogenic compounds.

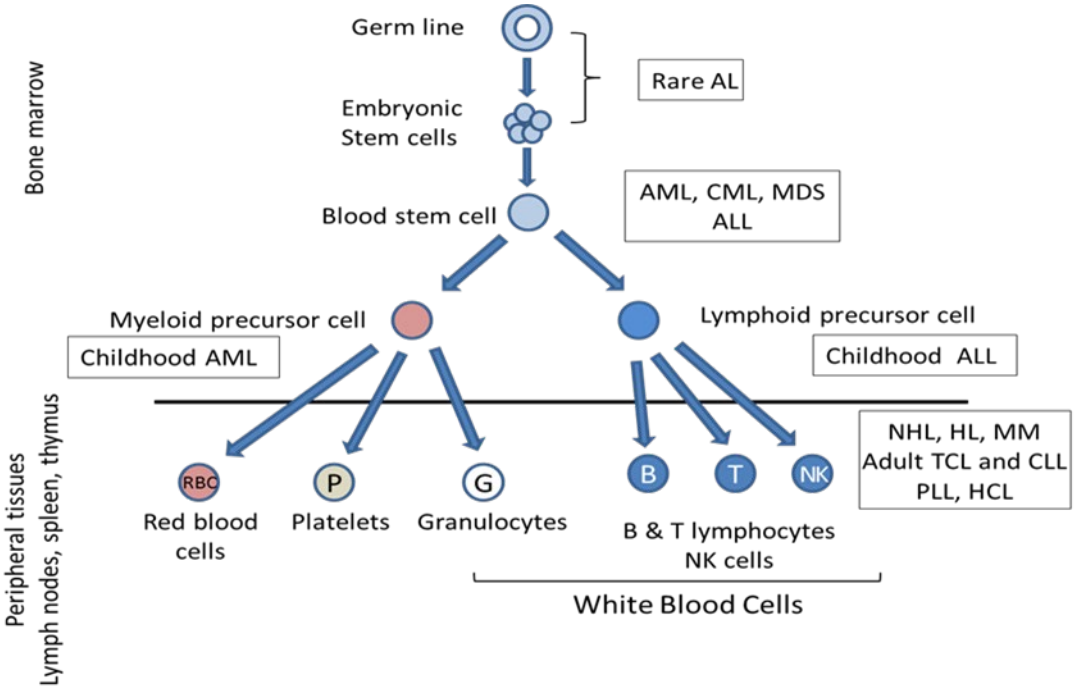


Figure 3-35. The hematopoietic pathway and likely sites of neoplastic transformation for LHPs.

Abbreviations: AML = acute myeloid leukemia; CML = chronic myeloid leukemia; MDS = myelodysplastic syndrome; ALL = acute lymphoblastic leukemia; NHL = non-Hodgkin lymphoma; HL = Hodgkin lymphoma; MM = multiple myeloma; TCL = T cell lymphoma; CLL = chronic lymphocytic leukemia; PLL = prolymphocytic leukemia; HCL = hairy cell leukemia (adapted from: https://www.seattlecca.org/diseases/chronic-myeloid-leukemia-cml/cml-facts-0).

Lymphohematopoietic Cancers in Human Studies

Each specific type of LHP cancer (myeloid leukemia, lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma) is reviewed and evaluated independently in the sections below. For each type of LHP cancer, the evidence is organized by considerations that inform the strength of evidence (e.g., consistency, exposure-response) and evaluation of the potential for bias and insensitivity in individual studies to affect the estimates of relative risk (RR). Evidence tables for each type of LHP cancer (Tables 3-63 through 3-66) are included that are organized first by the study evaluation conclusions (i.e., *high, medium, low*) and then by publication year.

Myeloid leukemia

Epidemiological evidence

The most specific classification of myeloid leukemia diagnosis that is commonly reported across the epidemiological literature has been based on the first three digits of the Eighth or Ninth Revision of the ICD code (i.e., myeloid leukemia ICD-8/9: 205) —although the smaller sets of studies that reported specific results for AML (ICD-8/9: 205.0) and CML (ICD-8/9: 205.1) are discussed. For the purposes of this evaluation, cancer cases reported as monocytic leukemia or nonlymphocytic leukemia were included as myeloid leukemia. Evidence describing the association between formaldehyde exposure and the risk of myeloid leukemia was available from 13 epidemiological papers reporting on 10 different study populations—three case-control studies (Talibov et al., 2014; Hauptmann et al., 2009; Blair et al., 2001) and ten cohort studies (Walrath and Fraumeni, 1983, 1984; Stroup et al., 1986; Saberi Hosnijeh et al., 2013; Pira et al., 2014; Ott et al., 1989; Meyers et al., 2013; Hayes et al., 1990; Coggon et al., 2014; Beane Freeman et al., 2009). Hauptmann et al. (2009) combined the study populations from Hayes et al. (1990) with those from Walrath and Fraumeni (Walrath and Fraumeni, 1983, 1984) and reconstructed individual exposure estimates. Checkoway et al. (2015) reanalyzed Beane Freeman et al. (2009) with a different definition of the exposure categories and presented results for specific subtypes of myeloid leukemia. These are the only formaldehyde studies that specifically evaluated the risk of myeloid leukemia. Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for myeloid leukemia (see Table 3-63) following the causal evaluation.

Consistency of the observed association

The majority of studies of the 10 populations reported elevated risks of myeloid leukemia (or a specific subtype) associated with exposure to formaldehyde for at least one metric of exposure, although four *low* confidence studies reported results based on fewer than 10 cases and two other *low* confidence studies reported relative effect estimates of RR = 1.02 and OR = 1.17.

These studies examined different populations, in different locations[36] and exposure settings, and using different study designs. The study results presented in Table 3-63 (by confidence level and publication date) detail all of the reported associations between exposures to formaldehyde and the risks of developing or dying from myeloid leukemia along with a summary graphic of any limitation and the confidence classification of the available effect estimates. Results for all studies are plotted in Figure 3-36 and grouped by the exposure-assessment methodology (e.g., population-level versus individual-level) and by the type of occupation of the exposed workers (e.g., anatomist/embalmers, industrial workers, garment workers). The same results for the *high* and *medium* confidence studies are plotted in Figure 3-37, and exposure-response trends describing the effect estimates of association between formaldehyde exposure and risk of myeloid leukemia in high confidence studies are shown in Table 3-62.

The first five studies in Figure 3-36 (Walrath and Fraumeni, 1983, 1984; Stroup et al., 1986; Pira et al., 2014; Hayes et al., 1990) shown at the left, under the header "Population-level exposure assessment" followed the health of a group of workers exposed to formaldehyde in a plastics manufacturing facility and four sets of anatomists and embalmers—professions known to be exposed to formaldehyde. These studies compared the risk of death from myeloid leukemia among those workers to the risk of death from myeloid leukemia among the general population. All five studies showed elevated RRs of myeloid leukemia mortality as measured by the mortality ratios, including two studies with 95% CIs that excluded the null, thereby decreasing the likelihood of chance as an alternative explanation for these findings. One study (Stroup et al., 1986) observed a much higher RR (standardized mortality ratio [SMR] 8.8) compared with the others (SMR ~1.4 to 2.0); this higher estimate was based on one subtype (CML), and was relatively imprecise (95% CI: 1.8, 22.5). The results from Pira et al. (2014) and Stroup et al. (1986) were classified with *low* confidence. The results from the other three studies (Walrath and Fraumeni, 1983, 1984; Hayes et al., 1990) were classified with *medium* confidence and are shown in Figure 3-36 to document their findings while acknowledging that these three studies populations were combined in (Hauptmann et al., 2009).

The second set of eight studies (Talibov et al., 2014; Saberi Hosnijeh et al., 2013; Ott et al., 1989; Meyers et al., 2013; Hauptmann et al., 2009; Coggon et al., 2014; Blair et al., 2001; Beane Freeman et al., 2009) is displayed in Figure 3-36 beneath the header of "Individual-level exposure assessment." A general strength of this second set of eight studies was their use of individualized exposure data, which, for six of the studies, allowed for the evaluation of exposure-response

[36] Unlike the available database for nasopharyngeal cancer, the background incidence rates for myeloid leukemia in the 10 study populations were less variable: Six populations were from the U.S., and there was one each from England, Finland, Italy, and Europe. The Age-standardized (world) incidence rate of myeloid leukemia in the U.S. was 4.8 per 100,000 people per year [SEER: 14 registries], the rates in England ranged from 3.4 to 4.0 per 100,000 people per year [Eight locations], the rate in Finland was 3.2 per 100,000 people per year, the rate in Italy ranged from 2.5 to 6.9 per 100,000 people per year [22 locations], based on the IARC publication *Cancer Incidence in Five Continents* (Curado et al., 2007). Rates for Europe, as a unit, were not specified in this source.

relationships with increased formaldehyde exposures using multiple metrics of exposure; additional detail of this consideration is included below under the *exposure-response relationships* section below. A further strength is that three of these studies had their effect estimates classified with *high* confidence (Meyers et al., 2013; Hauptmann et al., 2009; Beane Freeman et al., 2009) and were able to evaluate the impact of the timing of initial exposure relative to mortality; further detail of this consideration is included below under the *temporal relationship* section below. One study's results that were classified with *medium* confidence due to exposure measurement error (Coggon et al., 2014) showed a slightly elevated risk for those workers with the highest job exposures, but also slightly decreased risk for those with the highest duration of exposure. The results from the other four studies with individual-level exposure assessment were classified with *low* confidence due to the lower quality exposure assessment methods (Talibov et al., 2014; Saberi Hosnijeh et al., 2013; Ott et al., 1989; Blair et al., 2001). Additional findings from each of the studies are provided in Table 3-63. Different measures of exposure reflected different risks and this was true within studies and across studies but all provided some evidence of increased risk of dying from myeloid leukemia associated with formaldehyde exposure. One study showed the strongest relationship of myeloid leukemia mortality with duration of formaldehyde exposure (Hauptmann et al., 2009). Another showed increased risks for peak exposure and average exposure but not for cumulative exposure or "any" exposure (Beane Freeman et al., 2009). The Checkoway et al. (2015) reanalysis of Beane Freeman et al. (2009) reported nonsignificant increased risks of AML and CML after redefining the referent group to include all workers with peak exposures of less than 2 ppm as well as some originally classified as having peak exposures of greater than 4 ppm because those worker's peak exposures were thought to be either too frequent or too rare. The result of this change in exposure assessment shifted nine cases of myeloid leukemia from the highest exposure category to the lowest exposure category (Checkoway et al., 2015).[37] Because this change in methodology for exposure assessment blends the highly exposed people with the low and unexposed people and thereby induces bias toward the null reducing study sensitivity, these results were classified with *low* confidence. A third study showed increased risk in the study population as a whole that was stronger among workers with the longest duration of exposure and workers with the greatest length of time since first occupational exposure to formaldehyde (Meyers et al., 2013).

The pattern of increased risk of myeloid leukemia (ICD-8/9: '204') associated with exposure to formaldehyde reflects the associations seen within two subtypes, AML and CML. Among the studies with separate estimates by subtype, risks were elevated for both AML and CML, with the associations for CML appearing to be as strong as or stronger than the associations with AML. Four

[37]In Beane Freeman et al. (2009), for peak exposure there were four cases of ML who were unexposed, 14 cases with peak exposure from >0 to <2 ppm, 11 cases with peak exposure from 2 to <4 ppm, and 19 cases with peak exposure ≥4 ppm. In Checkoway et al. (2015), the new definition of peak exposure and the recategorization resulted in 27 cases of ML with peak exposures from 0 to <2 ppm, 11 cases with peak exposure from 2 to <4 ppm, and 10 cases with peak exposure ≥4 ppm. The Checkoway et al. (2015) results were classified with *low* confidence due to information bias and low sensitivity.

studies reported specific results for CML (Stroup et al., 1986; Saberi Hosnijeh et al., 2013; Checkoway et al., 2015; Blair et al., 2001). All four studies reported elevated risks of CML. Six studies reported specific results for AML; two were classified with *high* confidence (Meyers et al., 2013; Hauptmann et al., 2009), and four with *low* confidence (Talibov et al., 2014; Saberi Hosnijeh et al., 2013; Checkoway et al., 2015; Blair et al., 2001). Both of the high confidence results showed nonsignificantly elevated risks of AML associated with formaldehyde, as did three of four of the *low* confidence results—although substantially higher risks were reported in the *high* confidence results. One *low* confidence result showed a slight decrease in risk of AML (Blair et al., 2001). Results specific to AML are plotted in Figure 3-38. Four of these six studies reported effect estimates for both ML and AML (Saberi Hosnijeh et al., 2013; Meyers et al., 2013; Hauptmann et al., 2009; Checkoway et al., 2015) on a total of 14 specific metrics of exposure. To assess whether the results for AML were comparable to those for ML, the pair-wise effect estimates were evaluated.[38] The correlation between the AML results and the ML results was 0.72 ($p < 0.0001$) and the slope was 0.97 indicating a very strong alignment among these studies and strongly suggesting that the collective results for the broader group of ML cases may be inferred to represent AML as well.

Strength of the observed association

While reported relative effect estimates were consistently elevated above the null value of one across the 10 study populations, the magnitude of the relative effect estimates varied with the quality of the exposure assessment. Studies with higher quality exposure data based on individual-level exposure assessment generally reported higher relative effect estimates (stronger associations). The Hauptmann (2009) study reported the strongest association based on 34 cases of myeloid leukemia of whom 33 had ever performed an embalming (OR = 11.2, 95% CI 1.3, 95.6; p = .027); however, with just 1 case subject who had never embalmed in the reference group, the effect estimate, while statistically significant, is imprecise. The investigators conducted additional analyses that defined the reference group as having performed fewer than 500 embalmings so as to include five cases of myeloid leukemia in the reference group and those results are discussed below.

The results at the highest levels of formaldehyde exposure showed an approximately two- to three-fold relative increase in risk of mortality from myeloid leukemia (Meyers et al., 2013; Hauptmann et al., 2009; Blair et al., 2001; Beane Freeman et al., 2009) with one exception, which reported no increase in risk among those who had ever had a job in the highest category of exposure (Coggon et al., 2014). This may have been due to the choice in (Coggon et al., 2014) to classify as highly exposed all workers who ever worked in a highly exposed job, even if just for one year out of 20, a methodology that mixes workers with many years of high exposure together with

[38] Based on six paired effect estimates from Hauptmann et al. (2009), five paired estimates from Meyers et al. (2013), two paired effect estimates from Checkoway et al. (2015) and one pair of effect estimates from Saberi Hosnijeh et al. (2013).

workers with just a single year of high exposure, thereby potentially diluting the strength of the association. Results from other studies using a cruder exposure classification (i.e., exposed versus not exposed), and low to medium confidence, generally showed elevated risks in the 1.02– to 2–fold range (Talibov et al., 2014; Saberi Hosnijeh et al., 2013; Pira et al., 2014; Ott et al., 1989). Results from the studies with higher quality exposure data were judged with greater confidence.

Temporal relationship of the observed association

Two related aspects of time are encompassed in the consideration of temporality. One aspect is the necessity for the exposure to precede the onset of the disease. In each of the studies, the formaldehyde exposures among the study participants started prior to their diagnoses of myeloid leukemia or deaths from myeloid leukemia and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and was done in a blinded fashion with respect to outcome status. The second aspect involves the time course of formaldehyde exposures in relation to the incidence of myeloid leukemia and death from myeloid leukemia; this aspect of time is defined as the etiologically relevant window of time when exposure to a causal factor is relevant to the causation of disease. From the epidemiological literature of benzene-related leukemia, it is known that there can be an induction/latency period for some environmental agents and that the induction period may exceed 10 years (Rinsky et al., 1987). The epidemiological literature for formaldehyde and myeloid leukemia describes three studies that evaluated the impact of the TSFE (Meyers et al., 2013; Hauptmann et al., 2009; Beane Freeman et al., 2009). All three studies show some indication of an increase in risk at about 15–20 years of time since first exposure (TSFE) to formaldehyde that is consistent with a biologically relevant induction/latency period. However, the Hauptmann et al. (2009) study clearly shows increased risk at 20+ years of time since first exposure. (Beane Freeman et al., 2009) reported that the best fitting exposure lag length of time to potentially account for cancer latency was 18 years. While those three studies support the estimation of the beginning of the potentially relevant window of time, the window may also have an ending when exposures that have occurred a very long time before may no longer be relevant to the causation of disease.

In the mortality follow-up of this cohort through 1980, the High peak exposure had RR = 3.92 (95% CI 0.78, 19.67; *p*-trend = 0.12) (Blair et al., 1986); in the follow-up through 1994, the High peak exposure had RR = 2.79 (95% CI 1.08, 7.21; *p*-trend = 0.02) (Hauptmann et al., 2003); and in the follow-up through 2004 the RR = 1.78 (95% CI 0.87, 3.64; *p*-trend = 0.07). Beane Freeman (2009) reported the effect estimates for follow-up through every individual calendar year starting with 1965 and ending with 2004. Figure 1 of (Beane Freeman et al., 2009) shows the association between peak formaldehyde exposure and the risk of myeloid leukemia; risks of High exposures were compared against the lowest exposed category. Risks were significantly elevated in each year of follow-up during the 1990's before losing significance in the 2000's. Such a pattern may reflect the closing of the potentially relevant window of time when exposures are relevant to disease causation. With very long follow-up of a cohort, those workers who were highly exposed

may have experienced a window of increased risks of myeloid leukemia associated with exposure to formaldehyde that tapered off or closed. This phenomenon may occur as additional background cases of myeloid leukemia – unrelated to formaldehyde exposure, were added to both the High and the Low exposures groups thereby bringing the relative risks of these groups toward the null value of 1.00.

As formaldehyde exposure had ceased by 1980 for all but 3.5% of person-time and latency analyses showed higher risks in the period 15 to 25 years after first exposure with the best fitting exposure lag of 18 years (Beane Freeman et al., 2009), the 1994 follow-up of the NCI formaldehyde cohort (Hauptmann et al., 2003) which reported that High peak exposure had RR = 2.79 (95% CI 1.08, 7.21; *p*-trend = 0.02) may be a more informative estimate of the association between formaldehyde exposure and risks of myeloid leukemia. There is some indication that a similar phenomenon may have occurred in the study of garment worker and the mortality follow-up through 1988 (Pinkerton et al., 2004) which reports somewhat stronger results for workers with 20+ years TSFE than was reported in the 2008 follow-up (Meyers et al., 2013)(SMR = 1.91; $p < 0.05$ vs. SMR = 1.49 (95% CI 0.90, 2.32); and for duration longer than 10 years (SMR = 2.19 vs. SMR =1.84). If the follow-up of these two cohorts has exceeded the window of time when exposures are relevant to disease causation, then the evidence may be somewhat stronger than is evident in the reports from the most recent follow-ups.

Exposure-response relationship

Of the studies that provided evidence to evaluate the association between exposure to formaldehyde and the risk of myeloid leukemia, four studies (Walrath and Fraumeni, 1983, 1984; Stroup et al., 1986; Hayes et al., 1990) followed the health of anatomists and embalmers and did not have specific individual-level exposure data to assess an exposure-response relationship. One study (Ott et al., 1989) did assess individual-level exposures but did not report differentiated risks by exposure levels of formaldehyde. One study, Saberi Hosnijeh et al. (2013), which had risk analyses on three levels of exposure for other health endpoints, did not identify any people with high exposures to formaldehyde and thus could only compare risks of low exposures with risks of no exposures.

The remaining studies did present distinct risk estimates differentiated by formaldehyde exposure levels. Meyers et al. (2013) reported results by workers' year of first exposure, their time since first occupational exposure, and by their duration of exposure. Data on cumulative exposure was not available. The investigators considered that the initial study years (prior to 1963) had the highest formaldehyde exposures as ongoing industrial hygiene practices were thought to have decreased exposures over time. For first employment in the earliest period (before 1963), the overall SMR was 1.37 (95% CI 0.75, 2.30) while first employment in the middle (1963–1970) and late time periods (after 1970) had ORs of 1.13 and 1.15. There was an extensive investigation of exposure-response by duration of exposure with external and internal comparisons by strata of duration as well as multivariate Poisson modeling of exposure duration, all of which showed

increasing risk with longer duration (see Table 3-63). Multiple models all showed positive trends of increasing rate ratios with increasing exposure duration (see Figure 1B in (Meyers et al., 2013)), but the continuous model with duration was not statistically significant with rate ratio of 1.04 per one year increase in duration (95% CI 0.097, 1.12); (Meyers et al., 2013), for durations between 6.5 and 16 years, the rate ratio was 0.43 (95% CI 0.06, 2.39), for durations between 16 and 19 years, the rate ratio was 6.42 (95% CI 1.40, 32.2) and for durations greater than 19 years the rate ratio was 1.71 (95% CI 0.25, 11.0). The evidence from (Meyers et al., 2013) provides only modest evidence of an exposure-response relationship based on duration of exposure.

Beane Freeman et al. (2009) evaluated results by each worker's highest formaldehyde concentration during a "peak" exposure event, by average intensity of exposure, by cumulative exposure, and by duration of exposure. "Peak" exposure events were defined as short-term exposures (<15 minutes) that exceed the TWA formaldehyde intensity (Beane Freeman et al., 2009). Workers' "peak" exposures were defined as the highest concentration among their "peak" exposure events. Among only those workers with some "peak" exposure, the RR in the highest category compared to the lowest category was 1.78 (95% CI 0.87, 3.64) with a trend *p*-value of 0.13 for the continuous values of the peak exposure data. While the investigators considered the lowest group of exposed workers to be the most appropriate reference group (possibly due to a potential for selection bias between exposed and unexposed workers), had the unexposed group been used as the referent group, the RR would have been higher (~ RR of 2.17). This relationship between myeloid leukemia and high peak formaldehyde exposure is not only seen for the complete 2004 follow-up when the average length of follow-up was 42 years, but throughout the cohort experience ((Beane Freeman et al., 2009), see Figure 1 in the publication). These plots show that during the 1970s and 1980s, the RR > 10 until about 1970 and then remained elevated between RR = 4 and RR = 6 until about 1980 and then between about RR = 2 and RR = 3 through the end of follow-up in 2004. Such a consistent finding of a strong effect over many years of follow-up reduces the possibility that the results for the full follow-up period could be due to chance. Beane Freeman et al. (2009) reported that among all workers there was an exposure-response trend through follow-up in 2004 with *p*-value of 0.07 for the continuous values of the peak exposure data; and there was an exposure-response trend through follow-up in 1994 with *p*-value of 0.0087.

Beane Freeman et al. (2009) also reported that among those with any formaldehyde exposure in the 2004 follow-up, the RR in the highest category of average intensity of exposure was 1.61 (95% CI 0.76, 3.39) with little evidence of any trend for the continuous exposure data at nearly 40 years of follow-up ($p = 0.40$). However, the supplementary tables from Beane Freeman et al. (2009) reported that for follow-up through 1994, the exposure-response trend value for all workers was $p = 0.11$. No trend in RR was found for cumulative exposure (see Table 1-60). Overall, the evidence from Beane Freeman et al. (2009) provides limited evidence of an exposure-response relationship based on "peak" exposures.

Hauptmann et al. (2009) evaluated results by multiple metrics of exposure including exposure duration, number of embalmings, cumulative exposure, average formaldehyde intensity while embalming, time-weighted formaldehyde intensity, and peak exposure. Peak exposure levels were defined as the maximum of moving averages of any series of measurements covering 15 minutes. Results for two different reference groups were reported, the first set from the authors' Table 3 used unexposed people as the "a priori" reference group but as there was only one case of myeloid leukemia in this group, the results were statistically unstable with wide Cis. Those results showed an OR of 13.6 (95% CI 1.6, 119.7) for the highest category of duration with a statistically significant trend *p*-value of 0.020; and an OR of 9.5 (95% CI 1.1, 86.0) for the highest category of average exposure; and an OR of 13.0 (95% CI 1.4, 116.9) for the highest category of peak exposure. The second set of results redefined the reference category as those people with fewer than 500 lifetime embalmings. Thus, this referent group includes some exposed individuals, which mutes the categorical comparisons (i.e., this methodology causes bias toward the null and underestimates the effect estimates) but allows for more statistically stable effect estimates as there were five cases of myeloid leukemia in this reference group. Those results showed an OR of 3.9 (95% CI 1.2, 12.5) for the highest category of exposure duration, an OR of 2.3 (95% CI 0.7, 7.5) for the highest category of average exposure, and an OR of 2.9 (95% CI 0.9, 9.5) for the highest category of peak exposure.

Hauptmann et al. (2009) assessed two methodologies to measure potential exposure-response trends: (1) trends based on the complete range of continuous exposure metric data and (2) trends based on the ordinal levels of the categories of the difference exposure metrics, with the former method selected a priori. There was a statistically significant positive exposure-response trend for duration of formaldehyde exposure ($p = 0.020$) as well as a statistically significant positive trend for peak exposures ($p = 0.036$) and the trend *p*-value for average formaldehyde exposure was 0.058. For the other metrics of exposure, the continuous exposure metric data trend *p*-values were greater than 0.10. However, analyses using the ordinal levels of the exposure metrics also showed trends for the TWA8 intensity ($p = 0.021$), the number of embalmings ($p = 0.012$) and for cumulative exposure ($p = 0.023$). Table 3-62 provides a summary of the exposure-response trends reported by Hauptmann et al. (2009), Beane Freeman et al. (2009), and Meyers et al. (2013)—all three of which reported results that were judged to be of *high* confidence (see Table 3-63 and Appendix B.3.9).

Table 3-62. Summary high confidence studies of reported exposure-response trends describing the effect estimates of association between formaldehyde exposure and risk of myeloid leukemia

***High* confidence studies reporting exposure-response trend assessments**						
	Hauptmann et al. (2009)[a]		Beane Freeman et al. (2009)[a]		Meyers et al. (2013)[a]	
Exposure metric	Continuous	Categorical	Continuous 2004 follow-up	Continuous 1994 follow-up	Continuous	Categorical
Duration	p = **0.020**	NR	NR	NR	p = 0.30	NR
# of Embalmings	p = 0.314	p = **0.012**	NR	NR	NR	NR
Cumulative	p = 0.192	p = **0.023**	p = 0.44	p = 0.171	NR	NR
Average	p = 0.058	NR	p = 0.40	p = 0.110	NR	NR
TWA8	p = 0.396	p = **0.021**	NR	NR	NR	NR
Peak	p = **0.036**	NR	p = 0.07	p = **0.0087**	NR	NR

Abbreviations: TWA8 = 8-hour time-weighted average; NR = not reported.
[a]Formaldehyde exposure measured as a continuous variable among unexposed and exposed persons.

Coggon et al. (2014) classified workers' exposures according to the highest level of exposure ever experienced, which can be interpreted as an indicator of peak occupational exposure because each worker was assigned the highest exposure classification ever experienced, and reported exposure-level specific results with an OR of 1.10 (95% CI 0.51, 2.38) for workers with peak occupational exposure of low/moderate and an OR of 1.26 (95% CI 0.39, 4.08) for those workers who had ever worked in a job with high exposures. Among the group with high exposures, those with less than one year of employment at high exposure had an OR of 1.77 (95% CI 0.45, 7.03; 9 exposed cases) while those with 1 year or more at high exposure had an OR of 0.96 (95: CI: 0.24, 3.82; 4 exposed cases). The limitation of this study was the likelihood of nondifferential exposure misclassification due to the quality of the exposure assessment and the lack of any latency analysis. The expected impact is of a downward bias toward the null thereby muting any potential exposure-response. The evidence from Coggon et al. (2014), while potentially biased toward the null and statistically unstable within the "high" exposure category (nine exposed cases), provided only weak evidence of an exposure-response relationship with "peak exposure."

Blair et al. (2001) reported separate results for AML and CML by *low* and *high* intensity of exposure although data were only available to examine exposure-response for CML. Blair et al. (2001) reported an OR = 1.3 (95% CI 0.6, 3.1) for low exposure based on seven cases and an OR = 2.9 (95% CI 0.3, 24.5) for high exposure based on one case. Given that that the OR in the high exposure group was based on only one case, these results provided only weak evidence of an exposure-response relationship.

Talibov et al. (2014) reported results across three levels of cumulative formaldehyde exposure and showed some increasing risk with each increasing level of exposure from HR = 0.89

(95% CI: 0.81, 0.97) in the lowest group to HR = 0.92 (95% CI: 0.83, 1.03) in the middle group and HR = 1.17 (95% CI: 0.91, 1.51) in the highest exposure group. The test for trend showing an exposure-response had a *p*-value of 0.07. As with the other results classified with *low* confidence, the limitation of this study was the likelihood of nondifferential exposure misclassification due to the quality of the exposure assessment, which was based on decennial census records. The expected impact is of a downward bias toward the null thereby muting any potential exposure-response.

The evidence for an exposure-response relationship is most strongly supported by the study of embalmers by Hauptmann et al. (2009), which reported statistically significant trends for five of the six exposure metrics evaluated including duration of exposure, the number of embalmings, cumulative exposure, average intensity of exposure, TWA8 exposure, and "peak" exposure; and a borderline significant trend for the sixth exposure metric (average intensity of exposure). Beane Freeman et al. (2009) reported a borderline significant exposure-response trend for the measure of "peak" exposure that was shown to be statistically significant over the course of more than 30 years of annual follow-up but which faded somewhat as the maturity of the cohort approached 40 years of follow-up—a span of time that far exceeds the latency of all but a few cancers such as mesothelioma. Meyers et al. (2013) also provided solid evidence of an exposure-response relationship based on duration of exposure. Coggon et al. (2014), a *medium* confidence study, found little evidence for an exposure-response relationship.

While it is not known which of these exposure metrics is of greatest biological relevance for myeloid leukemia, all of the exposure metrics reflect different aspects of increased exposure to formaldehyde and associations with increased risks of myeloid leukemia. As the different measures of exposure are all likely to be correlated with each other, it may not be possible at this time to single out one exposure metric as more biologically meaningful than another. It appears that these various trend results reflect some true underlying exposure-response relationship.

Observations of exposure-response relationships are strong evidence in support of an association consistent with causation (Hill, 1965) and against a spurious association because it would necessitate a third (uncontrolled) factor, which changes in the same manner (direction and magnitude) as the exposure of interest (CDC, 2004) to explain away each of the reported exposure-response relationships.

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias is an unlikely alternative explanation for the consistent evidence of increased risk of myeloid leukemia in people exposed to formaldehyde. Selection bias is unlikely in the case-control studies of myeloid leukemia as the case-control (Blair et al., 2001) and nested case-control studies (Hauptmann et al., 2009; Coggon et al., 2014) evaluated exposure status without regard to outcome status and had participation levels of 77-99%. Each of the cohort studies (Walrath and Fraumeni, 1983, 1984; Talibov et al., 2014; Stroup et al., 1986; Saberi Hosnijeh et al., 2013; Pira et al., 2014; Ott et al., 1989; Meyers et al., 2013; Hayes et al., 1990; Coggon et al., 2014; Beane Freeman

et al., 2009) included at least 75% of eligible participants and lost fewer than 3% of participants over the course of mortality follow-up.

Selection bias due to the comparison of a generally healthier group of workers to those in the general population (called the healthy worker effect) could have obscured a truly larger effect of formaldehyde exposure in analyses based on "external" comparisons with mortality in the general population in one study with an SMR = 0.64 for "all cancers" (Stroup et al., 1986), but would not influence analyses using "internal" or matched comparison groups (Meyers et al., 2013; Hauptmann et al., 2009; Coggon et al., 2014; Blair et al., 2001; Beane Freeman et al., 2009). The clearest example of the potential influence of the healthy worker effect is shown in the comparison on results from the study of garment workers (Meyers et al., 2013). That study compared SMRs using an external referent group based on the general population alongside standardized rate ratios (SRR) using an internal referent group of workers in the lowest category of duration of exposure. Compared to the general population (matched on sex, race, age, and calendar time), garment workers with less than a 3-year duration of exposure had an SMR of 0.65 (95% CI 0.18,1.65), which is a 35% lower risk of dying from myeloid leukemia than people in the general population. For workers with a 3- to 9-year duration, the SMR was 1.46, and for workers with 10 or more years of exposure, the SMR was 1.84. Internal comparisons were made by comparing the risk of dying from myeloid leukemia in workers with 3–9 years of exposure to the risk among those with less than 3 years of exposure for an SRR of 2.12. The SRR for workers with 10 or more years of exposure was 3.25. Selection bias may explain why results based on comparisons of mortality of workers with the general population are lower than comparisons of workers to workers. Selection bias does not explain increased risks in exposed workers.

Information bias is an unlikely alternative explanation for the consistent evidence of increased risk of myeloid leukemia in people exposed to formaldehyde. Information bias may distort epidemiological findings when subjects' true exposures are inaccurately assigned at the individual or group level. A differential misclassification, in which exposure status influences disease classification by the investigator (or disease status influences exposure classification), can lead to spurious (i.e., "false positive") associations. However, information bias is considered unlikely among these studies of myeloid leukemia mortality because the likelihood of differential misclassification based on these study designs is low. The assignment of exposure status or calculation of exposure measures in the cohort studies was done independent of knowledge of the cause of death. In the nested case-control studies by Coggon et al. (2014) and Hauptmann et al. (2009) the ascertainment of individual-level exposure levels was independent of the cause of death. In the case-control study by Blair et al. (2001), many different occupational exposures were evaluated based on interview data and subjects were unlikely to be aware of specific chemical exposure of interest in the study. Therefore, an exposure-related recall bias of their occupational histories is unlikely. The exposure assignments in Blair et al. (2001) were based on typical exposure characteristics of the individual's job and were made blinded to case/control status.

There does not appear to be any evidence of confounding that would provide an alternative explanation for the observed association of formaldehyde exposure with increased risk of myeloid leukemia seen in these studies. Chemicals and other coexposures that have not been independently associated with myeloid leukemia are not expected to confound results. However, other known risk factors for myeloid leukemia include exposure to benzene, ionizing radiation, and smoking. Benzene is not used in the embalming process (Stewart et al., 1992; Hayes et al., 1990) and was not a chemical coexposure in the garment plants (Stayner et al., 1985), and consequently, could not be a confounder of those results. Benzene was evaluated by Ott et al. (1989) and not found to be a risk factor (OR = 1.0), and thus, could not be a confounder. Benzene was specifically assessed as a potential confounder among the U.S. industrial workers (Beane Freeman et al., 2009) and found not to be a confounder. Ionizing radiation can be a coexposure for embalmers but the limited extent of such radiation exposure is unlikely to explain the observed association in embalmers (Hauptmann et al., 2009). Exposures to ionizing radiation were not mentioned as coexposures for the industrial workers or the garment workers, and would not be expected to be correlated with their formaldehyde exposures. Smoking was controlled for in the analyses of the embalmers (Hauptmann et al., 2009), which demonstrated a statistically significant exposure-response relation between both duration of formaldehyde exposure and peak exposures with increased risk of death from myeloid leukemia. Blair et al. (2001) also controlled for smoking in their analyses thereby reducing the likelihood of confounding by smoking. Smoking was not evaluated as a potential confounder in the industrial or garment worker cohorts (Meyers et al., 2013; Coggon et al., 2014; Beane Freeman et al., 2009). However, there is no evidence that smoking rates in the industrial or garment worker cohorts (Meyers et al., 2013; Beane Freeman et al., 2009) were correlated with formaldehyde exposures—a necessary condition for potential confounding. Moreover, the internal comparisons used in the analyses of the industrial cohort should mitigate any potential confounding effects of smoking because smoking rates within a cohort are likely to be more similar than compared to the general population.

Consistency across multiple studies is demonstrated by a pattern of increased risk in different populations, exposure scenarios, and time periods. Such consistency makes unmeasured confounding an unlikely alternative explanation for the observed associations. This consistency also reduces the likelihood of chance as an alternative explanation. The observations of exposure-response trends similarly reduce the likelihood that chance, confounding, or other biases can explain the observed association.

Summary of Human Evidence Synthesis Judgments, Causal Evaluation, and Conclusion

Summary of human evidence synthesis judgments

The following factors were most influential to the causal evaluation and synthesis conclusion:

- *Consistency and Study Confidence:* Consistent increases in risk observed across a set of high and medium confidence results from epidemiology studies of occupational formaldehyde levels using varied study designs and populations.

- *Strength and Precision:* The higher confidence results at the highest levels of formaldehyde exposure showed an approximately 2- to 3-fold relative increase in risk of mortality from myeloid leukemia with one exception. Results from studies using cruder exposure classifications generally showed elevated risks in the 1.02– to 2–fold range.

- *Coherence*: Biologically coherent temporal relationship consistent with a pattern of exposure to formaldehyde and subsequent death from myeloid leukemia, allowing time for cancer induction, latency, and mortality.

- *Dose-Response:* Reported exposure-response relationships showed that increased exposure to formaldehyde were associated with increased risk of dying from myeloid leukemia.

Causal evaluation

The human evidence synthesis judgments strongly support a causal conclusion and are further supported by a judgment of reasonable confidence that alternative explanations are ruled out, including chance, bias, and confounding within individual studies or across studies. Consistent observations of genotoxicity in peripheral blood lymphocytes across several occupational studies involving diverse exposure settings further supports the evidence in humans, as does evidence of perturbations to immune cell populations in peripheral blood with formaldehyde exposure.

Conclusion

- The available epidemiological studies provide *robust* evidence of an association consistent with causation between formaldehyde exposure and increased risk of myeloid leukemia.

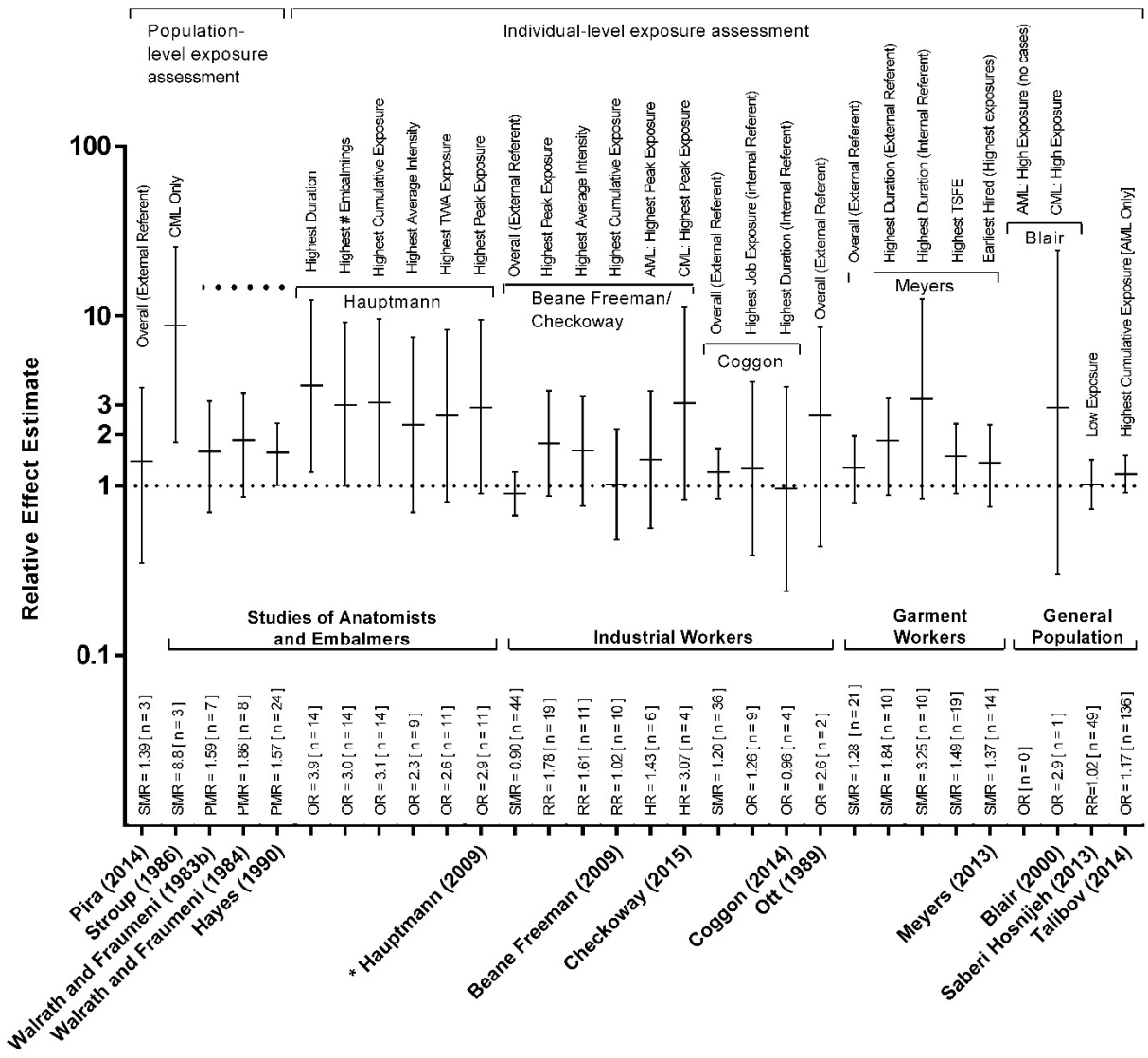


Figure 3-36. Epidemiological studies reporting myeloid leukemia risk estimates.

Results specifically for acute myeloid leukemia (AML) or chronic myeloid leukemia (CML) are noted by these abbreviations. Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for myeloid leukemia (see Table 3-63). SMR = standardized mortality ratio; PMR = proportionate mortality ratio; RR = relative risk; OR = odds ratio. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 3]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. *The dotted line extending from Hauptmann et al. (2009) reflects that study's inclusion of the original cohorts from Walrath and Fraumeni (Walrath and Fraumeni, 1983, 1984) and Hayes et al. (1990), which were combined with extended follow-up in Hauptmann et al. (2009) in a nested case-control study with internal referents.

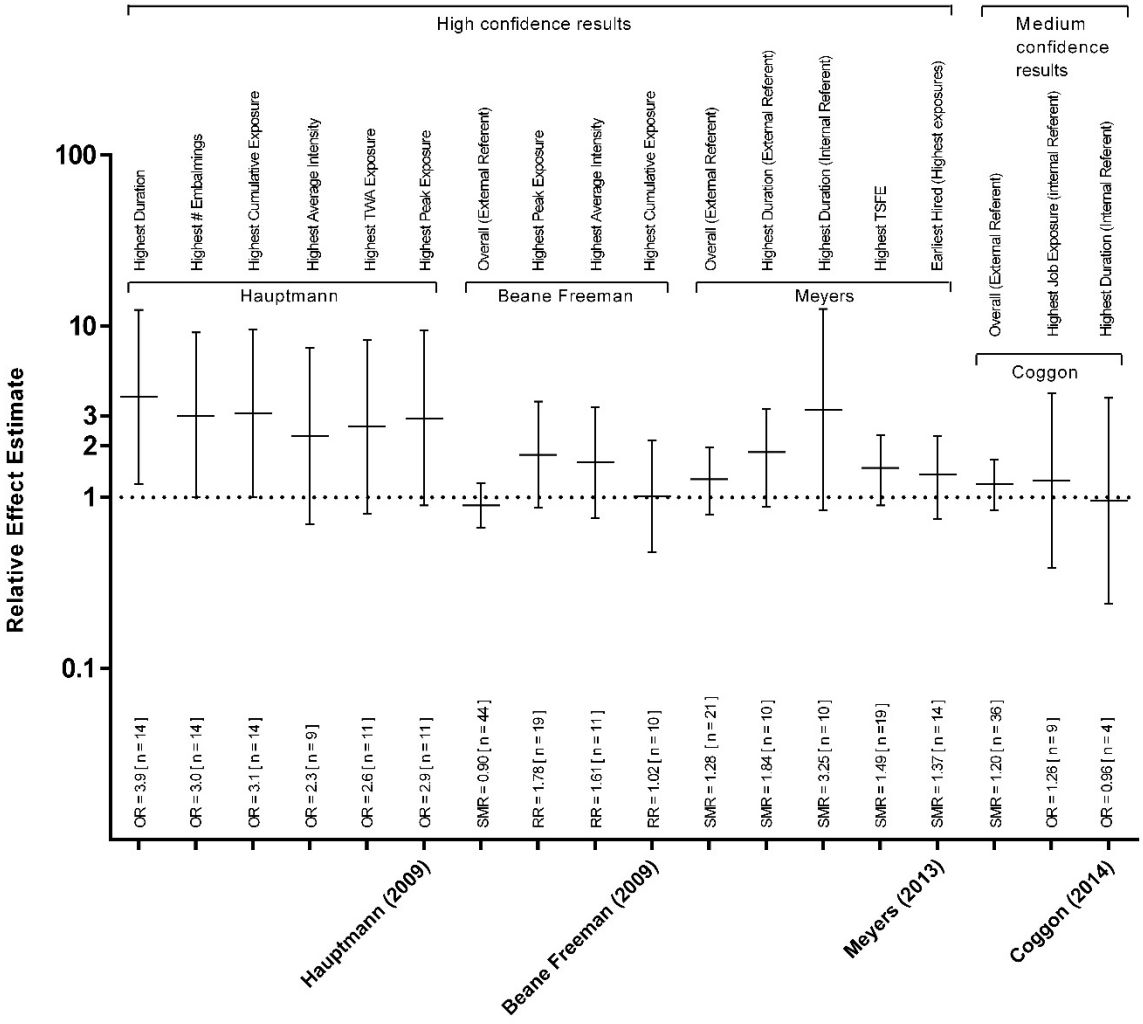


Figure 3-37. High and medium confidence epidemiological studies reporting myeloid leukemia risk estimates.

For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 14]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. Abbreviations: OR = odds ratio; RR = relative risk; SMR = standardized mortality ratio; HR = hazard ratio.

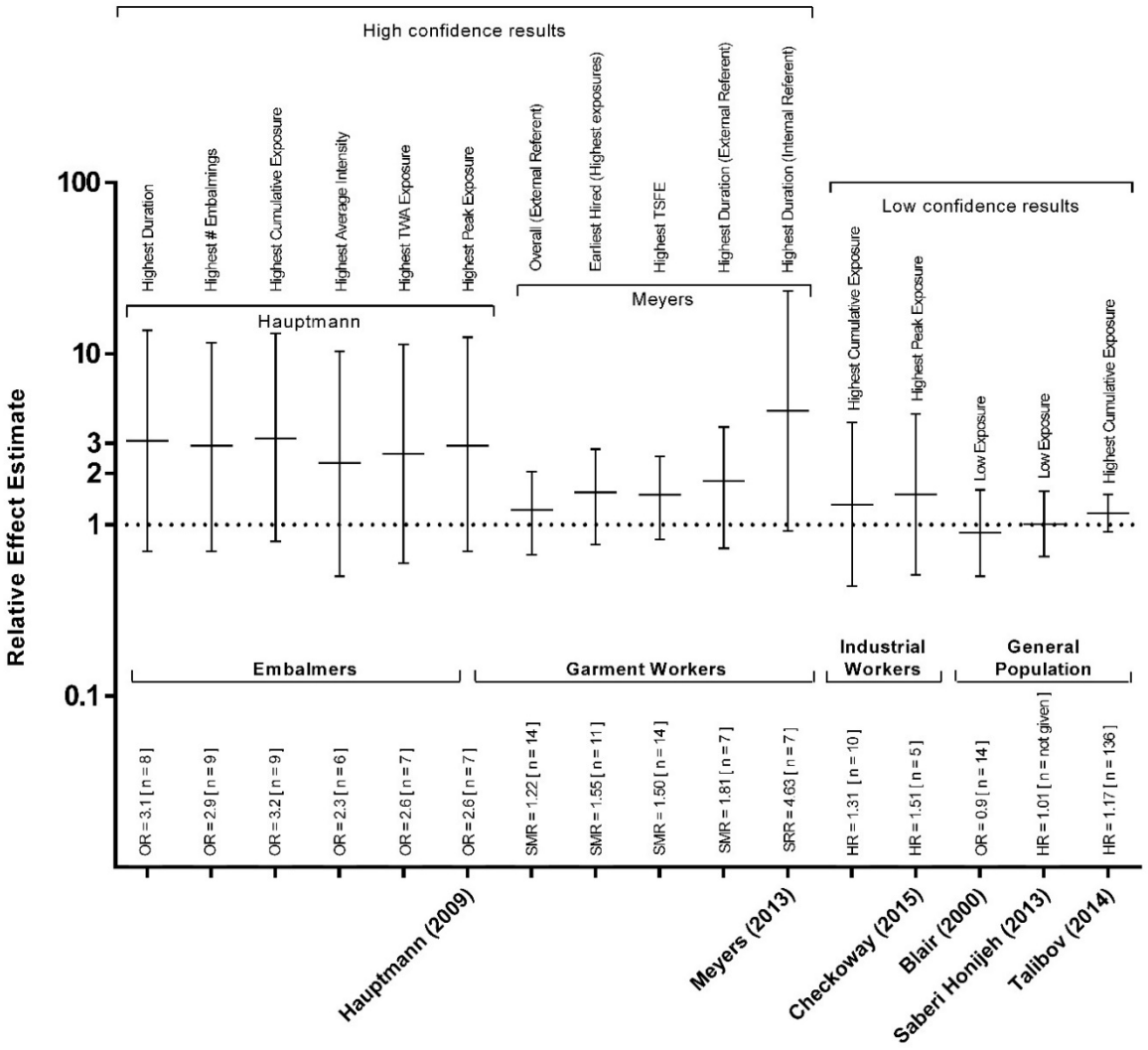


Figure 3-38. Epidemiological studies reporting acute myeloid leukemia risk estimates.

For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 8]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. Abbreviations: OR = odds ratio; RR = relative risk; SMR = standardized mortality ratio; HR = hazard ratio.

Table 3-63. Epidemiological studies of formaldehyde exposure and risk of myeloid leukemia

Study	Exposures	Results: effect estimate (95% CI) [# of cases]

Reference: Beane Freeman et al. (2009) with supplemental online tables.
 	
Population: 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the U.S., followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. Vital status was 97.4% complete and only 2.6% lost to follow-up.
 	
Outcome definition: Death certificates used to determine UCOD from myeloid leukemia (ICD-8: 205).
 	
Design: Prospective cohort mortality study with external and internal comparison groups.
 	
Analysis: RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency.
 	
SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates.
 	
Related studies:
Blair et al. (1986)
Hauptmann et al. (2003)
 	
Confidence in effect estimates:[a]
HIGH (No appreciable bias)
	Exposure assessment: Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists who took 2,000 air samples from representative jobs, and monitoring data from 1960 through 1980.
	
	Median TWA (over 8 hours) = 0.3 ppm (range 0.01–4.3).
	
	Median cumulative exposure = 0.6 ppm-years (range 0–107.4).
	
	Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data.
	
	Duration and timing: Exposure period from before 1946 through 1980. Median length of follow-up: 42 years. Duration and timing since first exposure were evaluated.
	
	Variation in exposure:
	For all variations in exposure:
	Level 1 (unexposed)
	
	Peak exposure:
	Level 2 (>0 to <2.0 ppm)
	Level 3 (2.0 to <4.0 ppm)
	Level 4 (≥4.0 ppm)
	Average intensity:
	Level 2 (>0 to <0.5 ppm)
	Level 3 (0.5 to <1.0 ppm)
	Level 4 (≥1.0 ppm)
	Cumulative exposure:
	Level 2 (>0 to <1.5 ppm-years)
	Level 3 (1.5 to <5.5 ppm-years)
	Level 4 (≥5.5 ppm-years)
	
	Coexposures: Exposures to 11 other compounds were identified and evaluated as potential confounders and found not be confounders.
	
	[As noted in Appendix B.3.9: There was no information on smoking; however, according to Blair et al. (1986), "The lack of a consistent
		Internal comparisons:
		Peak exposure:
		1980 follow-up:
		Highest peak RR = 3.92 (0.78–19.67)
		(*p*-trend = 0.12)
		1994 follow-up:
		Highest peak RR = 2.79 (1.08–7.21)
		(*p*-trend = 0.02)
		2004 follow-up:
		Level 1 RR = 0.82 (0.25-2.67) [4]
		Level 2 RR = 1.00 (Ref. value) [14]
		Level 3 RR = 1.30 (0.58–2.92) [11]
		Level 4 RR = 1.78 (0.87–3.64) [19]
		p-trend (exposed) = 0.13;
		p-trend (all) = 0.07
		
		Average intensity:
		Level 1 RR = 0.70 (0.23–2.16) [4]
		Level 2 RR = 1.00 (Ref. value) [24]
		Level 3 RR = 1.21 (0.56–2.62) [9]
		Level 4 RR = 1.61 (0.76–3.39) [11]
		p-trend (exposed) = 0.43;
		p-trend (all) = 0.40
		
		Cumulative exposure:
		Level 1 RR = 0.61 (0.20–1.91) [4]
		Level 2 RR = 1.00 (Ref. value) [26]
		Level 3 RR = 0.82 (0.36–1.83) [8]
		Level 4 RR = 1.02 (0.48–2.16) [10]
		p-trend (exposed) > 0.50;
		p-trend (all) = 0.44
		
		Duration of exposure:
		No evidence of association (data not shown).
		
		Time since first exposure:
		>0–15 years RR = 1.00 (Ref. value) [3]
		>15–25 years RR = 2.44 (0.45–13.25) [11]
		>25–35 years RR = 0.77 (0.11–5.24) [8]
		>35 years RR = 0.67 (0.09–4.88) [24]
		
		External comparisons:
		$SMR_{Unexposed}$ = 0.65 (0.25–1.74) [4]
		$SMR_{Exposed}$ = 0.90 (0.67–1.21) [44]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	elevation for tobacco-related causes of death, however, suggests that the smoking habits among this cohort did not differ substantially from those of the general population." Beane Freeman et al. (2013) reported that among a sample of 379 cohort members, they "found no differences in prevalence of smoking by level of formaldehyde exposure."]	
Reference: Beane Freeman et al. (2009) as re-analyzed by Checkoway et al. (2015) with differences noted. **Population:** No differences. **Outcome definition:** Death certificates used to determine UCOD from acute and chronic myeloid leukemia (ICD-8: 205.0 and 205.1). **Design:** No differences. **Analysis:** HRs estimated using Cox proportional hazards models controlling for age, sex, and race; adjusted for pay category compared to workers in the redefined lowest exposed category. Did not control for calendar year as did Beane Freeman et al. (2009). Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Blair et al. (1986) Hauptmann et al. (2003) Checkoway et al. (2015) [reviewed here] **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null)	**Exposure assessment:** No differences in measurements; however, the exposure metrics we redefined. Redefined peak exposures as having "at least one continuous month of employment in jobs identified in the original exposure characterization as likely having short-term exposure excursions of 2 ppm or more to less than 4 ppm or 4 ppm or more on a weekly or daily basis." Redefinition of peak exposures excluded "employment in jobs likely experiencing (1) short-term excursions more than 0 ppm and less than 2 ppm; (2) short-term excursions identified as occurring as frequently as hourly; and (3) short-term excursions identified as occurring as infrequently as monthly." **Duration and timing:** No differences. **Variation in exposure:** For all variations in exposure: Peak exposure: Level 1 (exposed to <2.0 ppm) Level 2 (2.0 to <4.0 ppm) Level 3 (≥4.0 ppm) Average intensity: Did not evaluate Cumulative exposure: Level 1 (exposed to <0.5 ppm-years) Level 2 (>0.5 to <2.5 ppm-years) Level 3 (≥2.5 to <5.5 ppm-years) **Coexposures:** Exposures to 11 other compounds were identified and evaluated as potential confounders by Beane Freeman et al. (2009) and	**Internal comparisons:** **Myeloid Leukemia** Peak exposure: Level 1 HR=1.00 (Ref. value) [27] Level 2 HR=2.09 (1.03–4.26) [11] Level 3 HR=1.80 (0.85–3.79) [10] *p*-trend = 0.06 Cumulative exposure: Level 1 HR=1.00 (Ref. value) [23] Level 2 HR=0.98 (0.47–2.03) [11] Level 3 HR=0.94 (0.47–1.86) [14] *p*-trend = 0.90 **AML** Peak exposure: Level 1 HR=1.00 (Ref. value) [21] Level 2 HR=1.71 (0.72–4.07) [7] Level 3 HR=1.43 (0.56–3.63) [6] *p*-trend = 0.31 Cumulative exposure: Level 1 HR=1.00 (Ref. value) [17] Level 2 HR=0.87 (0.36–2.12) [7] Level 3 HR=0.96 (0.43–2.16) [10] *p*-trend = 0.90 **CML** Peak exposure: Level 1 HR=1.00 (Ref. value) [6] Level 2 HR=2.62 (0.64–10.66) [3] Level 3 HR=3.07 (0.83–11.40) [4] *p*-trend = 0.07 Cumulative exposure: Level 1 HR=1.00 (Ref. value) [6] Level 2 HR=0.97 (0.24–3.93) [3] Level 3 HR=0.92 (0.25–3.36) [4] *p*-trend = 0.90

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	found not be confounders. Checkoway et al. (2015) did not re-evaluate potential confounding.	
Reference: Hauptmann et al. (2009) **Population:** 6,808 embalmers and funeral directors who died during 1960−1986. Identified from registries of the National Funeral Directors' Association, licensing boards and state funeral directors' associations, NY State Bureau of Funeral Directors, and CA Funeral Directors and Embalmers. Deaths were identified from the National Death Index. Next of kin interviews conducted for 96% of cases and 94% of controls. **Outcome definition:** Death certificates used to determine UCOD from myeloid leukemia (ICD-8: 205). **Design:** Nested case-control study within a prospective cohort mortality study using two internal comparison groups; the first composed of those who had never embalmed (1 case and 55 controls) and the second composed of those who had fewer than 500 embalmings (five cases and 83 controls). **Analysis:** ORs calculated using unconditional logistic regression adjusted for date of birth, age at death, sex, data source, and smoking. Lagged exposures were evaluated to account for cancer latency. These results are shown in table 3 of Hauptmann et al. (2009). Results from the second internal comparison group with <500 embalmings were selected to increase statistical stability. These results are shown in table 4 of Hauptmann et al. (2009) **Related studies:** Hayes et al. (1990) Walrath and Fraumeni (1983) Walrath and Fraumeni (1984) **Note:** The original cohorts from these three original studies were combined in Hauptmann et al. (2009) and follow-up	**Exposure assessment:** Occupational history obtained by interviews with next of kin and coworkers using detailed questionnaires. Exposure was assessed by linking questionnaire responses to an exposure assessment experiment providing measured exposure data. Exposure levels (peak, intensity, and cumulative) were assigned to each individual using a predictive model based on the exposure data. The model explained 74% of the observed variability in exposure measurements. Multiple exposure metrics including duration (mean = 33.1 years in cases), # of embalming, peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1932 through 1986. Duration of exposure was evaluated. Duration is also a surrogate for time because first exposure since dates of death was closely related to cessation of workplace exposures. **Variation in exposure:** For variations in exposure from table 3 of the publication: Level 1 (no exposure to embalming) For variations in exposure from table 4 of the publication: Level 1 (<500 embalming) Duration of exposure: Level 2 (<20 years) Level 3 (20–34 years) Level 4 (>34 years) Number of embalming: Level 2 (500–1,422) Level 3 (1,423–3,068) Level 4 (>3,068) Cumulative exposure: Level 2 (≤4,058 ppm-hrs) Level 3 (4,059–9,253 ppm-hrs)	**Internal comparisons (*from table 3 in the paper*):** Never embalming: OR = 1.00 (Ref. value) [1] Ever embalming: OR = 11.2 (1.3–95.6) [33] Duration of exposure: Level 1 OR = 1.00 (Ref. value) [1] Level 2 OR = 5.0 (0.5–51.6) [6] Level 3 OR = 12.9 (1.4–117.1) [13] Level 4 OR = 13.6 (1.6–119.7) [14] Number of embalming: Level 1 OR = 1.0 (Ref. value) [1] Level 2 OR = 7.6 (0.8–73.5) [7] Level 3 OR = 12.7 (1.4–116.7) [12] Level 4 OR = 12.7 (1.4–112.8) [14] Cumulative exposure: Level 1 OR = 1.0 (Ref. value) [1] Level 2 OR = 10.2 (1.1–95.6) [9] Level 3 OR = 9.4 (1.0–85.7) [10] Level 4 OR = 13.2 (1.5–115.4) [14] Average intensity (while embalming): Level 1 OR = 1.0 (Ref. value) [1] Level 2 OR = 11.1 (1.2–106.3) [10] Level 3 OR = 14.8 (1.6–136.9) [13] Level 4 OR = 9.5 (1.1–86.0) [10] TWA8 formaldehyde intensity: Level 1 OR = 1.0 (Ref. value) [1] Level 2 OR = 8.4 (0.8–79.3) [8] Level 3 OR = 13.6 (1.5–125.8) [13] Level 4 OR = 12.0 (1.3–107.4) [12] Peak exposure: Level 1 OR = 1.0 (Ref. value) [1] Level 2 OR = 15.2 (1.6–141.6) [12] Level 3 OR = 8.0 (0.9–74.0) [9] Level 4 OR = 13.0 (1.4–116.9) [12] **Internal comparisons (from table 4):** Duration of exposure: Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 0.5 (0.1–2.9) [2] Level 3 OR = 3.2 (1.0–10.1) [13] Level 4 OR = 3.9 (1.2–12.5) [14] Number of embalming: Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 1.2 (0.3–5.5) [3] Level 3 OR = 2.9 (0.9–9.1) [12] Level 4 OR = 3.0 (1.0–9.2) [14] Cumulative exposure: Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 2.1 (0.5–8.1) [5]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
was extended so the case-series overlap and are not independent. However, the three original cohorts used external reference groups for comparison while Hauptmann et al. (2009) selected internal controls, which were independent of the reference groups used in the original studies. **Confidence in effect estimates:**[a] **HIGH** (No appreciable bias)	Level 4 (≥9253 ppm-hrs) Average intensity (while embalming): Level 2 (≤1.4 ppm) Level 3 (>1.4–1.9 ppm) Level 4 (>1.9 ppm) TWA8 formaldehyde intensity: Level 2 (≤0.10 ppm) Level 3 (>0.10–0.18 ppm) Level 4 (>0.18 ppm) Peak exposure: Level 2 (<7.0 ppm) Level 3 (7.0 to <9.3 ppm) Level 4 (>9.3 ppm) **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	Level 3 OR = 2.2 (0.7–7.1) [10] Level 4 OR = 3.1 (1.0–9.6) [14] Average intensity (while embalming): Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 2.6 (0.8–8.7) [10] Level 3 OR = 2.8 (0.8–9.1) [10] Level 4 OR = 2.3 (0.7–7.5) [9] TWA8 formaldehyde intensity: Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 2.4 (0.7–8.2) [8] Level 3 OR = 2.6 (0.8–8.7) [10] Level 4 OR = 2.6 (0.8–8.3) [11] **Internal comparisons (from table 4):** Peak exposure: Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 2.9 (0.9–9.8) [9] Level 3 OR = 2.0 (0.6–6.6) [9] Level 4 OR = 2.9 (0.9–9.5) [11] **Additional:** Acute ML (ICD-8: 205.0) **Internal comparisons (from table 4):** Duration of exposure: Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 0.4 (0.04–4.9) [1] Level 3 OR = 2.9 (0.7–12.2) [8] Level 4 OR = 3.1 (0.7–13.7) [8] Number of embalming: Level 1 OR = 1.0 (Ref. value) [3] Level 2 no cases Level 3 OR = 2.9 (0.7–12.0) [8] Level 4 OR = 2.9 (0.7–11.6) [9] Cumulative exposure: Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 1.3 (0.2–9.4) [2] Level 3 OR = 1.9 (0.4–8.2) [6] Level 4 OR = 3.2 (0.8–13.1) [9] Average intensity (while embalming): Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 2.5 (0.6–10.9) [6] Level 3 OR = 2.0 (0.4–9.4) [5] Level 4 OR = 2.3 (0.5–10.3) [6] TWA8 formaldehyde intensity: Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 1.4 (0.3–7.8) [3] Level 3 OR = 2.6 (0.6–11.4) [7] Level 4 OR = 2.6 (0.6–11.3) [7] Peak exposure: Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 1.8 (0.4–9.3) [4] Level 3 OR = 2.1 (0.5–9.2) [5] Level 4 OR = 2.9 (0.7–12.5) [7]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Meyers et al. (2013) **Population:** 11,043 workers in three U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion. **Outcome definition:** Death certificates used to determine both the UCOD from myeloid leukemia (ICD code in use at time of death). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. SRRs calculated using LTAS.NET. Rate ratios calculated using Poisson regression analysis based on internal referents. **Related studies:** Stayner et al. (1985) Stayner et al. (1988) Pinkerton et al. (2004) **Confidence in effect estimates:**[a] **HIGH** (No appreciable bias)	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984 with 12–73 within each department. Formaldehyde levels across all departments and facilities were similar. Geometric TWA8 exposures ranged from 0.09-0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm, (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 through 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were evaluated. **Variation in exposure:** Duration of exposure: Level 1 (<3 years) Level 2 (3–9 years) Level 3 (10 + years) Time since first exposure: Level 1 (<10 years) Level 2 (10–19 years) Level 3 (20 + years) Duration of exposure (Poisson modeling–lagged 2 years): Level 1 (<1.6 years) Level 2 (1.6 to <6.5 years) Level 3 (6.5 to <16 years) Level 4 (16 to <19 years) Level 5 (19 + years) **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	**External comparisons:** SMR = 1.28 (0.79–1.96) [21] **Within-study external comparisons:** Duration of exposure: Level 1 SMR = 0.65 (0.18–1.65) [4] Level 2 SMR = 1.46 (0.59–3.02) [7] Level 3 SMR = 1.84 (0.88–3.28) [10] TSFE: Level 1 SMR = 0.90 (0.02–4.99) [1] Level 2 SMR = 0.40 (0.01–2.21) [1] Level 3 SMR = 1.49 (0.90–2.32) [19] Year of first exposure: <1963 SMR = 1.37 (0.75–2.30) [14] 1963-1970 SMR = 1.13 (0.37–2.63) [5] 1971 + SMR = 1.15 (0.14–4.17) [2] **Internal comparisons:** Duration of exposure: Level 1 SRR = 1.00 (Ref. value) [4] Level 2 SRR = 2.12 (0.57-7.85) [7] Level 3 SRR = 3.25 (0.84–12.63) [10] Duration of exposure (Poisson modeling–lagged 2 years) [# of cases not given]: Level 1 rate ratio = 1.00 (Ref. value) Level 2 rate ratio = 1.38 (0.39–5.51) Level 3 rate ratio = 0.43 (0.06–2.39) Level 4 rate ratio = 6.42 (1.40–32.2) Level 5 rate ratio = 1.71 (0.25–11.0) **Additional:** Acute myeloid leukemia (ICD: 205.0) SMR = 1.22 (0.67–2.05) [14] Chronic myeloid leukemia (ICD: 205.1) SMR = 1.35 (0.44–3.15) [5] Acute myeloid leukemia (ICD: 205.0) **Internal comparisons:** Duration of exposure: Level 1 SMR = 0.46 (0.06–1.68) [2] Level 2 SMR = 1.52 (0.49–3.56) [5] Level 3 SMR = 1.81 (0.73–3.73) [7] Time since first exposure: Level 1 SMR = 0 (0.00–6.66) [0] Level 2 SMR = 0 (0.00–2.32) [0] Level 3 SMR = 1.50 (0.82–2.52) [14] Year of first exposure: <1963 SMR = 1.55 (0.77–2.77) [11] 1963-1970 SMR = 0.64 (0.08–2.30) [2] 1971 + SMR = 0.83 (0.02–4.60) [1]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories which produced formaldehyde. Cohort mortality followed from 1941 through 2012. Cause of deaths was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378 deaths through 2012. Vital status was 98.9% complete and only 1.1% lost to follow-up through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from myeloid leukemia (ICD-9: 205). **Design:** Cohort mortality study with external comparison group with a nested case-control study. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency analysis with attenuation of association. **(Potential bias toward the null↓)** **IB**: Exposure is Group B; lack of latency analysis	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941−1982. Duration was evaluated as more, or less, than one year only among the high exposure group. Timing since first exposure was not evaluated. **Variation in exposure:** Highest exposure level attained Level 1 (Background) Level 2 (low/moderate) Level 3 (High) Duration of "High" exposures Level 1 (Background) Level 2 (<1 year) Level 3 (1 year or more) **Coexposures:** Not evaluated as potential confounders. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium; explanation for underlining: [As noted in Appendix B.3.9: Styrene is associated with LHP cancers. Asbestos is associated with URT cancers, but not with LHP cancers. Other coexposures are not known risk factors for this outcome. Authors stated that the extent of coexposures was expected to be low. Potential for confounding may be mitigated by low coexposures.]	**External comparisons:** SMR = 1.20 (0.84-1.66) [36] **Within-study external comparisons:** Highest exposure level attained Level 1 SMR = 1.16 (0.60-2.02) [12] Level 2 SMR = 1.46 (0.84-2.38) [16] Level 3 SMR = 0.93 (0.40-1.82) [8] **Internal comparisons:** Highest exposure level attained Level 1 OR = 1.00 (Ref. value) [17] Level 2 OR = 1.10 (0.51-2.38) [19] Level 3 OR = 1.26 (0.39-4.08) [9] Duration of high exposures Level 1 OR = 1.00 (Ref. value) [17] Level 2 OR = 1.77 (0.45-7.03) [5] Level 3 OR = 0.96 (0.24-3.82) [4]
Reference: Hayes et al. (1990) **Population:** 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975–1985. Death certificates	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. Exposure based on occupation which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to	**External comparisons:** PMR = 1.57 (1.01-2.34) [24] **Additional:** Acute myeloid leukemia (ICD-8: 205.0) PMR = 1.52 (0.85-2.52) [# not given] Chronic myeloid leukemia (ICD-8: 205.1)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
obtained for 79% of potential study subjects (*n* = 6,651) with vital status unknown for 21%. **Outcome definition:** Death certificates and licensing boards used to determine cause of death from myeloid leukemia (ICD-8: 205). **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association	3.99 ppm (low ventilation) with peaks up to 20 ppm. Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975–1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60–74 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	PMR = 1.84 (0.79-3.62) [# not given]
Reference: Walrath and Fraumeni (1984) **Population:** 1,007 deceased white male embalmers from the California Bureau of Funeral Directing and Embalming who died during 1925–1980. Death certificates obtained for all. **Outcome definition:** Myeloid leukemia (ICD-8: 205) listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a]	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1916–1978. Birth year ranged from 1847 through 1959. Median age of death was 62 years. Most deaths were among embalmers with active licenses. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation.	**External comparisons:** Observed: 8 myeloid leukemia deaths (including 2 acute monocytic leukemia) Expected: 4.3 myeloid leukemia deaths (including 0.3 acute monocytic leukemia) PMR = 1.86 (0.86–3.53)† [8] **Additional:** Observed: 6 acute myeloid leukemia deaths (including 2 acute monocytic leukemia) Expected: With 4.3 myeloid leukemia deaths expected, EPA used data from Selvin et al. (1983) on the expected ratio of AML:CML (2.2:1) among males ages 25+ to estimate 2.96 expected cases of AML out of the 4.3 expected myeloid leukemia deaths. Acute myeloid leukemia (ICD-8: 205.0) PMR = 2.03 (0.82–4.22)† [6]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Medium ↓ (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association.	Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	†**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))
Reference: Walrath and Fraumeni (1983) **Population:** 1,132 deceased white male embalmers licensed to practice during 1902–1980 in New York who died during 1925–1980 identified from registration files. Death certificates obtained for 75% of potential study subjects (*n* = 1,678). **Outcome definition:** Myeloid leukemia (ICD-8: 205) listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1902–1980. Median year of birth was 1901. Median year of initial license was 1931. Median age at death was 1968. Expected median duration of exposure was 37 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**External comparisons:** Observed: 7 myeloid leukemia deaths (including 1 acute monocytic leukemia) Expected: 4.4 myeloid leukemia deaths (including 0.3 acute monocytic leukemia) PMR = 1.59 (0.70–3.15)† [7] **Additional:** Observed: 6 acute myeloid leukemia deaths (including 1 acute monocytic leukemia) Expected: With 4.4 myeloid leukemia deaths expected, EPA used data from Selvin et al. (1983) on the expected ratio of AML:CML (2.2:1) among males ages 25+ to estimate 3.03 expected cases of AML out of the 4.4 expected myeloid leukemia deaths. Acute myeloid leukemia (ICD-8: 205.0) PMR = 1.98 (0.80–4.12)† [6] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))
Reference: Talibov et al. (2014) **Population:** Individuals from Finland, Iceland, Norway, and Sweden who were recorded in various censuses from 1960 to 1990. Acute myeloid leukemia cases identified by national registries up until 2003–2005 depending on the country.	**Exposure assessment:** Occupational history from census records were linked to the Nordic Occupational Cancer Study (NOCCA) JEM to code each cohort member as exposed to formaldehyde. Exposures were quantified based on the proportion of people in each occupation considered to be exposed and the mean level of exposure during specific periods.	**Internal comparisons:** Acute Myeloid Leukemia (ICD-9: 205.0) Level 1 OR = 1.00 (ref value) [13781] Level 2 OR = 0.89 (0.81-0.97) [580] Level 3 OR = 0.92 (0.83-1.03) [485] Level 4 OR = 1.17 (0.91-1.51) [136] *p*-trend = 0.07

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Outcome definition: Diagnosis of incident cancer reported to the National Cancer Registries. **Design:** Multicountry case-control study. **Analysis:** HRs calculated for categories of cumulative formaldehyde exposure using conditional logistic regression controlling for year of birth, sex, country, solvents and other coexposures. A 10-year latency period was assumed. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association.	Coexposures to solvents was evaluated. **Duration and timing:** Exposure period based on occupational histories prior to 1983. Duration and timing since first exposure were considered in the exposure metric but were not evaluated separated. **Variation in exposure:** Cumulative exposure: Level 1 (unexposed) Level 2 (low): ≤0.171 ppm-years Level 3 (moderate): 0.171–1.6 ppm-years Level 4 (high): >1.6 ppm-years **Coexposures:** Solvents and coexposures controlled for in multivariate models included: aliphatic and alicyclic hydrocarbons, aromatic hydrocarbons, benzene, toluene, trichloroethylene, 111-trichloroethane, methylene chloride, perchloroethylene, other organic solvents, and ionizing radiation.	

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Pira et al. (2014) **Population:** 2,750 workers employed at a laminated plastic factory in Italy for at least 180 days between 1947 and 2011 followed until May 2011. Deaths were identified from population registries. Vital status was 96.9% complete and only 3.1% lost to follow-up. **Outcome definition:** Death certificates used to determine UCOD from myeloid leukemia (ICD-9: 205). **Design:** Prospective cohort mortality study with external comparison group. **Analysis:** RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, and 5-year calendar periods using mortality rates from the Piedmont region. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) and lack of latency analysis with attenuation of association. Confounding possible. Low sensitivity (few cases).	**Exposure assessment:** Formaldehyde is a byproduct from the resins used in production process and all workers were presumed to have been exposed. **Duration and timing:** Exposure period from 1947 through 2011. Median length of follow-up: 23.6 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated.	**External comparisons:** Observed: 3 myeloid leukemia deaths Expected: 2.16 myeloid leukemia deaths based on authors' assumption that 40% of leukemia deaths are from myeloid leukemia and 5.3 leukemia deaths were expected. Myeloid Leukemia (ICD-9: 205) SMR = 1.39 (0.35-3.78)† [3] †**Note:** EPA derived CIs using the Mid-P Method [See Rothman and Boice (1979)]
Reference: Saberi Hosnijeh et al. (2013) **Population:** 241,465 men and women recruited from 10 European countries during 1992–2000. Participants were predominantly ages 35–70 at recruitment and were followed up through 2010. **Outcome definition:** Incident primary leukemias. **Design:** Prospective multinational cohort incidence study with internal comparison groups.	**Exposure assessment:** Individual occupational histories obtained by questionnaire about ever working in any of 52 occupations considered to be at high risk of developing cancer. Occupational exposures estimated as "high," "low," and no exposure by linking to a JEM. **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** Exposure to formaldehyde:	**Internal comparisons:** Exposure to formaldehyde: Level 1 RR = 1.00 (Ref. value) [130] Level 2 RR = 1.02 (0.73-1.42) [49] Level 3 RR = No data [0]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Analysis: HRs calculated controlling for age, sex, smoking, alcohol, physical activity, education, BMI, family history of cancer, country, other occupational exposures, and radiation. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group C) and lack of latency analysis with attenuation of association.	Level 1 (none) Level 2 (low) Level 3 (high) **Coexposures:** Coexposure included pesticides, herbicides, insecticides, aromatic solvents, benzene, chlorinated solvents, trichloroethylene, metals, and contact with animals or animal products, ionizing radiation. [As noted in Appendix B.3.9: Coexposures were not controlled for. Potential for confounding is unknown but could have inflated the observed effect. Potential for confounding may be mitigated by low correlation between exposures in the general population.]	
Reference: Blair et al. (2001) **Population:** White men, 30 years of age or older, identified from the Iowa cancer registry and the Minnesota hospital surveillance network during 1980–1983. Participation of eligible cases was 86% and approximately 77–79% for controls including 77% for surrogate respondents for deceased subjects. **Outcome definition:** Diagnosis of leukemia was confirmed by pathology review for all cases. **Design:** Population-based case-control study of 513 white men with leukemia from Iowa and Minnesota cancer surveillance networks. 1,087 controls were frequency matched on 5-year age groups, vital status, and state. **Analysis:** ORs calculated for job titles, employment duration, and exposure intensity using unconditional logistic regression controlling for age, state, direct/surrogate response, and coexposures, including smoking. Analyses by year of first exposure were also conducted to evaluate latency.	**Exposure assessment:** Individual-level exposure estimates developed based on a JEM for each job held for more than 1 year, the industry where employed, and starting and ending year the job was held. Exposure intensity and probability assessed for formaldehyde and other exposures. Exposure intensity refers to the level likely experienced and considered a TWA8 over a year. **Duration and timing:** Exposure period based on occupational histories prior to 1983. Duration and timing since first exposure were evaluated. **Variation in exposure:** Intensity of exposure: Level 1 (unexposed) Level 2 (low) Level 3 (high) **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Other exposures evaluated included **benzene**, other organic solvents, petroleum-based oils and greases, cooking oils, ionizing radiation, paper dusts, gasoline and exhaust vapors,	**Internal comparisons:** Acute myeloid leukemia (ICD-9: 205.0) Level 1 OR = 1.0 (Ref. value) [118] Level 2 OR = 0.9 (0.5-1.6) [14] Level 3 no cases Chronic myeloid leukemia (ICD-9: 205.1) Level 1 OR = 1.0 (Ref. value) [38] Level 2 OR = 1.3 (0.6-3.1) [7] Level 3 OR = 2.9 (0.3-24.5) [1] No notable findings were reported for duration of time since first exposure to formaldehyde.

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Confidence in effect estimates:[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group C) and lack of latency analysis with attenuation of association. Confounding possible.	**paints**, **metals**, **wood dust**, **asbestos**, asphalt, cattle, meat, solder fumes. However, analyses of formaldehyde exposures did not control for other exposures.]	
Reference: Ott et al. (1989) **Population:** 29,139 men employed at two large chemical manufacturing facilities and a research and development center who worked during 1940–1978. Vital status was known for 96.4%. Death certificates were available for 5,785 known descendants (95.4%). **Outcome definition:** Death certificates used to determine UCOD from nonlymphatic leukemia based on the ICD code in used at the time of death. **Design:** Nested case-control study within a prospective cohort mortality study. Twenty-nine cases of nonlymphatic leukemia were frequency matched to 100 controls on time from hire to death. **Analysis:** ORs calculated using unconditional logistic regression. **Related studies:** Rinsky et al. (1988) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and weak latency analysis with attenuation of association. Confounding possible. Low sensitivity due to rarity of exposure.	**Exposure assessment:** Individual-level exposure ascertained from employee's work assignments linked to records on departmental usage of formaldehyde. **Duration and timing:** Occupational exposures during 1940–1978. Timing of formaldehyde exposure not evaluated. **Variation in exposure:** Ever/never **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: 21 different chemicals were evaluated including **benzene** with much cross exposure. Benzene was not evaluated as a potential confounder and may be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect. Potential for confounding may be mitigated by rarity of coexposures among cases.]	**Internal comparisons:** OR = 2.6 (0.44-8.59)† [2] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))
Reference: Stroup et al. (1986) **Population:** 2,239 white male members of the American Association of Anatomists from 1888 to 1969 who died during 1925−1979. Death certificates obtained for 91% with 9% lost to follow-up.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1925–1979. Median birth year was 1912. By 1979, 33% of anatomists had	**Leukemias:** 10 total reported 1 lymphatic 5 myeloid (3 chronic, 1 acute, 1 unspecified) 1 acute monocytic 3 leukemia not otherwise specified **External comparisons:**

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Outcome definition: Myeloid leukemia (ICD-8: 205) listed as cause of death on death certificates. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for selection bias. Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Confounding possible for ML. Low sensitivity (few cases).	died. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and **ionizing radiation**. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely. Anatomists may also be coexposed to stains, benzene, toluene, xylene, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Benzene was not evaluated as a potential confounder and may be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	Chronic myeloid leukemia (ICD-8: 205.1) SMR = 8.8 (1.8–25.5) [3]

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: RR = relative risk; SMR = standardized mortality ratio; UCOD = underlying cause of death; OR = odds ratio; SRR = summary relative risk; SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis; TSFE = time since first exposure; URT = upper respiratory tract; LHP = lymphohematopoietic; HR = hazard ratio; PMR = proportionate mortality ratio; BMI = body mass index; JEM = job-exposure matrix.

Lymphatic leukemia

Epidemiological evidence

The most specific level of lymphatic leukemia diagnosis that is commonly reported across the epidemiological literature has been based on the first three digits of the Eighth or Ninth Revision of the ICD code (i.e., Lymphatic leukemia ICD-8: 204 and Lymphoid leukemia ICD-9: 204). Evidence describing the association between formaldehyde exposure and the specific risk of lymphatic leukemia was available from nine epidemiological studies—two case-control studies

(Hauptmann et al., 2009; Blair et al., 2001) and seven cohort studies (Walrath and Fraumeni, 1983, 1984; Saberi Hosnijeh et al., 2013; Ott et al., 1989; Meyers et al., 2013; Hayes et al., 1990; Beane Freeman et al., 2009). Six of the cohort studies ascertained lymphatic leukemia diagnoses from death certificates and one examined incident cases (Saberi Hosnijeh et al., 2013). All studies reported lymphatic leukemia outcomes based on the ICD-8 or ICD-9 diagnostic code 204 without separate results for acute lymphocytic leukemia and CLL. One case-control study (Hauptmann et al., 2009) ascertained lymphatic leukemia diagnoses from death certificates whereas the other ascertained incident cases of lymphatic leukemia from a cancer registry and a hospital network (Blair et al., 2001). Both studies reported specific results for CLL; however, while diagnoses of lymphatic leukemia reviewed here are those identified according to the ICD codes used at the time of diagnoses, in the ICD-10 coding rubric, CLL would be included as NHL. Study details are provided in the evidence table for lymphatic leukemia (see Table 3-64). Study results for ICD-7 code 204 were not included because this code includes all leukemias. Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for lymphatic leukemia (see Table 3-64) following the causal evaluation.

Consistency of the observed association

The point estimates and CIs of all eight informative studies were consistently around the null, which does not provide evidence of an association between formaldehyde exposure and the risk of developing or dying from lymphatic leukemia. The range of central relative effect estimates (selecting the highest exposure level results when there was more than one result) was from zero ((Walrath and Fraumeni, 1984); [zero cases]) to 2.6 ((Ott et al., 1989); [one case]) and both of these results were classified with *low* confidence. The three results classified with *high* or *medium* confidence were SMR = 0.71 in Meyers et al. (2013), OR = 1.0 in Hauptmann et al. (2009), and SMR = 1.15 in Beane Freeman et al. (2009). The study results presented in Table 3-64 (by confidence level and publication date) detail all of the reported associations between exposures to formaldehyde and the risks of developing or dying from lymphatic leukemia along with a summary graphic of any major limitation and the confidence classification of the effect estimate. Results are plotted in Figure 3-39.

Strength of the observed association

Summary effect estimates for the association between formaldehyde exposure and the risk of mortality from lymphatic leukemia ranged from zero to 2.6 and clustered around the null.

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants occurred before their lymphatic leukemia was detected and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and was done in a blinded fashion with respect to outcome status. None of the eight studies provided analyses of a

temporal relationship between the timing of exposure and the diagnoses of lymphatic leukemia or deaths from lymphatic leukemia.

Exposure-response relationship

None of the studies evaluated the effect of duration of formaldehyde exposure on the mortality risk of lymphatic leukemia. There were only two sets of results, one classified with *medium* confidence and one with *low* confidence, which evaluated any form of exposure-response for increasing measures of formaldehyde exposure (Blair et al., 2001; Beane Freeman et al., 2009) and neither showed a pattern of increasing risk with increasing formaldehyde exposure.

Potential impact of selection bias, information bias, confounding bias, and chance

There was potential for selection bias in two studies that were only able to ascertain death certificated for 75–79% of the decedents (Walrath and Fraumeni, 1983; Ott et al., 1989), but there was no evidence that inclusion rates may have been related to either exposure or outcome, and thus, there is little concern about selection bias. Among the studies reporting on the risk of lymphatic leukemia, which only indicated the equivalent of ever/never exposure to formaldehyde, there was little potential for information bias. In fact, results consistently showed no evidence of an association—regardless of the quality of exposure assessment further. Confounding is another potential bias that could arise if another cause of lymphatic leukemia was statistically associated with formaldehyde exposure. However, there does not appear to be any evidence of negative confounding, which could have obscured a real but unobserved effect. While there did not appear to be an association between exposure to formaldehyde and the risk of lymphatic leukemia, given the limited database of specific results, and the possibility of biases that could obscure any true effect, the available epidemiological data are inadequate to conclude that formaldehyde is not likely to be carcinogenic to humans.

Summary of Human Evidence Synthesis Judgments, Causal Evaluation, and Conclusion

Summary of human evidence synthesis judgments

The following factors were most influential to the causal evaluation and synthesis conclusion:

- *Consistency and Study Confidence:* Generally consistent pattern of results around the null across *high*, *medium,* and *low* confidence studies, although there was a limited database from which to evaluate the potential risk to sensitive populations or lifestages.
- *Strength and Precision:* Studies reporting results for lymphatic leukemia were generally small with case counts ranging from zero to 36 cases with seven of nine studies reporting 10 or fewer cases. Variable strength of the association across studies reporting relative effect estimates from 0.71 to 2.6 all with confidence intervals including the null.

- *Coherence*: In each of the studies, the formaldehyde exposures among the study participants occurred before their lymphatic leukemia was detected.
- *Dose-Response:* In this database, there was an absence of exposure-response relationships showing that increased exposure to formaldehyde was associated with increased risk of lymphatic leukemia.

Causal evaluation

The human evidence synthesis judgments do not support a causal conclusion although there was a limited database. Although consistent observations of genotoxicity in peripheral blood lymphocytes across several occupational studies involving diverse exposure settings, these data were not interpreted as sufficient to further strengthen the judgment on the human evidence of lymphatic leukemia.

Conclusion

- The available epidemiological studies provide *indeterminate* evidence to assess the carcinogenic potential evidence of an association between formaldehyde exposure and an increased risk of lymphatic leukemia.

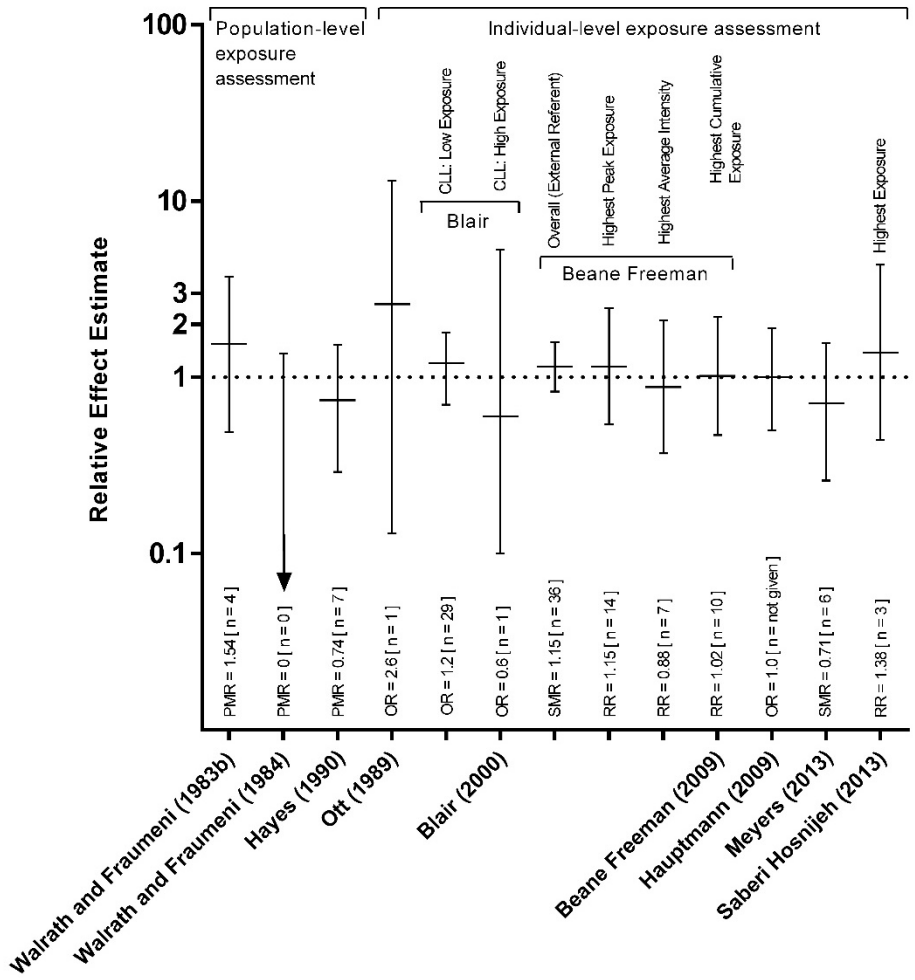


Figure 3-39. Epidemiological studies reporting lymphatic leukemia risk estimates.

Results specifically for chronic lymphatic leukemia (CLL) are noted by these abbreviations. Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for lymphatic leukemia (see Table 3-64). SMR = standardized mortality ratio; PMR = proportionate mortality ratio; RR = relative risk; OR = odds ratio. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 4]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure.

Table 3-64. Epidemiological studies of formaldehyde exposure and risk of lymphatic leukemia

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Meyers et al. (2013) **Population:** 11,043 workers in three U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion. **Outcome definition:** Death certificates used to determine both the UCOD from lymphocytic leukemia (ICD code in use at time of death). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. Poisson regression analysis based on internal referents. **Related studies:** Stayner et al. (1985) Stayner et al. (1988) Pinkerton et al. (2004) **Confidence in effect estimates:**[a] **HIGH** (No appreciable bias)	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984. Geometric TWA8 exposures ranged from 0.09 to 0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 through 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were not evaluated. **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	**External comparisons:** SMR = 0.71 (0.26–1.56) [6]
Reference: Beane Freeman et al. (2009) with supplemental online tables. **Population:** 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the U.S. followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. Vital status was 97.4% complete and only 2.6% lost to follow-up. **Outcome definition:** Death certificates used to determine UCOD from lymphatic leukemia (ICD-8: 204).	**Exposure assessment:** Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists, and monitoring data through 1980. Median TWA (over 8 hours) = 0.3 ppm (range 0.01–4.3). Median cumulative exposure = 0.6 ppm-years (range 0–107.4). Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1946 through 1980. Median length of follow-up: 42 years. Duration and	**Internal comparisons:** Peak exposure Unexposed RR = 0.27 (0.03–2.13) [1] Level 1 RR = 1.00 (Ref. value) [14] Level 2 RR = 0.81 (0.33–1.96) [8] Level 3 RR = 1.15 (0.54–2.47) [14] *p*-trend (exposed) >0.50; *p*-trend (all) = 0.30 Average intensity Unexposed RR = 0.26 (0.03–2.01) [1] Level 1 RR = 1.00 (Ref. value) [22] Level 2 RR = 0.92 (0.39–2.16) [7] Level 3 RR = 0.88 (0.37–2.11) [7] *p*-trend (exposed) >0.50; *p*-trend (all) >0.50 Cumulative exposure Unexposed RR = 0.24 (0.03–1.88) [1] Level 1 RR = 1.00 (Ref. value) [21]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Design: Prospective cohort mortality study with external and internal comparison groups. **Analysis:** RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Blair et al. (1986) Hauptmann et al. (2003) **Confidence in effect estimates:**[a] **HIGH** (No appreciable bias)	timing since first exposure were not evaluated. **Variation in exposure:** Peak exposure: Level 1 (>0 to <2.0 ppm) Level 2 (2.0 to <4.0 ppm) Level 3 (≥4.0 ppm) Average intensity: Level 1 (>0 to <0.5 ppm) Level 2 (0.5 to <1.0 ppm) Level 3 (≥1.0 ppm) Cumulative exposure: Level 1 (>0 to <1.5 ppm-years) Level 2 (1.5 to <5.5 ppm-years) Level 3 (≥5.5 ppm-years) **Coexposures:** Exposures to 11 other compounds were identified and evaluated as potential confounders.	Level 2 RR = 0.57 (0.21–1.54) [5] Level 3 RR = 1.02 (0.47–2.21) [10] *p*-trend (exposed) = 0.46; *p*-trend (all) = 0.41 **External comparisons:** $SMR_{Unexposed}$ = 0.26 (0.04–1.82) [1] $SMR_{Exposed}$ = 1.15 (0.83–1.59) [36]
Reference: Hauptmann et al. (2009) **Population:** 6,808 embalmers and funeral directors who died during 1960–1986. Identified from registries of the National Funeral Directors' Association, licensing boards, and state funeral directors' associations, NY State Bureau of Funeral Directors, and CA Funeral Directors and Embalmers. Deaths were identified from the National Death Index. Next of kin interviews conducted for 96% of cases and 94% of controls. **Outcome definition:** Death certificates used to determine UCOD from CLL (ICD-8: 204.1). [Note that while CLL was classified as lymphocytic leukemia in ICD-8, in ICD-10, it is included as non-Hodgkin lymphoma] **Design:** Nested case-control study within a prospective cohort study. **Analysis:** ORs calculated using unconditional logistic regression adjusted for date of birth, age at death, sex, data source, and smoking.	**Exposure assessment:** Occupational history obtained by interviews with next of kin and coworkers using detailed questionnaires. Exposure was assessed by linking questionnaire responses to an exposure assessment experiment providing measured exposure data. Exposure levels (peak, intensity, and cumulative) were assigned to each individual using a predictive model based on the exposure data. The model explained 74% of the observed variability in exposure measurements. Multiple exposure metrics including duration (mean = 33.1 years in cases), # of embalming, peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1932 through 1986. Duration of exposure was evaluated. Duration is also a surrogate for time because first exposure since dates of death were closely related to cessation of workplace exposures **Variation in exposure:** For variations in exposure from table 3 in the publication: Level 1 (no exposure to embalming)	**Internal comparisons:** **Embalming:** Never: OR = 1.0 (Ref. value) [# not given] Ever: OR = 1.0 (0.5–1.9) [# not given]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Lagged exposures were evaluated to account for cancer latency. **Related studies:** Hayes et al. (1990) Walrath and Fraumeni (1983) Walrath and Fraumeni (1984) **Note:** The original cohorts from these three related studies were combined in Hauptmann et al. (2009) and follow-up was extended so the case-series overlap and are not independent. However, the three related cohorts used external reference groups for comparison while Hauptmann et al. (2009) select internal controls, which were independent of the reference groups used in the other studies. **Confidence in effect estimate:**[a] **MEDIUM ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association.	For variations in exposure from table 4 in the publication: Level 1 (<500 embalming) Duration of exposure: Level 2 (<20 years) Level 3 (20–34 years) Level 4 (>34 years) Number of embalming: Level 2 (500−1,422) Level 3 (1,423–3,068) Level 4 (>3,068) Cumulative exposure: Level 2 (≤4,058 ppm-hrs) Level 3 (4,059–9,253 ppm-hrs) Level 4 (≥9,253 ppm-hrs) Average intensity (while embalming): Level 2 (≤1.4 ppm) Level 3 (>1.4–1.9 ppm) Level 4 (>1.9 ppm) TWA8 formaldehyde intensity: Level 2 (≤0.10 ppm) Level 3 (>0.10–0.18 ppm) Level 4 (>0.18 ppm) Peak Exposure: Level 2 (<7.0 ppm) Level 3 (7.0 to <9.3 ppm) Level 4 (>9.3 ppm) **Coexposures:** None evaluated. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	
Reference: Hayes et al. (1990) **Population:** 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975–1985. Death certificates obtained for 79% of potential study subjects (*n* = 6,651) with vital status unknown for 21%.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. Exposure based on occupation, which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to 3.99 ppm (low ventilation) with peaks up to 20 ppm.	**External comparisons:** PMR = 0.74 (0.29–1.53) [7]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Outcome definition: Death certificates and licensing boards used to determine cause of death from lymphatic leukemia (ICD-8: 204). **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected deaths from the U.S. population. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association.	Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975–1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60–74 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	
Reference: Saberi Hosnijeh et al. (2013) **Population:** 241,465 men and women recruited from 10 European countries during 1992–2000. Participants were predominantly aged 35–70 at recruitment and were followed up through 2010. **Outcome definition:** Incident primary leukemias. **Design:** Prospective multinational cohort incidence study with internal comparison groups. **Analysis:** HRs calculated controlling for age, sex, smoking, alcohol, physical activity, education, BMI, family history of cancer, country, other occupational exposures, and radiation. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null)	**Exposure assessment:** Individual occupational histories obtained by questionnaire about ever working in any of 52 occupations considered to be at high risk of developing cancer. Occupational exposures estimated as "high," "low," and no exposure by linking to a JEM. **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (none) Level 2 (low) Level 3 (high) **Coexposures:** Coexposure included pesticides, herbicides, insecticides, aromatic solvents, benzene, chlorinated solvents, trichloroethylene, metals, contact with animals or animal products, ionizing radiation. [As noted in Appendix B.3.9: Coexposures were not controlled for.	**Internal comparisons:** Exposure to formaldehyde: Level 1 RR = 1.00 (Ref. value) [130] Level 2 RR = 1.08 (0.81–1.45) [64] Level 3 RR = 1.38 (0.44–4.35) [3]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
High potential for information bias due to uncertainty in exposure assessment (Exposure Group C) and lack of latency analysis with attenuation of association.	Potential for confounding is unknown but could have inflated the observed effect. Potential for confounding may be mitigated by low correlation between exposures in the general population.]	
Reference: Blair et al. (2001) **Population:** White men, 30 years of age or older, identified from the Iowa cancer registry and the Minnesota hospital surveillance network during 1980–1983. Participation of eligible cases was 86% and approximately 77–79% for controls including 77% for surrogate respondents for deceased subjects. **Outcome definition:** Diagnosis of leukemia was confirmed by pathology review for all cases. **Design:** Population-based case-control study of 513 white men with leukemia from Iowa and Minnesota cancer surveillance networks. 1,087 controls were frequency matched on 5-year age groups, vital status, and state. **Analysis:** ORs calculated for job titles, employment duration and exposure intensity using unconditional logistic regression controlling for age, state, direct/surrogate response and coexposures, including smoking. Analyses by year of first exposure conducted. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group C) and lack of latency analysis with attenuation of association. Confounding possible.	**Exposure assessment:** Individual-level exposure estimates developed based on a JEM for each job held for more than 1 year, the industry where employed, and starting and ending year the job was held. Exposure intensity and probability assessed for formaldehyde and other exposures. Exposure intensity refers to the level likely experienced and considered a TWA8 over a year. **Duration and timing:** Exposure period based on occupational histories prior to 1983. Duration and timing since first exposure were evaluated. **Variation in exposure:** Intensity of exposure: Level 1 (unexposed) Level 2 (low) Level 3 (high) **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Other exposures evaluated included benzene, other organic solvents, petroleum-based oils and greases, cooking oils, ionizing radiation, paper dusts, gasoline and exhaust vapors, paints, metals, wood dust, asbestos, asphalt, cattle, meat, solder fumes. However, analyses of formaldehyde exposures did not control for other exposures.]	**Internal comparisons:** Acute lymphatic leukemia (ICD-9:204.0) No exposed cases Chronic lymphatic leukemia (ICD-9: 204.1) Level 1 OR = 1.0 (Ref. value) [483] Level 2 OR = 1.2 (0.7–1.8) [29] Level 3 OR = 0.6 (0.1–5.3) [1] No notable findings were reported for duration of time since first exposure to formaldehyde.
Reference: Ott et al. (1989)	**Exposure assessment:** Individual-level exposure ascertained from employee's	**Internal comparisons:** OR = 2.6 (0.13–13.0)† [1]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Population: 29,139 men employed at two large chemical manufacturing facilities and a research and development center who worked during 1940–1978. Vital status was known for 96.4%. Death certificates were available for 5,785 known descendants (95.4%). **Outcome definition:** Death certificates used to determine UCOD from lymphatic leukemia based on the ICD code in used at the time of death. **Design:** Nested case-control study within a prospective cohort mortality study. Eighteen cases of lymphatic leukemia were frequency matched to 100 controls on time from hire to death. **Analysis:** ORs calculated using unconditional logistic regression. **Related studies:** Rinsky et al. (1988) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and weak latency analysis with attenuation of association. Confounding possible. Low sensitivity due to rarity of exposure.	work assignments linked to records on departmental usage of formaldehyde. **Duration and timing:** Occupational exposures during 1940–1978. Timing of formaldehyde exposure not evaluated. **Variation in exposure:** Ever/never **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: 21 different chemicals were evaluated including benzene with much cross exposure. Benzene was not evaluated as a potential confounder and may be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect. Potential for confounding may be mitigated by rarity of coexposures among cases.]	†**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))
Reference: Walrath and Fraumeni (1984) **Population:** 1,007 deceased white male embalmers from California who died during 1925–1980. Death certificates obtained for all. **Outcome definition:** Lymphatic leukemia (ICD-8: 204) listed as cause of death on death certificate. **Design:** Proportionate mortality cohort study with external comparison group.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1916–1978. Birth year ranged from 1847 through 1959. Median age of death was 62 years. Most deaths were among embalmers with active licenses. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated.	**External comparisons:** Observed: 0 lymphatic leukemia deaths Expected: 2.2 lymphatic leukemia deaths PMR = 0 (0–1.36)† [0 vs. 2.2 expected] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Analysis: PMRs calculated using sex, race, age, and calendar-year-expected deaths from the U.S. population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	
Reference: Walrath and Fraumeni (1983) **Population:** 1,132 deceased white male embalmers licensed to practice during 1902–1980 in New York who died during 1925–1980 identified from registration files. Death certificates obtained for 75% of potential study subjects (*n* = 1,678). **Outcome definition:** Lymphatic leukemia (ICD-8: 204) listed as cause of death on death certificate. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected deaths from the U.S. population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1902–1980. Median year of birth was 1901. Median year of initial license was 1931. Median age at death was 1968. Expected median duration of exposure was 37 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**External comparisons:** Observed: 4 lymphatic leukemia deaths Expected: 2.6 lymphatic leukemia deaths PMR = 1.54 (0.49–3.71)† [4] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of

anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis; UCOD = underlying cause of death; GSD = geometric standard deviation; SMR = standardized mortality ratio; RR = relative risk; TWA8 = 8-hour time-weighted average; LHP = lymphohematopoietic; PMR = proportionate mortality ratio; BMI = body mass index; JEM = job-exposure matrix; OR = odds ratio.

Multiple myeloma

Epidemiological evidence

The most specific classification of multiple myeloma diagnosis that is commonly reported across the epidemiological literature has been based on the first three digits of the Eighth or Ninth Revision of the ICD code without further differentiation (i.e., Multiple myeloma ICD-8/9: 203). Evidence describing the association between formaldehyde exposure and the risk of developing or dying from multiple myeloma was available from 14 epidemiological studies—five case-control studies (Pottern et al., 1992; Ott et al., 1989; Heineman et al., 1992; Hauptmann et al., 2009; Boffetta et al., 1989) and nine cohort studies (Stellman et al., 1998; Pira et al., 2014; Meyers et al., 2013; Hayes et al., 1990; Edling et al., 1987b; Dell and Teta, 1995; Coggon et al., 2014; Beane Freeman et al., 2009; Band et al., 1997). One set of reported results from Fryzek et al. (2005) was classified as *not informative* due to likely confounding; for details see Appendix B.3.9. Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for multiple myeloma (see Table 3-65) following the causal evaluation.

Consistency of the observed association

The results of these studies appear to be mixed with some showing non-significant increases in risk and other showing non-significant decreases in risk. Nine of the 14 studies were low confidence (Stellman et al., 1998; Pottern et al., 1992; Pira et al., 2014; Ott et al., 1989; Edling et al., 1987b; Dell and Teta, 1995; Boffetta et al., 1989) with many results based on fewer than five cases. However, only the study by Beane Freeman et al. (2009) reported a result with *high* confidence showing an association between peak formaldehyde exposure and risk of multiple myeloma. The study results presented in Table 3-65 (by confidence level and publication date) and plotted in Figure 3-40 detail all of the reported associations between exposures to formaldehyde and the risks of developing or dying from multiple myeloma.

The first four studies shown at the left in Figure 3-40 followed the health of groups of occupationally exposed workers in three different industries and did not have individual-level exposure estimates (Hayes et al., 1990; Edling et al., 1987b; Dell and Teta, 1995). Respectively, these were: (1) workers making grinding wheels bound with formaldehyde resins, (2) embalmers, and (3) workers manufacturing plastics—professions known to be exposed to formaldehyde. Importantly, all of these professions were exposed to high peak concentrations of formaldehyde. Edling et al. (1987b) reported that the workers making grinding wheels bound with formaldehyde

resins were exposed to peak formaldehyde levels of up to 20–30 mg/m^3 (15–23 ppm). Embalmers (Hayes et al., 1990) were also exposed to high peak formaldehyde concentrations with mean exposures of more than 2 ppm and peaks as high as 8.7 ppm (Stewart et al., 1992). Workers at the plastics manufacturing facilities studied by Dell and Teta (1995) were exposed to formaldehyde, formaldehyde resins, and formaldehyde molding compounds. An independent occupational hygiene survey of facilities producing similar products reported peak exposure for these activities of 1.88 ppm, 30.45 ppm, and 60.77 ppm, respectively (Stewart et al., 1987). The results of these three studies are displayed beneath the header of "Population-level exposure assessment." All three studies showed elevated RRs of multiple myeloma mortality as measured by the mortality ratios; although, none of the three was statistically robust enough to decrease the likelihood of chance as an alternative explanation. The Hayes et al. (1990) result (PMR = 1.37; 95% CI 0.84–2.12; *n* = 20) was classified with *medium* confidence but the other two results from Edling et al. (1987b) (SMR = 4.0; 95% CI 0.45–14.44; *n* = 2) and Dell and Teta (1995) (SMR = 2.62; 95% CI 0.85–6.11; *n* = 8) were classified with *low* confidence.

The second set of studies (*n* = 10) is displayed in Figure 3-40 (Stellman et al., 1998; Pottern et al., 1992; Ott et al., 1989; Meyers et al., 2013; Heineman et al., 1992; Hauptmann et al., 2009; Coggon et al., 2014; Boffetta et al., 1989; Beane Freeman et al., 2009; Band et al., 1997) beneath the header of "Individual-level exposure assessment." In principle, a general strength of this second set of studies was their use of individualized exposure data; however, the quality of the exposure assessment for each individual varied considerably across this set of studies. These 10 studies with individual-level exposure assessment can be divided into two groups based on the methods of individual exposure assessment. The first grouping gathered minimal information (e.g., questionnaire data on "ever" exposure to formaldehyde) on formaldehyde exposure (Stellman et al., 1998; Pottern et al., 1992; Heineman et al., 1992; Boffetta et al., 1989). The second grouping focused on workers who were occupationally exposed to formaldehyde and used work assignments or job histories matched to exposure data to assess workers' formaldehyde exposures (Ott et al., 1989; Meyers et al., 2013; Hauptmann et al., 2009; Coggon et al., 2014; Beane Freeman et al., 2009; Band et al., 1997).

The exposure assessment methodology for the first grouping of four studies with individual-level exposures was especially crude. Exposure assessment was limited to either a one-time questionnaire asking participants to check off a box if they were "ever" exposed to formaldehyde in the workplace or in daily life (Stellman et al., 1998; Boffetta et al., 1989) or using the occupation listed on individuals' most recent annual tax records to estimate previous occupational formaldehyde exposure as "none," "possible," or "probable" (Pottern et al., 1992; Heineman et al., 1992). While the large size of these studies was considered to be a strength, the weaknesses of their relatively low-quality exposure assessment outweighed that strength. It is well known that the use of low-quality exposure data in epidemiological studies may preclude the ability to detect all but the strongest association.

The second grouping of studies, with relatively higher quality individual-level exposure to formaldehyde, examined occupational histories at different points in time and linked this to measured or estimated exposures (Ott et al., 1989; Meyers et al., 2013; Hauptmann et al., 2009; Coggon et al., 2014; Beane Freeman et al., 2009; Band et al., 1997). While the relative effect estimates for multiple myeloma mortality in each of these cohorts compared to the general population did not show elevated risks (relative effect estimates of: 0.8, 1.4, 1.0, 0.94, 1.24, 0.99), two studies (Coggon et al., 2014; Beane Freeman et al., 2009) showed somewhat higher risks when analyses focused on the workers with highest peak exposure. Beane Freeman et al. (2009) evaluated results by each worker's highest formaldehyde concentration during a "peak" exposure event, by average intensity of exposure, by cumulative exposure, and by duration of exposure. Peak exposure events were defined as short-term exposures (<15 minutes) that exceeded the TWA formaldehyde intensity (Beane Freeman et al., 2009). Workers' peak exposures were defined as the highest concentration among their peak exposure events. In Beane Freeman et al. (2009), the highest peak exposure category represents the workers who had ever experienced short-term peak exposure to ≥4.0 ppm. The Beane Freeman et al. (2009) results in the high category of peak exposures were RR = 2.04 (95% CI 1.01–4.12). In Coggon et al. (2014), the "high" category of exposure represented workers who ever had a job in the highest formaldehyde exposure category (≥2 ppm). The Coggon et al. (2014) results in the high exposure category were, however, relatively weak SMR = 1.18 versus 0.99 for all workers.

Hauptmann et al. (2009) and Ott et al. (1989) assessed individual-level exposure but only presented results specific to formaldehyde exposures for the study population as a whole. Similarly, the study of garment workers (Meyers et al., 2013) relied on individual measures of the timing of exposure but did not have formaldehyde concentration data beyond the industrial hygiene data used to plan the study (Stayner et al., 1988). Continuous area monitoring showed that formaldehyde levels were relatively constant with no substantial peak levels over the work shift (Stayner et al., 1988). The results from Meyers et al. (2013) are mixed, with the strongest evidence showing a statistically significant decreased risk among workers with the longest duration of formaldehyde exposure in analyses compared to internal referents with less than a 3-year exposure duration (SRR = 0.28; 95% CI 0.08–0.99).

In summary, among all the studies that used individual-level exposure assessment, the study with the highest quality exposure assessment methodology was the National Cancer Institute study (Beane Freeman et al., 2009) among industrial workers at facilities either using formaldehyde or producing formaldehyde. Beane Freeman et al. (2009) reported on three different, but related, measures of exposure to formaldehyde based on different exposure assessment techniques highlighting peak, cumulative and average exposures and showed elevated risk across all three measures; the most pronounced effects showed a two-fold increased risk of mortality from multiple myeloma associated with the highest level of peak exposure to formaldehyde (RR = 2.04; 95% CI 1.01–4.12).

The three studies with population-level exposure assessment, (Hayes et al., 1990; Edling et al., 1987b; Dell and Teta, 1995), all had very high peak exposure and were consistent with Beane Freeman et al. (2013) in showing an elevated risk although none was able to rule out chance. The large population studies with only crude measures of formaldehyde exposure reported mixed results with only a slightly higher risk for those judged to be "Probably" exposed (see Figure 3-40). The studies of industrial workers did not show increased risks in their populations as a whole but did report somewhat higher risks among the workers with highest exposure when individual-level exposures were considered (Coggon et al., 2014; Beane Freeman et al., 2009).

A better understanding of the etiologic progression of multiple myeloma may be needed to interpret these findings but there is some consistent epidemiological evidence suggesting an association between peak formaldehyde exposures and increased risk of multiple myeloma and possibly an increased risk at shorter durations, which could select out the responsive individuals leaving the nonresponsive individuals without additional risks. However, it could also be the case from these data that only peak exposures are associated with multiple myeloma.

Strength of the observed association

While reported relative effect estimates were consistently elevated above the null value of one across the studies, the magnitude of the relative effect estimates varied with the quality of the exposure assessment. Studies with higher quality exposure data based on individual-level exposure assessment generally reported higher relative effect estimates (stronger associations)

Setting aside the large population-based studies with crude exposure assessment (Stellman et al., 1998; Pottern et al., 1992; Heineman et al., 1992; Boffetta et al., 1989) and focusing on individual-level exposure results where possible, the strength of the associations ranged from 1.2 to 4.0, but the upper end of that range was based on two studies with very few formaldehyde-exposed cases. The results at the highest levels of peak formaldehyde exposure showed an approximately two-fold relative increase in risk of death from multiple myeloma (Beane Freeman et al., 2009).

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants started prior to their multiple myeloma diagnosis and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and was done in a blinded fashion with respect to outcome status. The epidemiological literature for formaldehyde and multiple myeloma describes only one study that evaluates the impact of TSFE (Meyers et al., 2013); however, while those results showed what appeared to be a slight downward trend toward lower risks at shorter times since first exposure, the CIs around those estimated risks were wide and overlapped substantially. Such findings do not add much additional information.

Exposure-response relationship

There was limited evidence of exposure-response relationships in three multiple myeloma studies. The study by Beane Freeman et al. (2009) reported on three different measures of exposure to formaldehyde and showed elevated risk across all three measures, most strongly for peak exposure (RR = 2.04; 95% CI 1.01–4.12) for the highest category (trend p = 0.08). There was also a finding of greater risks of multiple myeloma at shorter durations of exposure compared to longer durations; in two analyses of duration using both internal and external comparison groups, those workers with the longest duration of exposure (10+ years) were at lower risk than those with 3–9 years of exposure. This would be inconsistent with an exposure-response pattern for duration of exposure or cumulative exposure but is not necessarily inconsistent with the finding of an exposure-response for higher levels of peak exposure. Coggon et al. (2014) reported a very modest increase in risk among those workers in the high exposure category (SMR = 1.18; 95% CI 0.57–2.18); however, the risk among workers in the low/moderate category was even higher (SMR = 1.47; 95% CI 0.82–2.43). Pottern et al. (1992) reported increasing relative risks with the qualitative likelihood of exposure with "possible" exposure having RR = 1.1 (95% CI 0.8–1.6) and "probable" exposure having RR = 1.6 (95% CI 0.4–5.3).

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias is an unlikely bias in the epidemiological studies of multiple myeloma as the case-control studies evaluated exposure status without regard to outcome status and had participation levels of 77–100% and each of the cohort studies included at least 79% of eligible participants and lost fewer than 6% of participants over the course of mortality follow-up. The healthy worker effect and the healthy worker survivor effect could obscure a truly larger effect of formaldehyde exposure in analyses based on "external" comparisons with mortality in the general population (Ott et al., 1989; Meyers et al., 2013; Hayes et al., 1990; Edling et al., 1987b; Dell and Teta, 1995; Coggon et al., 2014; Beane Freeman et al., 2009), but would not influence analyses using "internal" or matched comparison groups (Stellman et al., 1998; Pottern et al., 1992; Heineman et al., 1992; Hauptmann et al., 2009; Boffetta et al., 1989; Beane Freeman et al., 2009).

Differential exposure misclassification is considered unlikely among these studies of multiple myeloma mortality. Random measurement error or nondifferential misclassification has the effect of causing bias toward the null, thereby obscuring potentially real effects by underestimating their magnitude. This may explain the generally null findings of the four large studies that relied on very crude assessments of exposure (Stellman et al., 1998; Pottern et al., 1992; Heineman et al., 1992; Boffetta et al., 1989).

Confounding is a potential bias that could arise if another cause of multiple myeloma was also associated with formaldehyde exposure. There does not appear to be any evidence of confounding that would provide an alternative explanation for the observed association of formaldehyde exposure with increased risk of multiple myeloma seen in these studies. Known risk

factors for multiple myeloma include age, sex, race, and exposure to benzene (Vlaanderen et al., 2011). Chemical, and other coexposures that have not been independently associated with multiple myeloma are not expected to confound results. Pentachlorophenol is considered to be a likely carcinogen (U.S. EPA, 2010) and the only study with likely coexposure to pentachlorophenol was classified as *not informative* due to the likelihood of confounding (Robinson et al., 1987). Risks of multiple myeloma are higher with advancing age, among men, and the age-adjusted mortality rate in black Americans was more than twice as high as among white Americans in 2008 (NCI, 2012). All of the epidemiological studies controlled for age and sex. Only one study reported results according to race (Hayes et al., 1990) who reported statistically significant increased risks among "nonwhites" showing a PMR = 3.69 (95% CI 1.59–7.26).

Benzene was not noted as a coexposure in the studies of workers making grinding wheels (Edling et al., 1987b), garment plant workers (Meyers et al., 2013), or embalmers (Hayes et al., 1990) and consequently, would not be expected to be a confounder of those results. In the study of workers manufacturing plastics, Dell and Teta (1995) examined possible coexposures with benzene but concluded that there were no obvious common exposures. Benzene exposures were not reported in the study of British industrial workers (Coggon et al., 2003); although, it is a possible coexposure. However, in a cohort of U.S. industrial workers with similar occupational activities, benzene was specifically assessed as a potential confounder among the U.S. industrial workers (Beane Freeman et al., 2009) and found not to be a confounder.

A single *high* confidence result supports an association between peak formaldehyde exposures and increased risks of multiple myeloma (Beane Freeman et al., 2009) with support from three results of studies of high peak formaldehyde exposure settings with *low* to *medium* confidence (Hayes et al., 1990; Edling et al., 1987b; Dell and Teta, 1995). However, risk estimates using other exposure metrics from the same study with the high confidence result (Beane Freeman et al., 2009) did not find increased risks and it is not known which metric of exposure is likely to be the most biologically relevant. Bias is unlikely to explain these findings, but chance could be an alternative explanation.

Summary of Human Evidence Synthesis Judgments, Causal Evaluation, and Conclusion

Summary of human evidence synthesis judgments

The following factors were most influential to the causal evaluation and synthesis conclusion:

- *Consistency and Study Confidence:* Results were heterogeneous with many reporting results near the null—but effects were consistently elevated in four studies where workers were exposed to high peak exposures including one high confidence result.
- *Strength and Precision:* The strength of the association showing an approximate 1.2- to 4-fold increase in risk with the highest quality evidence showing a two-fold increase in risk with high peak exposures.

- *Coherence*: Biologically coherent temporal relationship consistent with a pattern of exposure to formaldehyde and subsequent death from myeloid leukemia, allowing time for cancer induction, latency, and mortality although only one study evaluated the impact of time since first exposure.
- *Dose-Response:* Limited evidence of an exposure-response trend from a single high confidence study showing that increased exposure to formaldehyde was associated with increased risk of multiple myeloma.

Causal evaluation

The causal evaluation for formaldehyde exposure and the risk of developing or dying from multiple myeloma placed the greatest weight on five particular considerations: (1) the observations of increases in risk across one *high*, one *medium*, and two *low* confidence studies of occupational formaldehyde levels, but limited to groups of people who experienced high peak exposures; analyses based on other exposure metrics did not report associations in several populations; (2) the strength of the association showing an approximate 1.2- to 4-fold increase in risk with the highest quality evidence showing a two-fold increase in risk with high peak exposures; (3) the limited evidence of an exposure-response trend from a single high confidence study showing that increased exposure to formaldehyde was associated with increased risk of multiple myeloma; (4) reasonable confidence that alternative explanations are ruled out, including bias and confounding within individual studies or across studies, but chance could be an alternative explanation; and (5) confidence was diminished by reports of inverse relationships with duration of exposure and TSFE.

Given the uncertainties outlined above, and although formaldehyde is genotoxic, the consistent observations of genotoxicity in peripheral blood lymphocytes observed across several occupational studies were not interpreted as sufficient to further strengthen the judgment on the human evidence of multiple myeloma beyond *slight*.

Conclusion

The available epidemiological studies provide *slight* evidence of an association consistent with causation between formaldehyde exposure and an increased risk of multiple myeloma—primarily with respect to peak exposure.

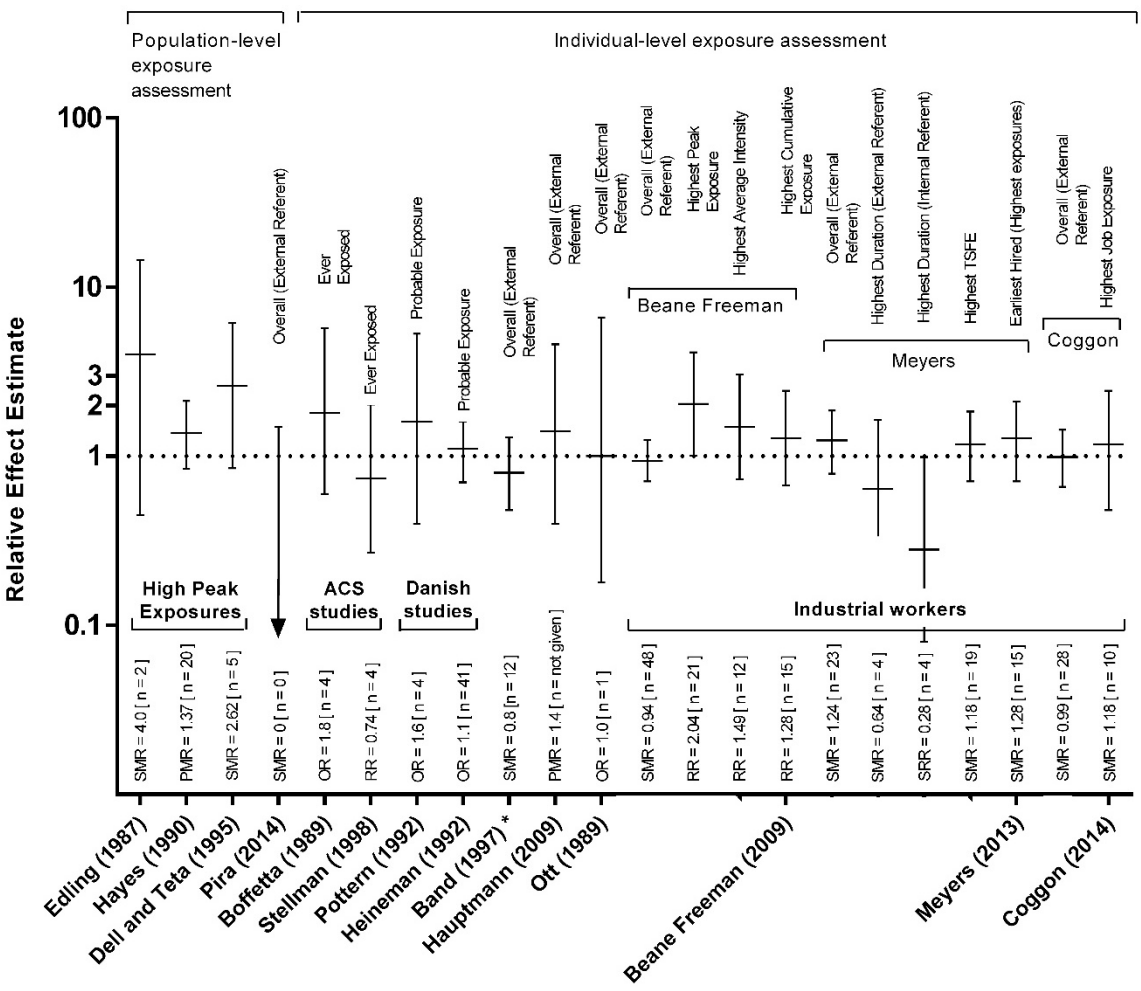


Figure 3-40. Epidemiological studies reporting multiple myeloma risk estimates.

Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for multiple myeloma (see Table 3-65). SMR = standardized mortality ratio; PMR = proportionate mortality ratio; RR = relative risk; OR = odds ratio. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 3]). Results are grouped by the exposure-assessment methodology (e.g., population-level versus individual-level) and the source of the cancer data (e.g., American Cancer Society or Danish Cancer Registry) or type of occupation of exposed workers (e.g., industrial workers). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. *Note that the CIs for Band et al. (1997) are 90% rather than 95%.

Table 3-65. Epidemiological studies of formaldehyde exposure and risk of multiple myeloma

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Beane Freeman et al. (2009) with supplemental online tables **Population:** 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the U.S. followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. 676 workers (3%) were lost to follow-up. Vital status was 97.4% complete and only 2.6% lost to follow-up. **Outcome definition:** Death certificates used to determine UCOD from multiple myeloma (ICD-8: 203). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Blair et al. (1986) Hauptmann et al. (2003) **Confidence in effect estimates:**[a] **HIGH** (No appreciable bias) **[NB:** Checkoway et al. (2015) below] **Reference:** Beane Freeman et al. (2009) as re-analyzed by Checkoway et al. (2015) with differences noted **Population:** No differences. **Outcome definition:** Death certificates used to determine UCOD from acute and chronic myeloid leukemia (ICD-8: 205.0 and 205.1).	**Exposure assessment:** Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists, and monitoring data through 1980. Median TWA (over 8 hours) = 0.3 ppm (range 0.01–4.3). Median cumulative exposure = 0.6 ppm-years (range 0–107.4). Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1946 to 1980. Median length of follow-up: 42 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Peak exposure: Level 1 (>0 to <2.0 ppm) Level 2 (2.0 to <4.0 ppm) Level 3 (≥4.0 ppm) Average intensity: Level 1 (>0 to <0.5 ppm) Level 2 (0.5 to <1.0 ppm) Level 3 (≥1.0 ppm) Cumulative exposure: Level 1 (>0 to <1.5 ppm-years) Level 2 (1.5 to <5.5 ppm-years) Level 3 (≥5.5 ppm-years) **Coexposures:** Exposures to 11 other compounds were identified and evaluated as potential confounders and found not be confounders. [As noted in Appendix B.3.9: There was no information on smoking; however, according to Blair et al. (1986), "The lack of a consistent elevation for tobacco-related causes of death, however, suggests that the smoking habits among this cohort did not differ substantially from those of the general population."	**Internal comparisons:** Peak exposure Unexposed RR = 2.74 (1.18–6.37) [11] Level 1 RR = 1.00 (Ref. value) [14] Level 2 RR = 1.65 (0.76–3.61) [13] Level 3 RR = 2.04 (1.01-4.12) [21] *p*-trend (exposed) = 0.08; *p*-trend (all) >0.50 Average intensity Unexposed RR = 2.18 (1.01–4.70) [11] Level 1 RR = 1.00 (Ref. value) [25] Level 2 RR = 1.40 (0.68–2.86) [11] Level 3 RR = 1.49 (0.73–3.04) [12] *p*-trend (exposed) >0.50; *p*-trend (all) >0.50 Cumulative exposure Unexposed RR = 1.79 (0.83–3.89) [11] Level 1 RR = 1.00 (Ref. value) [28] Level 2 RR = 0.46 (0.18–1.20) [5] Level 3 RR = 1.28 (0.67–2.44) [15] *p*-trend (exposed) >0.50; *p*-trend (all) >0.50 **External comparisons:** $SMR_{Unexposed}$ = 1.78 (0.99–3.22) [11] $SMR_{Exposed}$ = 0.94 (0.71–1.25) [48]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Design: No differences. **Analysis:** HRs estimated using Cox proportional hazards models controlling for age, sex, and race; adjusted for pay category compared to workers in the redefined lowest exposed category. Did not control for calendar year as did Beane Freeman et al. (2009). Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Blair et al. (1986) Hauptmann et al. (2003) Checkoway et al. (2015) [reviewed here] **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group D due to reclassification of peak exposures as unexposed) with attenuation of association.		**Checkoway** **External comparisons:** $SMR_{Unexposed}$ = 1.82 (1.01–3.29) [11] $SMR_{Exposed}$ = 0.93 (0.70–1.24) [48]
Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories that produced formaldehyde. Cohort mortality followed from 1941 through 2012. Cause of deaths was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378 deaths through 2012. Vital status was 98.9% complete and only 1.1% lost to follow-up through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from multiple myeloma (ICD-9: 203). **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates.	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941–1982. Duration was evaluated as more, or less, than 1 year only among the high exposure group. Timing since first exposure was not evaluated. **Variation in exposure:** Highest exposure level attained Level 1 (Background) Level 2 (low/moderate) Level 3 (High) Duration of high exposures Level 1 (<1 year) Level 2 (1 year or more) **Coexposures:** Not evaluated as potential confounders. Potential low-level exposure to styrene, ethylene	**External comparisons:** SMR = 0.99 (0.66–1.43) [28] **Within-study external comparisons:** Highest exposure level attained Level 1 SMR = 0.31 (0.06–0.91) [3] Level 2 SMR = 1.47 (0.82–2.43) [15] Level 3 SMR = 1.18 (0.57–2.18) [10]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Related studies: Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency analysis with attenuation of association.	oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. [As noted in Appendix B.3.9: Styrene is associated with LHP cancers. Asbestos is associated with URT cancers, but not with LHP cancers. Other coexposures are not known risk factors for this outcome. Authors stated that the extent of coexposures was expected to be low. Potential for confounding may be mitigated by low coexposures.]	
Reference: Meyers et al. (2013) **Population:** 11,043 workers in three U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion **Outcome definition:** Death certificates used to determine both the UCOD from multiple myeloma (ICD code in use at time of death). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Stayner et al. (1985) Stayner et al. (1988) Pinkerton et al. (2004) **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due lack of latency analysis with attenuation of association.	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984. Geometric TWA8 exposures ranged from 0.09 to 0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 through 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were evaluated. **Variation in exposure:** Duration of exposure: Level 1 (<3 years) Level 2 (3–9 years) Level 3 (10+ years) Time since first exposure: Level 1 (<10 years) Level 2 (10–19 years) Level 3 (20+ years) **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	**External comparisons:** SMR = 1.24 (0.79–1.86) [23] **Within-study external comparisons:** Duration of exposure: Level 1 SMR = 1.16 (0.50–2.29) [8] Level 2 SMR = 2.03 (1.01–3.64) [11] Level 3 SMR = 0.64 (0.17–1.64) [4] Time since first exposure (TSFE): Level 1 SMR = 1.73 (0.04–9.61) [1] Level 2 SMR = 1.63 (0.34–4.76) [3] Level 3 SMR = 1.18 (0.71–1.84) [19] Year of first exposure: <1963 SMR = 1.28 (0.71–2.11) [15] 1963–70 SMR = 0.81 (0.22–2.08) [4] 1971+ SMR = 2.16 (0.59–5.52) [4] **Internal comparisons:** Duration of exposure: Level 1 SRR = 1.00 (Ref. value) [8] Level 2 SRR = 1.22 (0.46–3.26) [11] Level 3 SRR = 0.28 (0.08–0.99) [4]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Hauptmann et al. (2009) **Population:** 6,808 embalmers and funeral directors who died during 1960–1986. Identified from registries of the National Funeral Directors' Association, licensing boards and state funeral directors' associations, NY State Bureau of Funeral Directors, and CA Funeral Directors and Embalmers. Deaths were identified from the National Death Index. Next of kin interviews conducted for 96% of cases and 94% of controls. **Outcome definition:** Death certificates used to determine UCOD from multiple myeloma (ICD-8: 203). **Design:** Nested case-control study within a prospective cohort mortality study using two internal comparison groups; the first composed of those who had never embalmed (one case and 55 controls) and the second composed of those who had fewer than 500 embalmings (5 cases and 83 controls). **Analysis:** ORs calculated using unconditional logistic regression adjusted for date of birth, age at death, sex, data source, and smoking. Lagged exposures were evaluated to account for cancer latency. Results from the second internal comparison group with <500 embalmings were selected to increase statistical stability. **Related studies:** Hayes et al. (1990) Walrath and Fraumeni (1983) Walrath and Fraumeni (1984) **Note:** The original cohorts from these three related studies were combined in Hauptmann et al. (2009) and follow-up was extended so the case-series overlap and are not independent. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null)	**Exposure assessment:** Occupational history obtained by interviews with next of kin and coworkers using detailed questionnaires. Exposure was assessed by linking questionnaire responses to an exposure assessment experiment providing measured exposure data. Exposure levels (peak, intensity, and cumulative) were assigned to each individual using a predictive model based on the exposure data. The model explained 74% of the observed variability in exposure measurements. Multiple exposure metrics including duration (mean = 33.1 years in cases), # of embalming, peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1932 through 1986. Year of birth ranged from 1876 through 1959. Year of deaths ranged from 1960 through 1986. Duration of exposure was evaluated. Duration is also a surrogate for time since first exposure since dates of death were closely related to cessation of workplace exposures **Variation in exposure:** Ever/never **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**External comparisons:** Ever embalming: OR = 1.4 (0.4–5.6) [# not given]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association.		
Reference: Hayes et al. (1990) **Population:** 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975–1985. Death certificates obtained for 79% of potential study subjects (*n* = 6,651) with vital status unknown for 21%. **Outcome definition:** Death certificates and licensing boards used to determine cause of death from multiple myeloma (ICD-8: 205). **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. Exposure based on occupation, which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to 3.99 ppm (low ventilation) with peaks up to 20 ppm. Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975–1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60–74 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**External comparisons:** PMR = 1.37 (0.84–2.12) [20] **Additional:** By Race White PMR = 0.97 (0.50–1.69) [12] Nonwhite PMR = 3.69 (1.59–7.26) [8]
Reference: Pira et al. (2014) **Population:** 2,750 workers employed at a laminated plastic factory in Italy for at least 180 days between 1947 and 2011 followed until May 2011. Deaths were identified from population registries. Vital status was 96.9% complete and only 3.1% lost to follow-up.	**Exposure assessment:** Formaldehyde is a byproduct from the resins used in production process and all workers were presumed to have been exposed. **Duration and timing:** Exposure period from 1947 through 2011. Median length of follow-up: 23.6 years. Duration and timing since first exposure were not evaluated.	**External comparisons:** Observed: 0 multiple myeloma deaths Expected: 2 multiple myeloma deaths Myeloid Leukemia (ICD-9: 205) SMR = 0 (0–1.50)† [0] †**Note:** EPA derived CIs using the Mid-P Method [See Rothman and Boice (1979)]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Outcome definition: Death certificates used to determine UCOD from multiple myeloma (ICD-9: 203). **Design:** Prospective cohort mortality study with external comparison group. **Analysis:** RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, and 5-year calendar periods using mortality rates from the Piedmont region. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) and lack of latency analysis with attenuation of association. Confounding possible. Low sensitivity (few cases).	**Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated	

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Stellman et al. (1998) **Population:** 317,424 U.S. men enrolled in the American Cancer Society's Cancer Prevention Study II during 1982 with sufficient data on occupation. Cohort mortality followed until August 1988 with 98% complete follow-up. **Outcome definition:** Death certificates used to determine cause of deaths from multiple myeloma (ICD-9: 203). **Design:** Prospective cohort study with internal comparison group. **Analysis:** RR calculated using Poisson regression controlling for sex, age, smoking. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group C) and lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Exposure assessment:** Individual-level exposure ascertained from questionnaire on occupation with specific exposure to formaldehyde based on checkbox. Formaldehyde analyses limited to workers not in wood-related occupations. **Duration and timing:** Occupational exposures prior to 1982. Timing of formaldehyde exposure not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Wood dust excluded. [As noted in Appendix B.3.9: Coexposures included: asbestos and wood dust. However, these coexposures are not associated with LHP endpoints so confounding is unlikely.]	**Internal comparisons:** RR = 0.74 (0.27–2.02) [4]
Reference: Band et al. (1997) **Population:** 30,157 male workers with at least 1 year of employment accrued by January 1950. Followed through December 1982. Loss to follow-up was less than 6.5% for workers exposed to the sulfate process (67% of original cohort of 30,157) and less than 20% for workers exposed to the sulfite process. **Outcome definition**: Cause of death obtained from the National Mortality Database based on ICD version in effect at time of death and standardize to ICD-9 version; multiple myeloma (ICD-9 203). **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the Canadian population. **Confidence in effect estimates:**[a] **↓** (Potential bias toward the null)	**Exposure assessment:** Occupational data limited to hire and termination dates for all workers and type of chemical process of pulping (sulfate vs. sulfite). No job-specific data available. Presumed exposure to formaldehyde known to be used in the plant. Formaldehyde is known to be an exposure for pulp and paper mill workers: job-specific median exposures ranging from 0.04 to 0.4 ppm with peaks as high as 50 ppm (Korhonen et al., 2004). **Duration and timing:** Duration and timinge since first exposure were not evaluated. **Variation in exposure:** No variation in formaldehyde exposure was reported. Results presented by pulping process (sulfate vs. sulfite) but there is no information on differential exposures between the two processes. **Coexposures:** Not evaluated as confounders.	**External comparisons:** All workers SMR = 0.80 (90% CI 0.48–1.29) [12]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) with attenuation of association. Confounding possible.	[As noted in Appendix B.3.9: Potential confounders for these outcomes include chlorophenols, acid mists, dioxin, and perchloroethylene and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	
Reference: Dell and Teta (1995) **Population:** 5,932 men employed at a New Jersey plastics manufacturing plant for at least 7 months during 1946–1967. Cohort mortality followed through 1988. Vital status was 94% complete and only 6% lost to follow-up. Death certificates obtained for 98%. **Outcome definition:** Death certificates used to determine UCOD from multiple myeloma based on ICD code at time of death. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. and local populations. **Confidence in effect estimates:**[a] **SUMMARY for MM: LOW ↓** (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment (Exposure Group C) with attenuation of association. Confounding possible.	**Exposure assessment:** Presumed exposure to formaldehyde known to be used in the plant. Only 111 men had assignments involving formaldehyde. **Duration and timing:** Exposures during 1946–1967. Duration and timing since first exposure were not evaluated. **Variation in exposure:** By department: Plant Services and Research and Development. By pay status: salaried and hourly. **Coexposures:** Not evaluated as confounders. [As noted in Appendix B.3.9 coexposures include: acrylonitrile, asbestos, benzene, carbon black, epichlorohydrin, PVC (vinyl chloride), styrene, and toluene and would likely be positively correlated with formaldehyde exposure. Asbestos is not associated with LHP cancers. Benzene and styrene were not evaluated as potential confounders and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	**External comparisons:** All salaried workers SMR = 2.62 (0.85–6.11) [5] Research and Development: Hourly workers SMR = 2.73 (0.55–7.97) [3]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Pottern et al. (1992) **Population:** Danish women registered in both the National Cancer Registry and pension fund. All women with a specific occupational history other than "homemaker" were included. **Outcome definition:** Incident cases of multiple myeloma reported to the Danish Cancer Registry during 1970–1984. **Design:** Population-based case-control study of 363 women with 1,517 age- and sex-matched controls alive at time of case diagnosis. **Analysis:** ORs calculated for occupation, industry, and likelihood of exposure using logistic regression controlling for age. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) and lack of latency analysis with attenuation of association.	**Exposure assessment:** Individual-level exposure estimated by industrial hygienists based on occupation listed on most recent annual income tax documents and the industry associated with that occupation. **Duration and timing:** Exposure period preceding cancer incidence (<1984). Duration and timing since first exposure were not evaluated. **Variation in exposure:** Likelihood of exposure: Level 1 (unexposed) Level 2 (possible) Level 3 (probable) **Coexposures:** Many other compounds were identified and evaluated as independent risk factors. [As noted in Appendix B.3.9: Other exposures evaluated included 19 categories grouping 47 substances. Coexposures were not evaluated for confounding but exposure to organic solvents (including benzene) and radiation were not risk factors for multiple myeloma so confounding is unlikely.]	**Internal comparisons:** Likelihood of exposure Level 1 RR = 1.0 (Ref. value) [303] Level 2 RR = 1.1 (0.8–1.6) [56] Level 3 RR = 1.6 (0.4–5.3) [4]
Reference: Heineman et al. (1992) **Population:** Danish men registered in both the National Cancer Registry and pension fund. All men with a specific occupational history were included. **Outcome definition:** Incident cases of multiple myeloma reported to the Danish Cancer Registry during 1970–1984. 92% of cases were histologically confirmed. **Design:** Population-based case-control study of 1,098 men with 4,169 age- and sex-matched controls alive at time of case diagnosis. **Analysis:** ORs calculated for occupation, industry, and likelihood of exposure using logistic regression controlling for age. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null)	**Exposure assessment:** Individual-level exposure estimated by industrial hygienists based on occupation listed on most recent tax documents. **Duration and timing:** Exposure period preceding cancer incidence (<1984). Duration and timing since first exposure were not evaluated. **Variation in exposure:** Likelihood of exposure: Level 1 (unexposed) Level 2 (possible) Level 3 (probable) **Coexposures:** Other compounds were identified and evaluated as independent risk factors including: gasoline, oil products, engine exhausts, **benzene**, dyes, phthalates, vinyl chloride, **asbestos**, and pesticides.	**Internal comparisons:** Likelihood of exposure Level 1 RR = 1.0 (Ref. value) [913] Level 2 RR = 1.0 (0.8–1.3) [144] Level 3 RR = 1.1 (0.7–1.6) [41]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) and lack of latency analysis with attenuation of association.	[As noted in Appendix B.3.9: Other exposures evaluated included 19 categories grouping 47 substances. Asbestos is not a risk factor for LHP. "Possible" benzene exposure was associated with MM but not "probable" benzene exposure, so confounding is considered to be unlikely.]	
Reference: Boffetta et al. (1989) **Population:** 508,637 U.S. men and 676,613 women enrolled in the American Cancer Society's Cancer Prevention Study II during 1982 with sufficient data on occupation. Cohort mortality followed until August 1986 with 98.5% complete follow-up. **Outcome definition:** Death certificates used to determine cause of deaths from incident cases of multiple myeloma (ICD-9: 203) since follow-up began. **Design:** Population-based matched nested case-control within prospective cohort study. **Analysis:** RR calculated using Poisson regression controlling for sex, age, smoking, education, diabetes, X-ray treatment, farming, pesticide, and herbicide exposure. **Confidence in effect estimates:**[a] **SUMMARY: LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group C) and lack of latency analysis with attenuation of association. Low sensitivity (few exposed cases).	**Exposure assessment:** Individual-level exposure ascertained from questionnaire on occupation with specific exposure to formaldehyde based on checkbox. **Duration and timing:** Occupational exposures prior to 1982. Timing of formaldehyde exposure not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Various coexposures were controlled for in the analyses. [As noted in Appendix B.3.9: Matching controlled for sex, age, ethnic group, residence, smoking, education, diabetes, X-ray treatment, farming, pesticide, and herbicide exposure. Other coexposures were not associated with LHP cancers.]	**Internal comparisons:** OR = 1.8 (0.6–5.7) [4]
Reference: Ott et al. (1989) **Population:** 29,139 men employed at two large chemical manufacturing facilities and a research and development center who worked during 1940–1978. Vital status was known for 96.4%. Death certificates were available for 5,785 known descendants (95.4%).	**Exposure assessment:** Individual-level exposure ascertained from employee's work assignments linked to records on departmental usage of formaldehyde. **Duration and timing:** Occupational exposures during 1940–1978. Timing of formaldehyde exposure not evaluated. **Variation in exposure:** Ever/never	**Internal comparisons:** OR = 1.0 (0.05–4.9) [1] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Outcome definition: Death certificates used to determine UCOD from multiple myeloma based on the ICD code in used at the time of death. **Design:** Nested case-control study within a prospective cohort mortality study. Twenty cases of multiple myeloma were frequency matched to 100 controls on time from hire to death. **Analysis:** ORs calculated using unconditional logistic regression. **Related studies:** Rinsky et al. (1988) **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and weak latency analysis with attenuation of association. Confounding possible. Low sensitivity due to rarity of exposure.	**Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: 21 different chemicals were evaluated including benzene with much cross exposure. Benzene was not evaluated as a potential confounder and may be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect. Potential for confounding may be mitigated by rarity of coexposures among cases.]	
Reference: Edling et al. (1987b) **Population:** 521 Swedish male blue collar workers in an abrasive production plant with at least 5 years of employment between 1955 and 1983. Cohort mortality followed through 1983 with 97% known vital status. **Outcome definition:** Cancer mortality ascertained using UCOD from the National Death Registry. Cancer incidence ascertained from the National Cancer Registry. Mortality and incidence of multiple myeloma based on ICD-8:203. **Design:** Cohort mortality and incidence study with external comparison group. **Analysis:** SMRs calculated using sex, age, and calendar-year-specific Swedish mortality rates. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency	**Exposure assessment:** Manufacture of grinding wheels bound by formaldehyde resins exposed workers to 0.1–1 mg/m^3 formaldehyde; 59 workers manufacturing abrasive belts had low exposure to abrasives with intermittent exposures with peaks up to 20–30 mg/m^3 formaldehyde. **Duration and timing:** Exposures during 1955–1983. Duration and timing since first exposure were evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Aluminum oxide and silicon carbide were coexposures but were not evaluated as confounders. [As noted in Appendix B.3.9: Coexposures are not known risk factors for this outcome.]	**External comparisons:** Cancer mortality No increase reported Cancer Incidence SMR = 4.0 (0.67–13.2)† [2] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
analysis with attenuation of association. Low sensitivity (few cases).		

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Results from *low* confidence studies are shaded; these findings are considered less reliable.

Abbreviations: SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis; UCOD = underlying cause of death; GSD = geometric standard deviation; SMR = standardized mortality ratio; RR = relative risk; TWA8 = 8-hour time-weighted average; URT = upper respiratory tract; LHP = lymphohematopoietic; PMR = proportionate mortality ratio; BMI = body mass index; JEM = job-exposure matrix; OR = odds ratio.

Hodgkin lymphoma

Epidemiological evidence

The most specific level of Hodgkin lymphoma diagnosis that is commonly reported across the epidemiological literature has been based on the first three digits of the Eighth or Ninth Revision of the ICD code (i.e., Hodgkin disease ICD-8/9: 201). Evidence describing the association between formaldehyde exposure and the specific risk of Hodgkin lymphoma was available from 15 epidemiological studies—one case-control study (Gérin et al., 1989) and 14 cohort studies (Walrath and Fraumeni, 1983, 1984; Stroup et al., 1986; Solet et al., 1989; Robinson et al., 1987; Meyers et al., 2013; Matanoski, 1989; Hayes et al., 1990; Hansen and Olsen, 1995; Hall et al., 1991; Coggon et al., 2003; Beane Freeman et al., 2009; Band et al., 1997; Andjelkovich et al., 1995). Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for Hodgkin lymphoma (see Table 3-66) following the causal evaluation.

Note that the confidence judgments are for the confidence in the reported effect estimate of an association from each study and not a confidence judgment in the overall study. Four sets of reported results from Fryzek et al. (2005), Hall et al. (1991), Solet et al. (1989), and Matanoski (1989) were classified as *not informative* due to multiple biases and uncertainties; for details see Appendix B.3.9.

Consistency of the observed association

The results of the 12 informative studies were not consistent. The study of the largest cohort of formaldehyde-exposed workers (Beane Freeman et al., 2009) reported an elevated risk of dying from Hodgkin lymphoma for the cohort as a whole (SMR = 1.42; 95% CI 0.96–2.1; 27 cases) and a pronounced increase in risk among those workers with the highest peak formaldehyde exposures (RR = 3.96; 95% CI; 1.31–12.02; 11 cases)—results that were classified with *medium* confidence. However, the other *medium* confidence result from Gérin et al. (1989) was an OR = 0.5 (95% CI 0.2–1.2; 8 cases). The results of the other 10 studies (all *low* confidence) were largely

based on small numbers of cases and yielded generally unstable CIs surrounding the RR (see Figure 3-41).

Compared with other LHP cancers, the 5-year survival rate for Hodgkin lymphoma is relatively high at 86% and mortality is rare. In contrast, the survival rate for myeloid leukemia is 38%. The high survival rate for Hodgkin lymphoma may indicate that mortality data are not as good a proxy for incidence data for this LHP cancer subtype. In this instance, these mortality data are potentially inadequate to evaluate causation. The low mortality rate for Hodgkin lymphoma results in few exposed cases and very low statistical power, which may have contributed to the apparently discordant results. Aside from the Beane Freeman et al. (2009) result (*medium* confidence), which reported 25 exposed deaths from Hodgkin lymphoma, only one other cohort study observed more than 10 deaths from Hodgkin lymphoma among exposed subjects (Hansen and Olsen, 1995); this study reported 12 observed deaths against 12 expected deaths—a result classified with *low* confidence.

The study results presented in Table 3-66 (by confidence level and publication date) detail all of the reported associations between exposures to formaldehyde and the risks of developing or dying from Hodgkin lymphoma along with a summary graphic of any major limitation and the confidence classification of the effect estimate. Results are plotted in Figure 3-41.

Strength of the observed association

Summary effect estimates for the association between formaldehyde exposure and Hodgkin lymphoma were highly variable and the risk of developing or dying from Hodgkin lymphoma were predominantly less than one (unity) and ranged from zero to 4.0 (Edling et al., 1987b). While the summary effect estimate from the study by Beane Freeman et al. (2009) was RR = 1.42 (95% CI 0.96–2.10), the strength of the association was substantially higher among those workers exposed to the highest peak levels (RR = 3.96). Beane Freeman et al. (2009) further showed plots presenting the RR from the internal analyses for each endpoint and for each year of follow-up. The association of Hodgkin lymphoma with formaldehyde exposure is not only seen for the complete 2004 follow-up when the average length of follow-up was 42 years, but throughout the cohort experience (see Figure 1 in (Beane Freeman et al., 2009)). These plots show that during the 1970s and 1980s, the RR ≈ 8 and remained elevated at about RR = 4 through the end of follow-up in 2004. Such a consistent finding of a strong effect over many years of follow-up reduces the possibility that the results for the full follow-up period could be due to chance.

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants occurred before their Hodgkin lymphoma was detected and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and was done in a blinded fashion with respect to outcome status. Only one study (Band et al., 1997) reported on analyses of the temporal relationship showing that risks were highest in workers with 15 or more

years since first formaldehyde exposure and 15 or more years of exposure duration (SMR = 1.62; 95% CI 0.55–3.71). However, this finding is without corroboration for Hodgkin lymphoma.

Exposure-response relationship

Only two studies evaluated any other form of exposure-response for increasing measures of formaldehyde exposure (Coggon et al., 2003; Beane Freeman et al., 2009). Coggon et al. (2003) reported a lower risk of dying from Hodgkin lymphoma among "highly" exposed workers based on a single death. Beane Freeman et al. (2009) reported a clear exposure-response relationship between increasing levels of peak formaldehyde and increased risk of dying from Hodgkin lymphoma among exposed workers (p = 0.01). Compared to exposed workers in the lowest exposure category of peak exposure, those in the middle category were at more than two-fold higher risk (RR = 3.30; 95% CI 1.04–10.50) while those workers in the highest category were at four-fold higher risk (RR = 3.96; 95% CI 1.31–12.02). Beane Freeman et al. (2009) also reported exposure-response relationships between increased risk of dying from Hodgkin lymphoma among exposed workers based on average formaldehyde intensity (OR range: 1.61–2.48; p = 0.05) and cumulative exposure (OR range: 1.30–1.71; p = 0.08).

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias is an unlikely bias in the epidemiological studies of Hodgkin lymphoma as the one case-control study was population-based and used other cancer cases as controls with exposure status evaluated without regard to outcome status and had a participation level of 83%. Each of the cohort studies included at least 72% of eligible participants and lost fewer than 9% of participants over the course of mortality follow-up.

The healthy worker effect including the healthy worker survivor effect could obscure a truly larger effect of formaldehyde exposure in analyses based on "external" comparisons with mortality in the general population (Walrath and Fraumeni, 1983, 1984; Stroup et al., 1986; Robinson et al., 1987; Meyers et al., 2013; Hayes et al., 1990; Hansen and Olsen, 1995; Coggon et al., 2003; Beane Freeman et al., 2009; Band et al., 1997; Andjelkovich et al., 1995), but would not influence analyses using "internal" or matched comparison groups (Gérin et al., 1989; Beane Freeman et al., 2009).

Information bias is unlikely to have resulted in bias away from the null—especially as the exposure assessment in these studies were generally of high quality; however, random measurement error or nondifferential misclassification is almost certain to have resulted in some bias toward the null among these studies of Hodgkin lymphoma.

Chemical exposures that have not been independently associated with Hodgkin lymphoma are not expected to confound results. The main support for concluding there is a *slight* association of formaldehyde exposure with increased risk of Hodgkin lymphoma is from the results for peak exposures reported by Beane Freeman et al. (2009) who specifically examined the potential for confounding from 11 substances including benzene and found that controlling for these exposures did not meaningfully change the results. This provides evidence against potential confounding by

these coexposures. There does not appear to be any evidence of confounding that would provide an alternative explanation for the observed association of formaldehyde exposure with increased risk of Hodgkin lymphoma reported by Beane Freeman et al. (2009). The evidence of an association with peak exposures reported by Beane Freeman et al. (2009) suggests an association whose risk increases with greater exposure.

Summary of Human Evidence Synthesis Judgments, Causal Evaluation, and Conclusion

Summary of human evidence synthesis judgments

The following factors were most influential to the causal evaluation and synthesis conclusion:

- *Consistency and Study Confidence:* Results were heterogeneous. Statistically robust evidence of increased risk of Hodgkin lymphoma in the highest peak exposure group among industrial workers. However, the results from the other medium confidence result showed some evidence of decreased risk and the other 10 studies (all *low* confidence) were largely based on small numbers of cases and yielded generally unstable CIs surrounding the effect estimate.

- *Strength and Precision:* Effect estimates ranged from zero to 4.0 with one result showing a statistically significant increase in risk.

- *Coherence*: Biologically coherent temporal relationship consistent with a pattern of exposure to formaldehyde and subsequent death from myeloid leukemia, allowing time for cancer induction, latency, and mortality although only one study evaluated the impact of time since first exposure.

- *Dose-Response:* Limited evidence of an exposure-response trend from a single *medium* confidence study showing that increased peak exposure to formaldehyde was significantly associated with increased risk of Hodgkin lymphoma.

Causal evaluation

The human evidence synthesis judgments are suggestive of an association between high peak exposure and the risk of Hodgkin lymphoma. Given the uncertainties outlined above, and although formaldehyde is genotoxic, the consistent observations of genotoxicity in peripheral blood lymphocytes observed across several occupational studies were not interpreted as sufficient to further strengthen the judgment on the human evidence of Hodgkin lymphoma beyond *slight*.

Conclusion

- The available epidemiological studies provide *slight* evidence of an association consistent with causation between formaldehyde exposure and an increased risk of Hodgkin lymphoma.

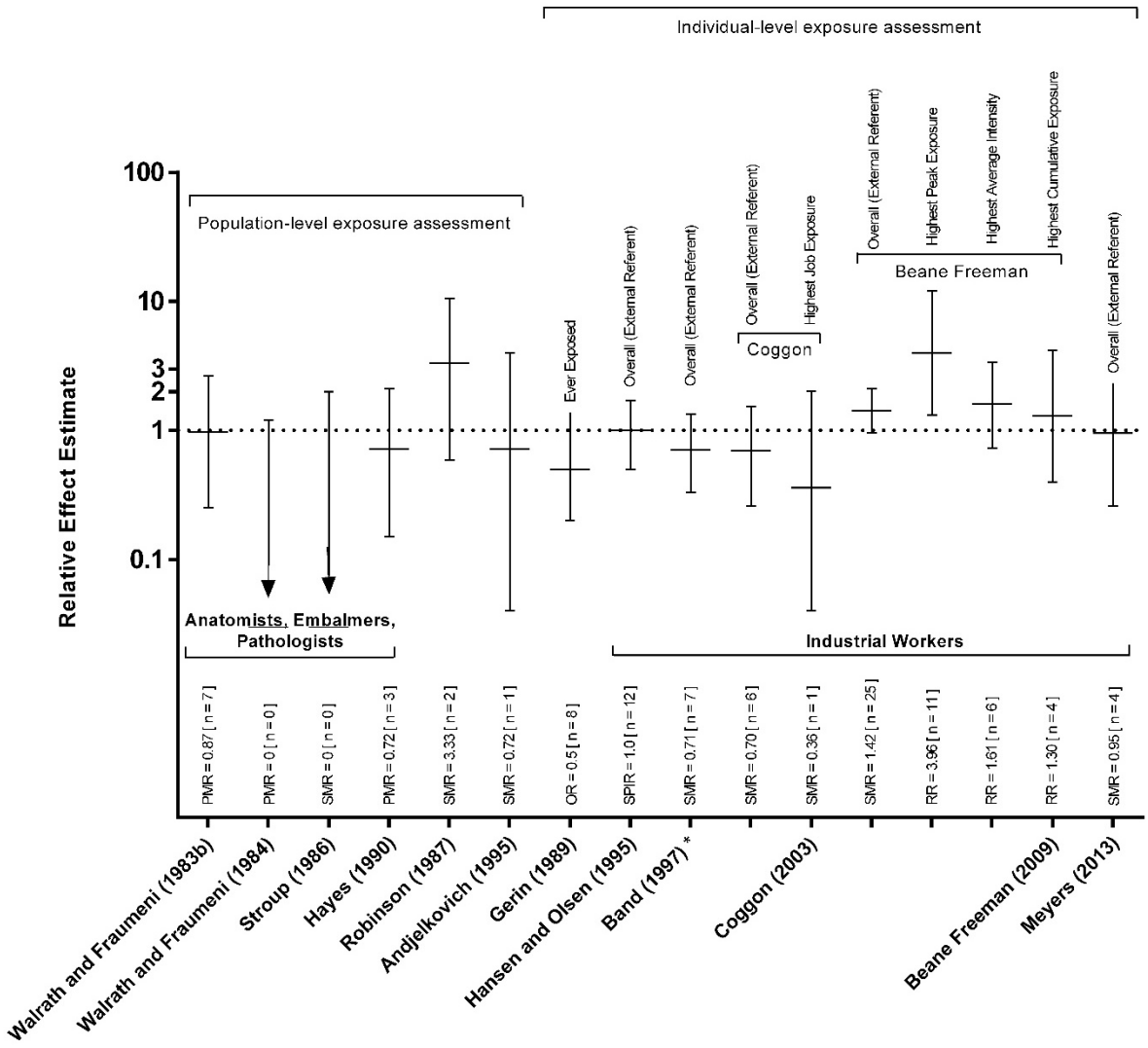


Figure 3-41. Epidemiological studies reporting multiple Hodgkin lymphoma estimates.

Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for Hodgkin lymphoma (see Table 3-66). SMR = standardized mortality ratio; PMR = proportionate mortality ratio; RR = relative risk; OR = odds ratio. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 7]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. *Note that the CIs for Band et al. (1997) are 90% rather than 95%.

Table 3-66. Epidemiological studies of formaldehyde exposure and risk of Hodgkin lymphoma

Study	Exposures	Results: effect estimate (95% CI) [# of cases]

Reference: Beane Freeman et al. (2009) with supplemental online tables
 	
Population: 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the U.S. followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. Vital status was 97.4% complete and only 2.6% lost to follow-up.
 	
Outcome definition: Death certificates used to determine underlying cause of death from Hodgkin disease (ICD-8: 201).
 	
Design: Prospective cohort mortality study with external and internal comparison groups.
 	
Analysis: RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency.
 	
SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates.
 	
Related studies:
Blair et al. (1986)
Hauptmann et al. (2003)
 	
Confidence in effect estimates:[a]
HIGH (No appreciable bias)
	Exposure assessment: Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists, and monitoring data from 1966 through 1980.
	
	Median TWA (over 8 hours) = 0.3 ppm (range 0.01–4.3).
	
	Median cumulative exposure = 0.6 ppm-years (range 0–107.4).
	
	Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data.
	
	Duration and timing: Exposure period from <1946 through 1980. Median length of follow-up: 42 years. Duration and timing since first exposure were evaluated.
	
	Variation in exposure:
	For all variations in exposure:
	Level 1 (unexposed)
	
	Peak exposure:
	Level 2 (>0 to <2.0 ppm)
	Level 3 (2.0 to <4.0 ppm)
	Level 4 (≥4.0 ppm)
	Average intensity:
	Level 2 (>0 to <0.5 ppm)
	Level 3 (0.5 to <1.0 ppm)
	Level 4 (≥1.0 ppm)
	Cumulative exposure:
	Level 2 (>0 to <1.5 ppm-years)
	Level 3 (1.5 to <5.5 ppm-years)
	Level 4 (≥5.5 ppm-years)
	
	Coexposures: Exposures to 11 other compounds were identified and evaluated as potential confounders and found not be confounders.
	
	[As noted in Appendix B.3.9: There was no information on smoking, however, according to Blair et al. (1986), "The lack of a consistent elevation for tobacco-related causes of death, however, suggests that the smoking habits among this cohort did not differ substantially from those of the general population."]
		Internal comparisons:
		Peak exposure
		1994 Follow-up:
		Highest peak RR = 3.30 (0.98–11.10)
		(*p*-trend = 0.04)
		2004 Follow-up:
		Peak exposure
		Level 1 RR = 0.67 (0.12–3.6) [2]
		Level 2 RR = 1.00 (Ref. value) [6]
		Level 3 RR = 3.30 (1.04–10.50) [8]
		Level 4 RR = 3.96 (1.31–12.02) [11]
		p-trend (exposed) = 0.01;
		p-trend (all) = 0.004
		
		Average intensity
		Level 1 RR = 0.53 (0.11–2.66) [2]
		Level 2 RR = 1.00 (Ref. value) [10]
		Level 3 RR = 2.48 (0.84–7.32) [9]
		Level 4 RR = 1.61 (0.73–3.39) [6]
		p-trend (exposed) = 0.05;
		p-trend (all) = 0.03
		
		Cumulative exposure
		Level 1 RR = 0.42 (0.09–2.05) [2]
		Level 2 RR = 1.00 (Ref. value) [14]
		Level 3 RR = 1.71 (0.66–4.38) [7]
		Level 4 RR = 1.30 (0.40–4.19) [4]
		p-trend (exposed) = 0.08;
		p-trend (all) = 0.06
		
		Duration of exposure
		No evidence of association (data not shown).
		
		Time since first exposure
		>0–15 years RR = 1.00 (Ref. value)
		>15–25 years RR = 1.54 (0.42–5.62)
		>25–35 years RR < 1.54
		>35 years RR < 1.54
		
		External comparisons:
		$SMR_{Unexposed}$ = 0.70 (0.17–2.80) [2]
		$SMR_{Exposed}$ = 1.42 (0.96–2.10) [25]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Gérin et al. (1989) **Population:** Male residents of Montreal, Canada aged 35–70 years. 4,510 eligible incident cancer cases were identified during 1979–1985 from 19 major area hospitals, which report to the Quebec Tumor Registry over 97% of all cancer diagnoses from the Montreal area. Interviews and questionnaires completed for 3,726 subjects (83% of eligible cases). 18% of interviews were completed by next of kin. **Outcome definition:** Histologically confirmed diagnosis of Hodgkin lymphoma (ICD: 201) **Design:** Population-based case-control study of 53 formaldehyde-exposed men with Hodgkin lymphoma. Cases were compared with two groups; first, against other cancer cases excluding those diagnosed with lung cancer (*n* = 2,599), and second against 533 male population controls selected from electoral list in the Montreal area. **Analysis:** ORs calculated by levels of a composite exposure index using logistic regression controlling for age, ethnic group, socio-economic status, smoking, and dirtiness of jobs held (white vs. blue collar). **Related studies:** Siemiatycki et al. (1987) **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency analysis with attenuation of association.	**Exposure assessment:** Individual-level exposure estimates developed based on a complete and detailed occupational history ascertained by interviewers using a standardized questionnaire. A team of chemists and hygienists translated each job into a list of potential formaldehyde exposures based on their confidence level, the frequency of exposure, and the duration of exposure. **Duration and timing:** Exposure period based on occupational histories prior to cancer diagnosis. Duration of exposure was evaluated. **Variation in exposure:** For cancer sites with fewer than 30 cases exposed to formaldehyde, results for the exposure subgroups were not shown. **Coexposures:** Additional occupational and nonoccupational potential confounders were included in analyses when the estimated exposure-disease OR changed by more than 10%.	**Internal comparisons:** Compared to other cancers OR = 0.5 (0.2–1.2) [8] Compared to population controls OR = 0.5 (0.2–1.4) [8]
Reference: Meyers et al. (2013) **Population:** 11,043 workers in three U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion **Outcome definition:** Death certificates used to determine the underlying cause of	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984. Geometric TWA8 exposures ranged from 0.09 to 0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher.	**External comparisons:** SMR = 0.95 (0.26–2.44) [4]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
death from Hodgkin lymphoma (ICD code in use at time of death). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Stayner et al. (1985) Stayner et al. (1988) Pinkerton et al. (2004) **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Potential for information bias due lack of latency analysis with attenuation of association.	**Duration and timing:** Exposure period from 1955 through 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	
Reference: Coggon et al. (2003) **Population:** 14,014 British men employed in six chemical industry factories that produced formaldehyde. Cohort mortality followed from 1941 through 2000. Vital status was 98.9% complete and only 1.1% lost to follow-up. **Outcome definition:** Death certificates used to determine cause of deaths from Hodgkin disease (ICD-9: 201). **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a] **MEDIUM ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group B; latency was not evaluated **Cf:** Potential confounding	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941–1982. Duration and timing since first exposure were not evaluated. **Variation in exposure:** TWA exposure Level 1 (low) Level 2 (moderate) Level 3 (high) **Coexposures:** Not evaluated as potential confounders. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. [As noted in Appendix B.3.9: Styrene is associated with LHP cancers. **Asbestos** is associated with URT cancers, but not with LHP cancers. Other coexposures are not known risk factors for this outcome. Authors stated that the extent of coexposures was expected to be low.	**External comparisons:** SMR = 0.70 (0.26–1.53) [6] **Within-study external comparisons:** Worked in high exposure jobs SMR = 0.36 (0.01–2.01) [1]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	Potential for confounding may be mitigated by low coexposures.]	
Reference: Walrath and Fraumeni (1983) **Population:** 1,132 deceased white male embalmers licensed to practice during 1902–1980 in New York who died during 1925–1980 identified from registration files. Death certificates obtained for 75% of potential study subjects (*n* = 1,678). **Outcome definition:** Hodgkin disease (ICD-8: 201) listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a] **MEDIUM ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group A; latency not evaluated	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1902–1980. Median year of birth was 1901. Median year of initial license was 1931. Median age at death was 1968. Expected median duration of exposure was 37 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**External comparisons:** Observed: 2 Hodgkin disease deaths Expected: 2.3 Hodgkin disease deaths PMR = 0.87 (0.15–2.87)† [7] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))
Reference: Band et al. (1997) **Population:** 30,157 male workers with at least 1 year of employment accrued by January 1950. Followed through December 1982. Loss to follow-up was less than 6.5% for workers exposed to the sulfate process (67% of original cohort of 30,157) and less than 20% for workers exposed to the sulfite process. **Outcome definition**: Cause of death obtained from the National Mortality Database based on ICD version in effect at time of death and standardize to ICD-9 version. Hodgkin lymphoma: ICD-9 201 **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the Canadian population. **Confidence in effect estimates:**[a] ↓ (Potential bias toward the null) Potential for information bias due to uncertainty in exposure assessment	**Exposure assessment:** Occupational data limited to hire and termination dates for all workers and type of chemical process of pulping (sulfate vs. sulfite). No job-specific data available. Presumed exposure to formaldehyde known to be used in the plant. Formaldehyde is known to be an exposure for pulp and paper mill workers: job-specific median exposures ranging from 0.04 to 0.4 ppm with peaks as high as 50 ppm (Korhonen et al., 2004) **Duration and timing:** Duration and timing since first exposure were evaluated. **Variation in exposure:** No variation in formaldehyde exposure was reported. Results presented by pulping process (sulfate vs. sulfite) but there is no information on differential exposures between the two processes **Coexposures:** Not evaluated as confounders. [As noted in Appendix B.3.9: Potential confounders for these outcomes include chlorophenols, acid mists, dioxin, and perchloroethylene and would likely be	**External comparisons:** All workers SMR = 0.71 (90% CI 0.33–1.34) [7] Work duration <15 years TSFE < 15 years SMR = 0.53 (90% CI 0.14–1.37) [3] Work duration ≥15 years TSFE ≥ 15 years SMR = 1.62 (90% CI 0.55–3.71) [4]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
(Exposure Group C) with attenuation of association. Confounding possible.	positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	
Reference: Andjelkovich et al. (1995) **Population:** 3,929 automotive industry iron foundry workers exposed from 1960 through 1987 and followed through 1989. **Outcome definition**: UCOD obtained from Social Security Administration, Pension Benefit Informations, and National Death Index) Hodgkin lymphoma: ICD 201 **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex-, age-, race-, and calendar-year-specific U.S. mortality rates. **Confidence in effect estimates:**[a] **LOW** ↓ (Potential bias toward the null) High potential for information bias due to uncertainty in exposure assessment (Exposure Group B) and lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Exposure assessment**: Individual-level exposure status (yes/no, quartile) based on review of work histories by an industrial hygienist. Exposure assessment blinded to outcome. Independent testing of iron foundries by NIOSH reported a range from 0.02 ppm to 18.3 ppm (cited in IPCS (1989) Env. Health Criteria 89: Formaldehyde). **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: Nickel and **chromium** are associated with URT but not LHP. Other coexposures are not known risk factors for these outcomes.]	**External comparisons:** $SMR_{Unexposed}$ = 0.70 (0.01–3.88) [1] $SMR_{Exposed}$ = 0.72 (0.01–4.00) [1]
Reference: Hansen and Olsen (1995) **Population:** 2,041 men with cancer who were diagnosed during 1970–1984 and whose longest work experience occurred at least 10 years before cancer diagnosis. Identified from the Danish Cancer Registry and matched with the Danish Supplementary Pension Fund. Ascertainment considered complete. Pension record available for 72% of cancer cases. **Outcome definition:** Hodgkin disease (ICD-7: 201) listed on Danish Cancer Registry file. **Design:** Proportionate incidence study with external comparison group. **Analysis:** Standardized proportionate incidence ratio calculated as the proportion of cases for a given cancer in formaldehyde-associated companies	**Exposure assessment:** Individual occupational histories including industry and job title established through company tax records to the national Danish Product Register. Subjects were considered to be exposed to formaldehyde if: (1) they had worked in an industry known to use more than 1 kg formaldehyde per employee per year and (2) subjects longest single work experience (job) in that industry since 1964 was ≥10 years prior to cancer diagnosis. All subjects were stratified based on job title as either low exposure (white collar worker), above background exposure (blue collar worker), or unknown (job title unavailable). **Duration and timing:** Exposure period not stated. Based on date of diagnosis during 1970–1984, and the requirement of exposure more than 10 years prior to	**External comparisons:** Overall (exposure to formaldehyde ≥10 years prior to cancer diagnosis) SPIR = 1.0 (0.5–1.7) [12]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
relative to the proportion of cases for the same cancer among all employees in Denmark. Adjusted for age and calendar time. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) with attenuation of association. Low sensitivity for NPC (few cases).	diagnosis, the approximate period was 1960–1974. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix B.3.9: While other coexposures were not evaluated, the overall correlation between coexposures in multiple occupational industries is likely to be low.]	
Reference: Hayes et al. (1990) **Population:** 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975–1985. Death certificates obtained for 79% of potential study subjects (*n* = 6,651) with vital status unknown for 21%. **Outcome definition:** Death certificates and licensing boards used to determine cause of death from Hodgkin disease (ICD-8: 201). **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected deaths from the U.S. population. **Confidence in effect estimates:**[a] **MEDIUM ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. Exposure based on occupation, which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to 3.99 ppm (low ventilation) with peaks up to 20 ppm. Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975–1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60–74 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**External comparisons:** PMR = 0.72 (0.15–2.10) [3]
Reference: Robinson et al. (1987) **Population:** 2,283 plywood mill workers employed at least one year during 1945–1955 followed for mortality until 1977 with vital status for 98% and death certificates for 97% of deceased.	**Exposure assessment:** Presumed exposure to formaldehyde-based glues used to manufacture and patch plywood. Subcohort of 818 men coexposed to formaldehyde and pentachlorophenol worked for one year or more in the relevant exposure categories of	**External comparisons:** Whole cohort of mill workers (*n* = 2,283) SMR = 1.11(0.20–3.50) [2] Subcohort of highly exposed workers (*n* = 818)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Outcome definition: Death certificates used to determine UCOD from Hodgkin disease as coded by trained nosologist using ICD-7:201. **Design:** Prospective cohort mortality study with external comparison group. A subcohort of 818 men coexposed to formaldehyde and pentachlorophenol were also evaluated. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Potential selection bias. High potential for information bias due to uncertainty in exposure assessment (Exposure Group D) and lack of latency analysis with attenuation of association. Low sensitivity (few cases).	veneer pressing and drying, glue mixing, veneer and panel gluing and patching. **Duration and timing:** Exposures during 1945–1955. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Duration of exposure Latency (time since first exposure) **Coexposures:** Pentachlorophenol [As noted in Appendix B.3.9: EPA concluded that pentachlorophenol is likely to be carcinogenic based on strong evidence from epidemiological studies of increased risk of multiple myeloma. Pentachlorophenol is not a known risk factor for Hodgkin lymphoma and thus is not expected to be a confounder.]	SMR = 3.33(0.59–10.49) [2]
Reference: Stroup et al. (1986) **Population:** 2,239 white male members of the American Association of Anatomists from 1888 through 1969 who died during 1925−1979. Death certificates obtained for 91% with 9% lost to follow-up. **Outcome definition:** Hodgkin disease (ICD-8: 201) listed as cause of death on death certificates. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) High potential for selection bias. Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Confounding possible for ML. Low sensitivity (few cases).	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1925–1979. Median birth year was 1912. By 1979, 33% of anatomists had died. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely. Anatomists may also be coexposed to stains, benzene, toluene xylene, chlorinated hydrocarbons, dioxane, and osmium tetroxide.	**External comparisons:** SMR = 0 (0–2.0) [0]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	Benzene was not evaluated as a potential confounder and may be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	
Reference: Walrath and Fraumeni (1984) **Population:** 1,007 deceased white male embalmers from the California Bureau of Funeral Directing and Embalming who died during 1925–1980. Death certificates obtained for all. **Outcome definition:** Hodgkin disease (ICD-8: 201) listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a] **LOW ↓** (Potential bias toward the null) Low potential for information bias due to uncertainty in exposure assessment (Exposure Group A). Potential for information bias due lack of latency analysis with attenuation of association. Low sensitivity (few cases).	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1916–1978. Birth year ranged from 1847 through 1959. Median age of death was 62 years. Most deaths were among embalmers with active licenses. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix B.3.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**External comparisons:** Observed: 0 Hodgkin disease deaths Expected: 2.5 Hodgkin disease deaths PMR= 0 (0–1.20)† [0] †**Note:** EPA derived CIs using the Mid-P Method (See (Rothman and Boice, 1979))

[a]Evaluation of sources of bias or study limitations (see details in Appendix B.3.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Abbreviations: SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis; UCOD = underlying cause of death; GSD = geometric standard deviation; SMR = standardized mortality ratio; RR = relative risk; TWA8 = 8-hour time-weighted average; URT = upper respiratory tract; LHP = lymphohematopoietic; PMR = proportionate mortality ratio; OR = odds ratio; SPIR = standardized proportional incidence ratio.

Lymphohematopoietic Cancers in Animal Studies

This section considers incidence data for histopathological lesions associated with leukemia or lymphoma; other evidence supportive of the development of these cancers (e.g., hematological changes) is discussed in the *Evidence on Mode of Action for Lymphohematopoietic Cancers* Section. Few animal bioassays have adequately evaluated the carcinogenic potential of inhaled formaldehyde with respect to LHP malignancies. The majority of formaldehyde exposure studies in animals focused primarily on the respiratory tract and did not provide routine examination of other

tissues, limiting the detection of leukemia and lymphoma. The *medium* confidence study conducted by Battelle-Columbus Laboratories for CIIT (Battelle, 1982) is currently the only chronic duration inhalation study to report detailed information on formaldehyde-induced leukemia or lymphoma in rodents (results not published). Given the paucity of available information and difficulties interpreting the Battelle (Battelle, 1982) results, the evidence available from animal studies is considered *indeterminate* for drawing conclusions as to whether or not formaldehyde exposure might cause leukemia or lymphoma.

This discussion focuses on the few available studies evaluating tumors of the lympho-hematopoietic system (leukemia and lymphomas), with the evidence organized by species and study confidence (see Table 3-68). The largest and most comprehensive cancer bioassay evaluating formaldehyde inhalation exposure in animals is the *medium* confidence chronic study (Battelle, 1982) conducted at the Battelle Columbus Laboratory in B6C3F1 mice and F344 rats. This was also the only study to evaluate the majority of tissues relevant to LHP cancers (e.g., no other study reported histopathological evaluation of the spleen or thymus). The summary reports of these experiments in the published literature do not discuss leukemia or lymphoma rates (Swenberg et al., 1980b; Kerns et al., 1983). However, tissue slides were examined histopathologically in all animals from the control and 17.6 mg/m^3 dose groups at each interim and terminal necropsy; the lesions examined included lymphoma and leukemia (note: increased bone marrow hyperplasia, a nonmalignant lesion that was significantly increased in exposed rats, is also included in Table 3-68 and further discussed in the *Evidence on Mode of Action* Section). At the intermediate dose groups of 2.5 mg/m^3 and 6.9 mg/m^3 exposure concentrations, only the target (i.e., the nasal passages) tissues were examined unless unusual tissue masses or gross lesions were noted, or if the animals died spontaneously, and the study report does not provide incidence at these doses in their summary findings (Battelle, 1982). As stated in the report, survival rates for rats were decreased by formaldehyde exposure at the 17.6 mg/m^3 exposure for males and females. For the mice, there was no differential mortality across exposure groups; however, there appeared to be decreased survival in all exposure groups after 6 months. The cumulative incidences of lymphoma (in B6C3F1 mice) and leukemia (in F344 rats) as reported by Battelle (see Tables 7–10 in (Battelle, 1982)) are shown in Table 3-67. The *p*-values reported by the authors were based on a Cox-Tarone test for the comparison that adjusts for reduced survival (Battelle, 1982). There was a suggestion of a possible increased incidence in lymphoma (*p*-value, 0.06) in female mice, and a decreased incidence in leukemia in female rats (*p*-value, 0.006) at the high dose. The possible increase in lymphoma incidence in mice is of interest for future study, as low incidences of lymphomas were also observed in two strains of p53 deficient mice after formaldehyde exposure, whereas no lymphomas were observed in control groups [(Morgan et al., 2017); see additional discussion in the Evidence on Mode of Action for Lymphohematopoietic Cancers Section]. It is problematic to infer from these results because of the lack of information at the intermediate dose groups and the adverse effect on survival rates. It is also difficult to interpret the apparent slight increase in lymphoma in mice

alongside the slight but statistically significant decrease in leukemia in female rats. Taken together with the exposure-induced increases in bone marrow hyperplasia in rats, this represents an area of uncertainty warranting additional study.

Table 3-67. Cumulative incidence of hematopoietic cancers in B6C3F1 mice and F344 rats

Endpoint, species	Sex	Incidence or percentage incidence		*p*-Values
		0 ppm	17.6 mg/m^3	
Lymphoma, mice	Male	0/119 (0%)	0/115 (0%)	
	Female	19/121 (16%)	27/121 (22%)	0.062
Leukemia, rats	Male	11/120 (9%)	5/120 (4%)	0.690
	Female	11/120 (9%)	7/120 (6%)	0.006

A separate, *medium* confidence study in rats did not report any significant differences in histopathological evaluations of tissues relevant to leukemia or lymphoma (Kamata et al., 1997), although specific incidence data for non-nasal lesions were not provided. Although the two other available studies also failed to observe statistically significant, treatment-related increases in LHP cancers in potentially sensitive mice (Morgan et al., 2017) or rats (Sellakumar et al., 1985), these results were interpreted with *low* confidence due primarily to concerns regarding insensitivity due to a very short exposure duration (8 weeks; (Morgan et al., 2017)), or histopathological evaluations of LHP tissues only when gross lesions were noted (Sellakumar et al., 1985).

Overall, the available data are *indeterminate* for drawing conclusions regarding the potential for formaldehyde exposure to induce LHP cancers in rodent bioassays. It should be emphasized that the detection of leukemia/lymphoma in the available animal studies (i.e., other than the 0 versus 17.6 mg/m^3 group comparisons in the Battelle study) may be limited by study design due to limited statistical power, a lack of routine evaluation of tissues potentially related to LHP cancers (studies focused on histopathological evaluation of nasal tissue), or early mortality from toxicities other than LHP cancer, particularly given the few suggestive changes that were reported (i.e., bone marrow hyperplasia in rats and slight but uncertain increases in lymphomas in mice). To make definitive conclusions regarding the development of LHP cancers in formaldehyde-exposed animals, there is a need for studies specifically designed to target these cancers as the main endpoint.

Table 3-68. Summary of animal evidence of lymphohematopoietic cancers and bone marrow histopathology following inhalation exposure to formaldehyde

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Rats</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Kamata et al. (1997)
Rats: Fischer 344; male; 32/group
Exposure: nose-only 6 hours/day, 5 days/week for 28 months; interim sacrifices at months 12, 18, and 24
Test article: Formalin (and methanol control)
Analytic concentrations: 0, 0.40 (± 0.09), 2.67 (± 0.40), or 18.27 (± 2.73) mg/m^3. Methanol in the 0 and 18.27 groups was estimated at 5.2 mg/m^3. A room control served as a no exposure group.
Histopathology: Relevant tissues included mesenteric lymph nodes and femur; and other tissues with noted gross lesions.

Main limitations: Formalin (gaseous methanol levels were not analytically measured in the control and exposed groups, even though a methanol control was included); no histopathological examinations of non-nasal tissues unless gross lesions present; incidence data not reported.</td><td>No lesions attributable to formaldehyde exposure were detected in organs other than the nasal cavity.</td></tr>
<tr><td>Kerns et al. (1983), Battelle (1982)
Rats: Fischer 344; males and females; 119 to 121/sex/group
Exposure: whole-body 6 hr/d, 5 d/week for up to 24 months; recovery examined at 27 and 30 months
Test article: Paraformaldehyde analytic concentrations: 0, 2.5 (± 0.01), 6.9 (± 0.02), and 17.6 (± 0.05) mg/m^3
Histopathology: Relevant tissues included femur, mandibular and mesenteric lymph nodes, spleen, and thymus.

Main limitations: Limited evaluation and reporting of LHP cancers, namely no histopathological examinations of non-nasal tissues for 2.5 and 6.9 mg/m^3 groups (see text) unless gross lesions present; transient viral infection noted at 1 year; high mortality in high exposure group.</td><td>Rats, leukemia (all)
<table>
<tr><th></th><th>0 mg/m^3</th><th>2.5 mg/m^3</th><th>6.9 mg/m^3</th><th>17.6 mg/m^3</th></tr>
<tr><td>Female</td><td>11/109 (9%)</td><td>NA</td><td>NA</td><td>7/113 (6%)</td></tr>
<tr><td>Male</td><td>11/109 (9%)</td><td>NA</td><td>NA</td><td>5/115 (4%)</td></tr>
</table>
Rats, bone marrow hyperplasia
<table>
<tr><th></th><th>0 mg/m^3</th><th>2.5 mg/m^3</th><th>6.9 mg/m^3</th><th>17.6 mg/m^3</th></tr>
<tr><td>Female</td><td>7/106 (6%)</td><td>NA</td><td>NA</td><td>28/87* (24%)</td></tr>
<tr><td>Male</td><td>6/108 (5%)</td><td>NA</td><td>NA</td><td>26/85* (23%)</td></tr>
</table>
NA = Only nasal tissue was systematically analyzed
*p = 0.0001 (note: see Table 1-64 for leukemia p-values)

Mortality was significantly higher than controls at 17.6 mg/m^3 in both sexes and at 6.9 mg/m^3 in males. This increased mortality began at 12 months and became extreme by 24 months (> 50% in both sexes for the highest exposure group). A transient, commonly observed viral infection was noted at 1 year (not dose-related), along with transient weight decreases.</td></tr>
</table>

Reference and study design	Results
Low confidence	
Sellakumar et al. (1985) *Rats*: SD; male; 99–100/group *Test article*: Paraformaldehyde (slurry in paraffin oil) *Exposure*: 6 hr/d, 5 d/week for lifetime at 0 or 18.2 mg/m^3 (note: prior reporting of levels during first 588 days at 17.5 mg/m^3 (Albert et al., 1982) *Histopathology*: Histopathology conducted for LHP-relevant tissues (not specified) only when gross lesions were noted *Related study*: Albert et al. (1982) **Main limitations**: LHP tissues were only evaluated if gross lesions were noted.	No differences in tumors outside of the respiratory tract were noted between treated and control groups.

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Mice</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Kerns et al. (1983), Battelle (1982)
Mice: B6C3F1 mice; males and females; 119 to 121/sex/group
Exposure: whole-body 6 hr/d, 5 d/week for up to 24 months; recovery examined at 27 and 30 months
Test article: Paraformaldehyde
Analytic concentrations: 0, 2.5 (± 0.01), 6.9 (± 0.02), and 17.6 (± 0.05) mg/m^3
Histopathology: Relevant tissues included femur, mandibular and mesenteric lymph nodes, spleen, and thymus. Note:

Main limitations: Limited sampling and reporting of potential LHP cancers (histopathological examination was carried out only for gross tissue masses at 2.5 and 6.9 mg/m^3; see text); generally poorer survival of exposed male mice.</td><td>Mice, lymphoma (all)
<table><tr><th></th><th>0 mg/m^3</th><th>2.5 mg/m^3</th><th>6.9 mg/m^3</th><th>17.6 mg/m^3</th></tr><tr><td>Female</td><td>19/102 (16%)</td><td>NA</td><td>NA</td><td>27/121 (22%)</td></tr><tr><td>Male</td><td>0/119 (0%)</td><td>NA</td><td>NA</td><td>0/115 (0%)</td></tr></table>Mice, lymphoid hyperplasia (mandibular lymph node)
<table><tr><th></th><th>0 mg/m^3</th><th>2.5 mg/m^3</th><th>6.9 mg/m^3</th><th>17.6 mg/m^3</th></tr><tr><td>Female</td><td>19/59 (24%)</td><td>NA</td><td>NA</td><td>24/63 (28%)</td></tr><tr><td>Male</td><td>7/58 (11%)</td><td>NA</td><td>NA</td><td>14/49 (22%)</td></tr></table>Mice, lymphoid hyperplasia (spleen)
<table><tr><th></th><th>0 mg/m^3</th><th>2.5 mg/m^3</th><th>6.9 mg/m^3</th><th>17.6 mg/m^3</th></tr><tr><td>Female</td><td>25/90 (22%)</td><td>NA</td><td>NA</td><td>22/97 (18%)</td></tr></table>NA = Only nasal tissue was systematically analyzed.

Generally poorer survival of formaldehyde-exposed male mice (e.g., decreases in survival to at least 18 months were larger at higher exposure levels) was attributed to group housing.</td></tr>
<tr><td colspan="2">Low confidence</td></tr>
<tr><td>Morgan et al. (2017)
Mice: C3B6.129F1-Trp53^{tm1Brd} (C3B6 TP53±) and B6.129-Trp53^{tm1Brd} (B6 TP53±); males; 24–35/group
Exposure: Mice were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 day/week for 8 weeks.
Test article: Paraformaldehyde
Nominal concentrations were 0, 9.23, or 18.45 mg/m^3.[a]
Histopathology: Routine evaluations of relevant tissues included frontal plane sections of the femur (including bone marrow), and mesenteric, mandibular, mediastinal, and bronchial lymph nodes. Tissues with gross lesions were also evaluated.

Main limitations: Short duration and short follow-up period to allow for cancer development (note: authors based exposure duration, in part, on HSPC doubling).</td><td>The incidences of leukemia or lymphohematopoietic neoplasms were not statistically significantly increased by formaldehyde exposure in either strain.

Lymphomas were observed in several mice exposed to formaldehyde in both strains (i.e., in “B6” mice: 1/31 at 9.23 mg/m^3 and 1/35 at 18.45 mg/m^3; in “C3B6” mice: 1/24 at 9.23 mg/m^3 and 2/25 at 18.45 mg/m^3), while lymphomas were absent from control groups in both strains (the study authors determined these lesions were unrelated to treatment).</td></tr>
</table>

Organized by species, confidence, and then descending publication date. Results from low confidence studies are shaded; these findings are considered less reliable.

Abbreviations: LHP = lymphohematopoietic; FA = formaldehyde-specific antibody; HSPC = hematopoietic stem and progenitor cell.

Summary of Animal Evidence Synthesis Judgments

The available animal studies on lymphohematopoietic cancers provide *indeterminate* evidence of formaldehyde exposure-induced effects. The available animal evidence was judged as *indeterminate* and not *compelling evidence of no effect* given the insensitivity of the available study designs for detecting leukemia/lymphoma, particularly given the few suggestive changes that were reported (i.e., bone marrow hyperplasia in rats and slight but uncertain increases in lymphomas in mice). The following factors were most influential to the synthesis judgment.

- *Consistency and Study Confidence*: The available data do not provide evidence supporting the development of LHP cancers in a *medium* confidence chronic bioassay of rats and mice, a second *medium* confidence rat bioassay, and two other *low* confidence, long-term exposure studies.

- *Biological Plausibility*: Although some potentially relevant mechanistic changes have been observed in studies of exposed animals (e.g., inflammatory and immune changes in systemic tissues and bone marrow hyperplasia in rats), the evidence related to genotoxicity (i.e., in systemic tissues) or other more directly relevant changes were weak (e.g., only in *low* confidence studies) or not observed. Further, no potential MOA with evidentiary support exists to explain how inhaled formaldehyde might be capable of inducing these cancers.

Evidence on Mode of Action

Introduction

This section evaluates evidence supporting plausible mechanisms of LHP carcinogenesis following inhalation exposure to formaldehyde. As previously discussed, the strength of the evidence in humans was determined to be *robust* for myeloid leukemia and *slight* for multiple myeloma, although evidence in experimental animals is considered *indeterminate*. As a mode(s)-of-action has not been established for how formaldehyde inhalation may result in LHP cancers, the available evidence relevant to interpreting the biological plausibility of the observed associations in humans is presented in this section. This discussion includes consideration of how genotoxicity and other potential molecular and cellular events resulting from formaldehyde interactions in upper respiratory tract (URT) tissues might result in LHP cancers. Genotoxicity of formaldehyde in different experimental systems and in human populations is evaluated and described in detail in Appendix A.4; in this section, conclusions from these data are interpreted specifically as pertaining to LHP carcinogenesis. Additional evidence relevant to interpreting the biological plausibility of formaldehyde exposure-induced LHP carcinogenesis has been previously discussed, including DNA damage in peripheral blood cells, impacts on immune cell populations and inflammation in peripheral blood in human populations, systemic oxidative stress, and other health effects outside of the respiratory system, including developmental and reproductive toxicity, hazards for which the **evidence indicates** that effects in humans are likely. These data are discussed in Sections 3.2.3, 3.2.5, and 3.3.2.

Approach: consideration of mechanistic events plausibly relevant to LHP cancer induction following inhaled formaldehyde exposure

This section considers conclusions derived from the analyses of pertinent types of evidence as they relate to LHP cancer (discussed in detail elsewhere in this Toxicological Review), and further examines facets of the genotoxicity database and other mechanistic events specifically relevant to the potential cellular origins of LHP cancer. Rather than a single, linear MOA hypothesis to which formaldehyde-specific data can be applied and evaluated, a network of mechanistic events or pathways may be a more appropriate conceptual framework within which to consider the biological plausibility for many cancers, including LHP carcinogenesis potentially caused by formaldehyde inhalation. These plausible mechanistic events involve specific aspects of genotoxicity and mutagenicity, hematologic effects, and changes in gene expression or regulation, consistent with previous analytical frameworks employed in the evaluation of LHP carcinogenesis (NRC, 2014b). Additionally, this discussion includes consideration of mechanistic effects which have been previously described as hallmarks or enabling characteristics of cancer, as well as key characteristics of carcinogens [e.g., genomic instability and mutation, oxidative stress, inflammation, and avoidance of immune destruction; (Smith et al., 2016; Hanahan and Weinberg, 2011)].

Although there is evidence that exposure to formaldehyde is associated with changes in cell populations that are relevant to LHP cancer mechanisms, a number of studies have demonstrated that direct interactions of formaldehyde with cells in the bone marrow are not likely (see Appendix C.1). In the bone marrow of monkeys (Moeller et al., 2011), and in the bone marrow, liver, lung, spleen, thymus, and blood of rats (Lu et al., 2010a), DNA monoadducts were formed by interactions with endogenous formaldehyde, but adducts formed from exogenous formaldehyde were not found using highly sensitive detection methodology. Recently Lai et al. (2016) described an ultrasensitive mass spectrometry method, which distinguishes unlabeled DPX from $^{13}CD_2$-labeled DPXs induced from endogenous and exogenous formaldehyde, respectively. The authors demonstrated that inhalation exposure of stable isotope labeled ($^{13}CD_2$) formaldehyde to rats (18.45 mg/m^3; 6 hours/day; 1, 2, or 4 days) and monkeys (7.38 mg/m^3; 6 hours/day; 2 days) induced DPXs linked to exogenous formaldehyde in nasal passages in both species, but not in distal tissues, such as bone marrow and peripheral blood monocytes (rats and monkeys) and liver (monkeys), although DPXs linked to endogenous formaldehyde were detectable in all tissues. In light of this evidence, in vitro studies of direct administration of formaldehyde to cells from distal tissues, such as bone marrow and blood, were considered less relevant to the evaluation of hazard.).

The approach taken in this section was to identify mechanistic events possibly linking inhaled formaldehyde-induced effects to LHP cancer risk in humans, and then to evaluate the supporting evidence for these events and relationships. The primary focus was on evidence from mechanistic studies of exposed humans where available, incorporating results from in vivo animal

studies and in vitro experiments when such information was particularly instructive. The studies most informative to LHP mechanisms were those that examined changes in leukocyte populations or function along with genotoxicity in potential target cells (e.g., hematopoietic stem and progenitor cells [HSPCs], discussed below) or surrogate cell populations (e.g., peripheral blood lymphocytes [PBLs]) from the same human cohorts. Measuring genotoxicity in mature PBLs as surrogates for target cells of concern for LHP carcinogenesis (i.e., HSPCs) is a commonly adopted and reasonable experimental approach (Kirsch-Volders et al., 2014) because PBLs are much more abundant than HSPCs, which constitute only a fraction of a percentage of circulating leukocytes (Massberg et al., 2007; de Kruijf et al., 2014). Other studies selectively reporting hematotoxicity, altered immune function, or genotoxicity in circulating WBCs from formaldehyde-exposed humans or animals also provided useful information.

The mechanistic events specifically evaluated include:

3) Evidence of formaldehyde-induced DNA damage to peripheral blood leukocytes

    a. Genotoxicity in circulating myeloid progenitor cells (possible cancer target population)

    b. Genotoxicity in circulating lymphocytes (surrogate population)

4) Evidence of formaldehyde-induced impacts other than genotoxicity on circulating blood cell populations, including inflammatory changes or immune system dysfunction

5) Evidence of formaldehyde-induced systemic oxidative stress

6) Evidence of formaldehyde-induced changes in the bone marrow niche

7) Evidence of formaldehyde-induced changes in gene expression or posttranscriptional regulation in peripheral blood leukocytes or bone marrow

In each of the following sections, the formaldehyde-specific mechanistic evidence is briefly reviewed, then the relevance to LHP carcinogenesis is described alongside a discussion of the evidence (or lack thereof) addressing how formaldehyde exposure might cause the observed effects.

To frame the discussion of the plausible mechanistic events related to LHP carcinogenesis, relevant elements of HSPC physiology are briefly reviewed. Hematopoietic stem cells (HSCs) are cells residing in the blood or bone marrow that are functionally defined by their ability to replenish their own numbers as well as divide asymmetrically into less plastic progenitor cells. The HSCs reside in localized microenvironments within the bone marrow called "niches," which control their survival, mobilization, proliferation, self-renewal, and differentiation (Wilson et al., 2009). For example, a single HSC can give rise to common myeloid or lymphoid progenitor cells, which can in turn yield blast cells with dedicated differentiation into specific cell lineages, with a fraction becoming myeloblasts and lymphoblasts, respectively (see Figure 3-42). HSCs and progenitor cells (e.g., myeloblasts, common myeloid or lymphoid progenitors, etc.) are described together as HSPCs

(Massberg et al., 2007; Granick et al., 2012) (see Figure 3-42). As previously described (see Section 1.3.3, Overview of Lymphohematopoietic Cancer Biology), LHP cancers are a heterogeneous group. Most LHP cancers, including acute and chronic myeloid leukemias as well as multiple myeloma (i.e., LHP cancers best associated with formaldehyde exposure in epidemiology studies) are thought to arise from damage to HSPCs during hematopoietic and lymphopoietic development, or as a result of environmental exposure, often in a specific HSPC-type and lifestage-dependent manner (Greaves, 2004). However, some LHP cancer subtypes, including CLL and some lymphomas, may arise from mature leukocytes (Eastmond et al., 2014). Thus, this section discusses HSPCs as the most likely proximal target for LHP cancers (i.e., those of primary interest in the context of formaldehyde exposure), while mature leukocytes are discussed as surrogate populations for cancer target cells.

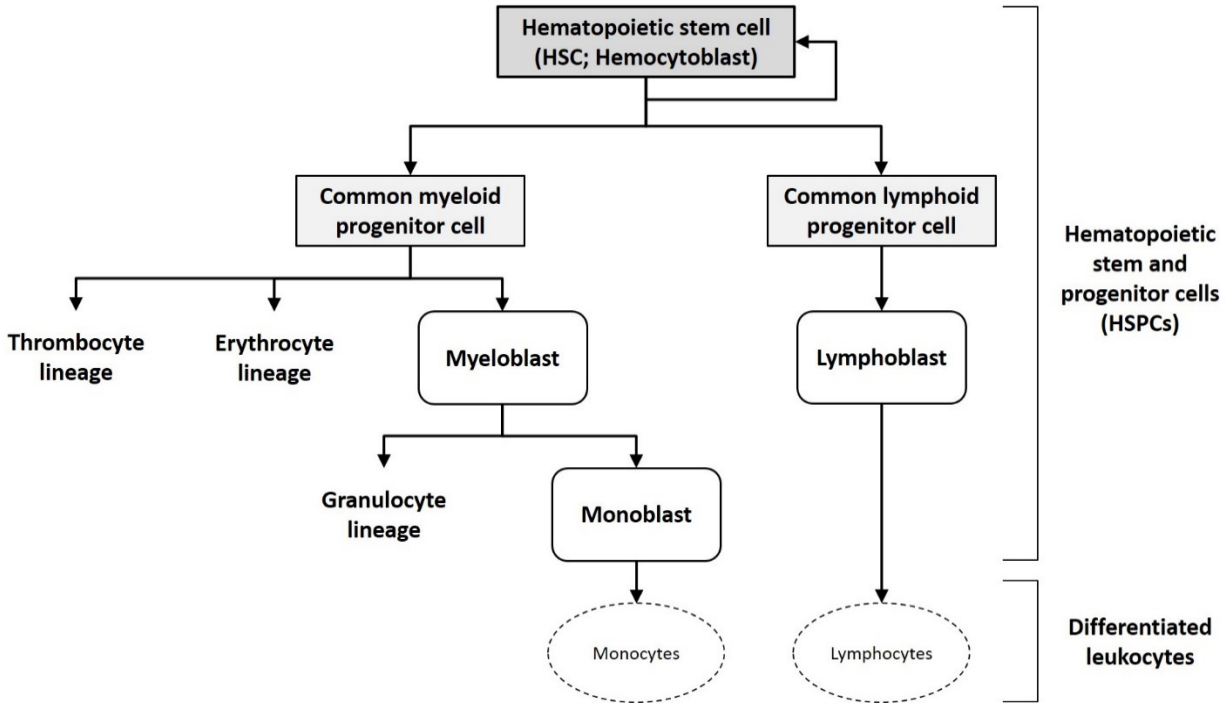


Figure 3-42. Simplified hematopoiesis.

Hematopoietic stem cells (HSC) are capable of self-renewal, and can asymmetrically divide to create progenitors committed to either myeloid or lymphoid lineages; together, the HSCs and more committed progenitors comprise hematopoietic stem and progenitor cells (HSPCs; (Massberg et al., 2007; Granick et al., 2012)). The progenitors then supply the precursor cells responsible for maintaining the population of more differentiated cell types within the committed lineage, as depicted. The likely candidate cellular targets for lymphohematopoietic (LHP) cancers are the varied progenitors associated with the monocyte and lymphocyte lineages (a few examples illustrated), as well as HSCs themselves.

Evidence of formaldehyde-induced DNA damage to peripheral blood leukocytes

The most pertinent and direct available evidence of formaldehyde-induced effects on target cells relevant to LHP carcinogenesis (i.e., those that may ultimately become neoplastic) is from two

studies of the same cohort reporting genotoxicity in myeloid progenitor cells in the peripheral blood of exposed human workers (Appendix C.3). In addition, several studies have been conducted documenting several measures of DNA and chromosomal damage and instability in PBLs of workers exposed to formaldehyde. As these exposures occurred in vivo and the effects are not formaldehyde-specific, no assumptions can be made regarding whether or not formaldehyde must directly interact with the HSPCs or PBLs (e.g., potentially while migrating through URT tissues) to induce the observed changes, or, alternatively, if these represent indirect effects. In vitro formaldehyde exposure of isolated PBLs may also provide some minimal supportive information, although substantially lower confidence exists regarding the relevance of these data, given the limited distribution of inhaled formaldehyde beyond the URT and the assumption that the inhaled formaldehyde concentrations these cells might encounter in URT tissues, if any, would be much lower than the in vitro levels applied. Notably, human PBLs may be less sensitive to potential in vivo genotoxicity compared with HSPCs, as murine HSPCs are more susceptible to aldehyde-induced DNA damage than mature, differentiated leukocytes (Oberbeck et al., 2014; Garaycoechea et al., 2012).

Genotoxic effects on circulating myeloid progenitor cells

Among the human occupational studies with formaldehyde exposure, two studies of the same cohort reported effects on myeloid progenitor cells cultured from peripheral blood of exposed workers (Zhang et al., 2010; Lan et al., 2015); (see Appendix C.3) compared to cells cultured from controls without occupational formaldehyde exposure. The specific hematopoietic progenitor cells assessed were identified as CFU-GMs, but not lymphocytes (i.e., myeloblasts in Figure 3-42). CFUs of less committed HSPC colonies (e.g., CFU-GEMMS which can give rise to granulocytes, erythrocytes, macrophages, and megakaryocytes) could not be directly assessed for technical reasons (Zhang et al., 2010; Lan et al., 2015). No information is available to determine if either progenitor cell type would be more or less susceptible to formaldehyde-induced genotoxicity.

In an initial pilot study, increased monosomy of chromosome 7 and trisomy of chromosome 8 was reported in CFU-GMs cultured from a group of 10 highly exposed subjects and 12 controls (8 hour TWA 2.6 versus 0.032 mg/m^3, respectively) evaluated only for aneuploidy in chromosomes 7 and 8. Decreased WBC counts and a 20% decrease in CFU-GM colony formation was also noted, suggesting hematotoxicity (Zhang et al., 2010). The initial finding of chromosome 7 monosomy was confirmed in a larger, more comprehensive analysis of the same cohort with 29 occupationally exposed subjects and 23 referents (1.7 versus 0.032 mg/m^3) wherein chromosome-wide aneuploidy and structural aberrations of all 24 chromosomes were examined (Lan et al., 2015). This follow-up study also reported significantly: (a) increased frequencies of monosomy in numerous chromosomes, with the greatest response for chromosomes 1, 5, and 7; (b) increased polysomy in several chromosomes including 1 and 5; and (c) increased tetrasomy in various other chromosomes. In addition to aneuploidy, increased breaks, deletions, and translocations of chromosome 5 were also reported, while trisomy of chromosome 8 was not significantly elevated

(Lan et al., 2015). Although the pilot study methods were criticized for not adhering to the assay protocol (Gentry et al., 2013), a clarification of the assay protocol was provided by the investigators with a description of how the study adhered to it (Rothman et al., 2017). Additional findings of monosomy, trisomy, tetrasomy, and structural aberrations of multiple chromosomes that were increased in formaldehyde-exposed workers in comparison to the unexposed referent group indicate that formaldehyde exposure is associated with a potential tendency toward cytotoxicity in CFU-GM cells that may arise either in vivo or during the in vitro cell culture period.

A more recent study in mice from the same researchers similarly suggests that *in vivo* formaldehyde exposure (3 mg/m^3 for 2 weeks) might affect the viability of progenitor cells of the granulocyte/monocyte (CFU-GM) or erythroid (BFU-E) lineage based on the ability to generate colonies of these cells in culture (Zhao et al., 2020a). Although they did not specifically examine changes in the blood, the authors reported consistent decrements (across two independent experiments) in BFU-E from the nose; BFU-E and CFU-GM from the bone marrow; and CFU-GM from the spleen. The authors also reported mixed evidence of decrements (across experiments) for CFU-GM from the nose; BFU-E and CFU-GM from the lung; and BFU-E from the spleen. However, the study results cannot be reliably interpreted as clear evidence of formaldehyde-induced effects due to use of formalin as the test article and small sample sizes.

In vitro formaldehyde exposure of cells isolated from healthy, unexposed humans provided mixed results. Formaldehyde exposure-induced aneuploidy in cultured human erythroid progenitor cells (Ji et al., 2014), but not in cultured myeloid progenitor cells (Kuehner et al., 2012). These results suggest either a more complex biological basis for susceptibility to chromosomal damage, or an inability of in vitro test conditions to detect or replicate formaldehyde-associated effects observed in the in vivo studies.

Of interest in the context of susceptibility, in mice, knockout of the genes encoding enzymes responsible for removal of endogenous formaldehyde, namely *Aldh2* and *Aldh5*, results in a phenotype of severely disrupted hematopoiesis and leukemia, including mutated and abnormal HSPCs, which is presumably linked to elevated formaldehyde levels (Pontel et al., 2015; Dingler et al., 2020; Burgos-Barragan et al., 2017b). Likewise, direct treatment of *Aldh5-/-* bone marrow cells with formaldehdye causes genotoxic effects and reduces HSPC formation, effects which are further exacerbated by loss of *Fancd2* (this latter deficiency is associated with increased sensitivity to DNA damage) (García-Calderón et al., 2018; Burgos-Barragan et al., 2017b). As reviewed and tested by Dingler et al. (2020), genetic deficiencies in these Aldh family genes have been linked to bone marrow failure and related diseases in humans, including specifically in children. Other changes in these mouse models and humans with reduced ALDH2 or ALDH5 activity that may be caused, at least in part, by uncontrolled endogenous formaldehyde include postnatal lethality, stunted growth, cognitive effects (see Section 3.3.1) and various cancers arising from DNA damage or deficient repair (Nakamura et al., 2020; Dingler et al., 2020). While formaldehyde inhalation does not seem to cause appreciable changes in formaldehyde levels in nonrespiratory regions (see Appendix A.2),

HSPCs expressing these enzymes are known to exist in many tissues. However, no studies in any species have specifically examined these possible linkages in relation to inhaled formaldehyde, limiting the use of the currently available studies in hazard identification to the identification of factors of interest to future studies on susceptibility.

Relevance to LHP carcinogenesis and mode of action interpretation

As described above, the cells used in these experiments represent a potential primary target for LHP carcinogenesis. The aneuploidy observed in chromosomes 5 and 7 is of particular relevance for chemically induced LHP carcinogenesis because the loss of whole or part of chromosomes 5 or 7 are common aberrations in therapy-related myelodysplastic syndrome (MDS) and acute myelogenous leukemia (Lessard et al., 2007), particularly those resulting from alkylation drug therapy (Smith et al., 2003; Pedersen-Bjergaard et al., 2006; Lan et al., 2015). Therefore, the observations of similar cytogenetic effects in asymptomatic formaldehyde-exposed workers supports the biological plausibility of the association between chronic formaldehyde exposure and elevated incidence of LHP cancers in other human cohorts (see Section 1.2.5, Evidence on Mode of Action for URT Cancers). Although exogenous formaldehyde may not be transported to or specifically affect the bone marrow in a fashion akin to other well-studied human leukemogens (e.g., benzene, chemotherapeutics, ionizing radiation, (Eastmond et al., 2014)), and may therefore not act via a similar MOA, similar aneuploidies in CFU-GMs from formaldehyde-exposed and benzene-exposed workers have been observed (i.e., monosomy and trisomy in chromosomes 5 and 7; (Zhang et al., 2011). Thus, the presence and type of aneuploidies observed in circulating myeloid progenitor cells from formaldehyde-exposed asymptomatic human workers are consistent with those reported in patients with leukemia, specifically MDS and AML, as well as those effects reported in other worker cohorts at increased risk of developing leukemias, providing further support for the plausibility of an association between chronic formaldehyde exposure and leukemogenesis.

While this evidence links formaldehyde exposure to chromosomal toxicity relevant to leukemogenesis, mechanistic evidence is lacking for how these events may occur. Although no evidence exists to evaluate the following potential scenarios, there are at least three ways in which formaldehyde exposure (with distribution limited to the URT) might cause these genotoxic effects: (1) direct interaction of formaldehyde with HSPCs in the URT; (2) indirect effects on circulating or bone marrow HSPCs due to secondary, systemic effects following formaldehyde-induced changes in the URT; and (3) modification and mobilization of precursor-type cells residing in the URT.

As part of their physiological function, HSPCs migrate via the vasculature to extramedullary tissues (outside medullary bone) such as the liver, lung, small intestine, skin, and kidneys, and return via lymphatics to the bone marrow by a process termed "homing," which is mediated by cytokines, growth factors, and hormones (Schulz et al., 2009; Massberg et al., 2007; Granick et al., 2012). Although their numbers in the peripheral blood at any one time constitute a small fraction of the total circulating leukocyte population in both mice (Massberg et al., 2007) and humans (Zhang

et al., 2010; de Kruijf et al., 2014), these cells can completely replenish bone marrow stem cell populations (Massberg et al., 2007). Unlike mature lymphocytes, HSPCs do not necessarily accumulate in lymphatic tissues (e.g., nasopharynx-associated lymphoid tissue or NALT), but travel primarily through the lymphatic vasculature (Massberg et al., 2007). HSPCs accumulate to some extent in peripheral nonlymphoid tissues and are replenished every few days; alternatively, HSPCs can divide locally and replenish populations of long-lived resident myeloid cells (e.g., macrophages, dendritic cells). In addition to triggering local differentiation, inflammatory stimuli can induce HSPC mobilization from the bone marrow (Wilson et al., 2009), and may increase recruitment of mobilized HSPCs to nonlymphoid epithelial tissues (Massberg et al., 2007). Such inducible migration to and from sites of inflammation (e.g., formaldehyde-induced URT inflammation, see Section 3.2.3) could be a mechanism by which HSPCs become more frequent targets of formaldehyde-induced toxicity. The available data suggest that very little, if any, inhaled formaldehyde penetrates beyond the URT (the portal of entry; POE), although it is likely that small amounts of formaldehyde are able to reach the superficial capillary layer of the URT in some exposure contexts (see Appendix C.1). In addition, whereas formaldehyde appears to preferentially target the respiratory and transitional epithelium of the nasal cavity, it is unclear which specific URT compartments (e.g., respiratory, transitional, or olfactory epithelium; stromal tissue layers) HSPCs may circulate through. Finally, although HSPCs may be more sensitive to genotoxic effects than other cell types, even if inhaled formaldehyde did directly encounter HSPCs, no data exist to draw inferences regarding theoretical concentrations of inhaled formaldehyde that might be required for genotoxicity. Despite these important uncertainties, it is possible that formaldehyde may be able to directly interact with potential target cell types present at the POE.

Alternatively, secondary effects resulting from toxicity, irritation, or other processes disrupted in the affected URT might be capable of causing genotoxicity in HSPCs at sites distal to the URT or in vascular regions proximal to the URT. Such secondary effects might include increased production of mediators of inflammation and oxidative stress, which have been reported after formaldehyde exposure in some studies (see Section 3.2.3), and which may result, indirectly, in cytotoxicity, genotoxicity, or other perturbations at distal sites containing HSPCs, resulting in genotoxicity in these cells. However, no data exist to evaluate this hypothesis, including the potential secondary mediators or what levels of these mediators might be required at target sites.

Lastly, some URT (i.e., rat nasal olfactory epithelium) cells have been shown to be "multipotent" in nature, in that they can repopulate rat hematopoietic tissues and differentiate into various leukocyte lineages in irradiated hosts; although, these cells act more similar to neural stem cells than to bone marrow stem cells (Murrell et al., 2005). While it might be possible that formaldehyde could interact with such a cell population, cause genotoxicity, and modify it in such a way that it becomes more HSPC-like and migrates to the bone marrow, this theory is somewhat implausible and without supportive evidence.

Overall, the evidence largely does not exist to determine whether any of the proposed processes explain how formaldehyde exposure might cause genotoxicity in HSPCs.

Genotoxic effects on circulating lymphocytes

Consistent with formaldehyde-induced genotoxicity in circulating myeloid precursor cells, formaldehyde exposure is associated with DNA and chromosomal damage in PBLs (see Appendix C.3 for detailed discussions). The studies in which we had more confidence based on evaluations of study methods reported consistent associations of formaldehyde exposure with DNA strand breaks or alkali-labile sites visualized using the comet assay, CAs, MN formation, and sister chromatid exchange (SCE). Formaldehyde was associated with a higher prevalence of chromosomal aberrations among workers in pathology laboratories (Santovito et al., 2011; Musak et al., 2013; Jakab et al., 2010; Costa et al., 2015); these effects included chromatid-type aberrations, chromosome-type aberrations, chromosomal exchange, and premature centromere division. Costa et al. (2015) also reported an increase in aneuploidies and in the number of aberrant and multiaberrant cells. Micronuclei frequency in PBLs was higher in exposed compared to referent workers by 40–50% with a concentration-related response beginning at concentrations of 0.1–0.2 mg/m^3 and above (Wang et al., 2019; Jiang et al., 2010; Costa et al., 2019). Micronuclei frequency (and centromeric micronuclei) increased with cumulative exposure (Wang et al., 2019; Suruda et al., 1993). A 1.5 to 3-fold difference in measures of DNA damage using the Comet assay was observed comparing exposed workers to their referent groups at average concentrations as low as 0.09 mg/m^3 (Zendehdel et al., 2017), 0.14 mg/m^3 (Jiang et al., 2010) or 0.04–0.11 mg/m^3 (Peteffi et al., 2015) and a clear concentration-related response was observed in plywood plant workers (Lin et al., 2013; Jiang et al., 2010). Costa et al. (2019) reported that the frequency of micronuclei in PBL and EBC were correlated in their study population. In addition, increased DPXs were observed in circulating WBCs from human workers exposed to formaldehyde concentrations ≥0.5 mg/m^3. In experimental animals, inhalation studies at relatively high formaldehyde concentrations (i.e., 12.3 and 18.45 mg/m^3) using paraformaldehyde as the test article have not observed genotoxicity including DNA adducts, chromosome aberrations, or SCEs in PBLs of rats (Lu et al., 2010a; Kligerman et al., 1984). Results of other studies using formalin as the inhalation source were mixed (Speit et al., 2009; Im et al., 2006), although these data are less reliable. While evidence from in vitro formaldehyde exposures is likely of minimal value in relation to LHP carcinogenesis, such evaluations also report increased mutations, DPX, and other DNA damage in human PBLs, whole blood cells or cultured human lymphoblast cell lines (i.e., TK6 cells) (see Appendix C.3).

Relevance to LHP carcinogenesis

Genotoxicity in PBLs may reflect formaldehyde-induced effects in HSPCs; because PBLs are more amenable to experimentation, primarily because they are far more abundant, they can allow for far more robust analyses (e.g., in terms of sample size), and possibly better detect changes.

Formaldehyde-induced chromosome damage may result from some combination of direct DNA reactivity in the URT, including downstream sequelae, and numerous indirect mechanisms such as deficiencies in DNA repair, chromosome segregation, DNA methylation and increased oxidative stress (see Section 3.2.5 Evidence on MOA; (Kirsch-Volders et al., 2014). Similar to the discussion of the HSPC-specific evidence, direct interactions of formaldehyde with DNA of lymphocytes and less committed progenitor cells could occur in URT tissue regions, although this has not been documented experimentally, or through indirect mechanisms occurring systemically (e.g., as a result of increased oxidative stress). Evidence exists supporting both aneuploidy in PBLs and clastogenicity in URT tissues; notably, the aneuploidy reported in PBLs is consistent with that observed in DNA of CFU-GM cells studied by Zhang et al. (2010) and Lan et al. (2015), and observed in relation to therapy-related MDS and AML as discussed above.

Evidence of formaldehyde-induced impacts other than genotoxicity on circulating blood cell populations, including inflammatory changes or immune system dysfunction

A number of studies indicate that formaldehyde exposure causes changes in hematopoietic cell constituents in blood (see Section 3.2.3); however, an understanding of the observed pattern of these changes in specific immune cell subtypes across studies, as well as how any of these changes might be induced, remains incomplete. While there are inconsistencies in the database that introduce uncertainty, the overall evidence supports that it is probable that formaldehyde inhalation causes blood cell changes including decreased total WBCs, CD8 + lymphocytes, and RBCs, particularly at higher formaldehyde concentrations (e.g., ≥1 mg/m^3; see Section 3.2.3). Relating to formaldehyde-induced decreases in CD8+ lymphocytes, one of the mouse studies discussed in Section 3.2.3 (Ma et al., 2020) provided evidence consistent with the possibility that formaldehyde exposure inhibits commitment to the CD8 lineage at early stages of cell development. Perhaps most relevant to LHP cancers, evidence of pancytopenia (i.e., decrease in RBCs, WBCs, and platelets in the same exposed population) was reported in peripheral blood samples from formaldehyde-melamine workers exposed to median formaldehyde concentrations of 1.6 mg/m^3, along with a 20% decrease in CFU-GM colony formation in vitro (Zhang et al., 2010), suggesting both a decrease in the circulating numbers of mature RBCs and WBCs as well as possible decreases in the replicative capacity of myeloblasts. This potential for formadehyde to selectively impact immature cells or progenitors is consistent with observations in mice by Liu et al. (2017) and Zhao et al. (2020b), although the use of formalin in these studies prevents reliable interpretation. Perhaps relatedly, a decrease in HSPC colony formation was reported for various CFU populations, including both CFU-GMs and CFU-GEMMs, cultured from human whole blood and exposed in vitro to 100–200 μM formaldehyde (Zhang et al., 2010); however, these experiments carry the same uncertainties as other in vitro assays (see above) including coexposure of the cells to methanol, which prevents reliable interpretation of these findings. In addition, a study of two strains of p53 deficient mice exposed to high levels of formaldehyde (>9 mg/m^3) for 8 weeks (a duration selected based on the HSPC pool turning over every 8 weeks) did not observe any significant increases in LHP cancers,

including leukemia (Morgan et al., 2017). Although studies other than Zhang et al. (2010) do not identify pancytopenia specifically, some report decreases in one or two of these cell types, but not all three (Zhang et al., 2013b; Lyapina et al., 2004; Kuo et al., 1997), or in one or more of these cell populations without examining all three (Ye et al., 2005; Thrasher et al., 1990); while other studies reported no changes or significant increases for specific cell subsets (Erdei et al., 2003; Costa et al., 2013; Aydın et al., 2013), these latter studies tested formaldehyde concentrations of approximately ≤0.36 mg/m^3. Interestingly, some effects (e.g., changes in T cell populations) tended to increase at lower formaldehyde concentrations (~ <0.5 mg/m^3), while decreases were observed at higher levels (~1 mg/m^3). While the data suggest biologic complexity, pancytopenia such as that reported by Zhang et al. (2010), is known to be associated with MDS and AML development (Paiva and Calado, 2014) and may be one of the hematotoxic consequences of exposure to formaldehyde, possibly only at concentrations >1 mg/m^3.

In an effort to examine potential linkages between effects observed in AML patients and those induced by formaldehyde, several studies have evaluated genotoxicity measures along with immune system effects in the same cohort of occupationally exposed human workers. These studies are considered highly informative to understanding the potential relationship between formaldehyde exposure and systemic toxicity pertaining to LHP carcinogenesis. In several analyses of the same occupationally exposed cohort in China with median exposures of 1.6 mg/m^3 formaldehyde, lower total peripheral blood cell counts (Zhang et al., 2010; Hosgood et al., 2013), including CTL memory cells, and changes in cytokine levels (Seow et al., 2015) were observed concurrently with genotoxicity in myeloid precursor cells [(Lan et al., 2015) and discussed above]. Findings in this cohort were consistent with findings from Chinese workers and students evaluated by another research group following short-term average formaldehyde exposures of approximately 0.51–0.99 mg/m^3, which observed decreases in various T lymphocyte populations, including CTLs (Ying et al., 1999; Ye et al., 2005), with a corresponding higher incidence of SCEs in worker lymphocytes at approximately 0.99 mg/m^3 (Ye et al., 2005). While CTLs were unchanged in several other studies testing lower formaldehyde concentrations (0.2–0.8 mg/m^3; (Jia et al., 2014; Costa et al., 2013; Aydın et al., 2013), one of these studies did report increased CD4 + T cells alongside evidence of genotoxicity at 0.36 mg/m^3 (Costa et al., 2013). While CTLs were generally decreased (increasing the ratio of CD4 + T cells to CTLs) in the blood of individuals exposed to formaldehyde concentrations >0.5 mg/m^3 (see Section 3.2.3), an understanding of how the observed cell number changes might relate to genotoxicity remains unclear.

A reanalysis of data from Zhang et al. (2010) reaffirmed the lower levels of specific immune cell populations, specifically WBCs, lymphocytes, RBCs and platelets in the exposed participants with respect to the unexposed group (Mundt et al., 2017). However, when immune cell population levels were compared within the exposed group using a cutpoint at the median of 1.6 mg/m^3 (1.3 ppm), no difference was observed between the higher and lower exposed groups. Likewise, no association with formaldehyde modeled as a continuous variable and cell population levels was

observed in regression analyses adjusted for sex and smoking. The 43 exposed participants were highly exposed, ranging from a TWA8 of 0.5 to 3.3 mg/m^3 (0.4 to 2.7 ppm) with one outlier at 6.9 mg/m^3 (5.6 ppm). Fifty percent of the exposed group was exposed to a TWA8 from 1.1 to 2.5 mg/m^3 (interquartile range). Therefore, the exposure levels in the study group did not include the breadth of exposure levels needed at lower formaldehyde levels to evaluate an exposure-response trend. The high formaldehyde exposure and the inadequate range of the concentrations limited the power of the study to detect a trend with exposure level of the expected magnitude based on those previously detected for benzene exposure (Rothman et al., 2017).

Changes in serum NK cells and B cells were not entirely consistent across studies, although the available data suggest that formaldehyde concentration may strongly influence the results, similar to findings for CTLs (see Section 3.2.3). For example, while NK cell numbers were decreased at 0.36 and 1.6 mg/m^3 (Hosgood et al., 2013; Costa et al., 2013) NK cells were actually increased at 0.2 and 0.25 mg/m^3 (Jia et al., 2014; Aydın et al., 2013) and unchanged at 0.8 mg/m^3 (Jia et al., 2014). Although changes in B cell counts were supported by moderate evidence across several medium or high confidence studies conducted after several months of exposure, for example at 0.99 mg/m^3 (Ye et al., 2005) and 0.2–0.8 mg/m^3 (Jia et al., 2014), other *medium* or *high* confidence studies testing formaldehyde exposures for several years, for example at 0.25 mg/m^3 (Aydın et al., 2013) and 1.6 mg/m^3 (Hosgood et al., 2013) did not report B cell changes, or reported B cell decreases at lower formaldehyde levels (0.36-0.47 mg/m^3) (Costa et al., 2013; Costa et al., 2019). Looking across studies, the overall pattern of these responses across exposure levels and exposure durations is difficult to interpret.

Although infrequently studied, some limited mechanistic information suggests the potential for stimulation of the immune system at lower formaldehyde exposures, and decreases in blood cell numbers at higher exposure concentrations. In one study evaluating immunological markers in a cohort of plywood workers, exposure to 0.2–0.8 mg/m^3 formaldehyde was positively correlated with increased serum interleukin (IL)-10 and IL-4, alongside decreased IL-8 and interferon-gamma (IFN–γ); no significant changes in total lymphocyte or T cell numbers were observed in this study (Jia et al., 2014). These cytokine changes are consistent with observations of increased plasma IL-4 and decreased IFN-γ in a short-term rat study at ≥6.2 mg/m^3 that reported corresponding lymphocyte genotoxicity (Im et al., 2006). Workers with higher formaldehyde exposure (i.e., 1.8 mg/m^3) exhibited formaldehyde-associated aneuploidy and had decreased peripheral blood levels of various chemokines and cytokines, including IL-10 (Seow et al., 2015). These observations suggest the possibility of a shift in the functional activation of immune effector cells such as T lymphocytes and macrophages at formaldehyde concentrations below which overt changes in cell number become observable; however, studies specifically testing this possibility have not been performed.

While changes in subpopulations of peripheral leukocytes and circulating levels of cytokines may indicate the potential for some manner of dysfunction in the host immune system,

direct observations of dysfunction would be most informative; however, only a few studies specifically examined the potential for events such as immunosuppression in either humans or experimental animals following formaldehyde exposure. In addition, while studies of immune function in the affected airways indicate a probable effect of formaldehyde exposure, studies evaluating immunosuppression at distal sites are inadequate (see Section 3.2.3). In the airways of exposed humans, indirect evidence of decreased immune capacity exists, including decreased resistance to URT infection at 0.9 mg/m^3 formaldehyde with chronic exposure (Lyapina et al., 2004), and an increased rate of LRT infection in infants exposed to 0.02 mg/m^3 during their first year of life (Roda et al., 2011). These observations in humans are consistent with the decreased bactericidal activity of leukocytes from the lungs of mice acutely exposed to ≥1 mg/m^3 formaldehyde (Jakab et al., 1992), and the enhanced malignancy and growth of lung tumors, in association with decreases in NK cell numbers and activity, formed by an injection of syngeneic melanoma cells in mice following exposure to 12 mg/m^3 (Kim et al., 2013a). Observations related to systemic immune dysfunction, including increased survival to Listeria monocytogenes infections and reduced melanoma tumor mass in B6C3F1 mice (Dean et al., 1984), and increased autoantibodies in exposed adults (Thrasher et al., 1990) are mixed and inconclusive. Thus, while it appears that formaldehyde exposure can suppress immune function in the airways, the pattern of effects across tissue compartments (i.e., URT, LRT, blood and lymphoid tissues) remains unclear.

Together, the evidence supports a decrease in peripheral blood WBC counts in formaldehyde-exposed humans (see Section 3.2.3), although some heterogeneity across studies has been reported in terms of the directionality and magnitude of changes in specific leukocyte subsets and in levels of soluble immunomodulatory molecules (see Section 3.2.3). Considerable heterogeneity has also been observed in relation to the formaldehyde concentration or exposure duration reported for the different observations, further complicating interpretation. Despite this variability, the available data suggest that formaldehyde exposure modifies immune system function across a range of concentrations and durations, with changes in specific leukocyte subpopulations becoming more robust and consistent following exposure to >0.5 mg/m^3 (see Section 3.2.3).

Relevance to LHP carcinogenesis

While many of the changes reported following formaldehyde exposure could create a more permissive environment favoring tumor growth and progression, evidence does not exist to determine whether these changes in immune cell populations or cytokine profiles significantly impact tumor immunosurveillance or cause chronic inflammation; therefore, any specific role for altered immune function in formaldehyde-associated leukemogenesis remains unclear. Changes in immune cell subpopulations, distribution, and activation have a complex relationship with carcinogenesis in terms of tumor suppressing or enhancing activity (Hanahan and Weinberg, 2011). For example, immune suppression is associated with a greater risk of hematopoietic cancers (Bassig et al., 2012), and chronically immunosuppressed human transplant recipients are at

increased risk for developing myeloid neoplasms (Morton et al., 2014). Together, this evidence shows that the immune system can operate as a significant barrier to LHP carcinogenesis (Corthay, 2014). In addition, impaired tumor immunosurveillance could result from deficiencies in the development or function of cytotoxic T lymphocytes (CTLs), type 1 T-helper (T_H1) cells, or NK cells, which might lead to demonstrable increases in tumor incidence (Hanahan and Weinberg, 2011). Conversely, inflammatory immune effector cells (i.e., neutrophils, macrophages, type 2 T-helper [T_H2] cells, and T and B lymphocytes) can release growth factors and other tolerogenic signaling mediators, which permit tumor growth. The release of reactive oxygen species (ROS) from such cells can be actively mutagenic for nearby cancer cells and accelerate their genetic evolution toward heightened malignancy (Coussens and Werb, 2002). While NK cells play a prominent role in infection and carcinogenesis in the airways (and likely elsewhere in the body), the studies and evidence reporting effects on these cells in any tissue system following formaldehyde exposure are considered weak. Overall, despite the potential for these associations, cell type-specific changes indicative of impaired immunosurveillance or enhanced tumor growth have not been conclusively demonstrated following formaldehyde exposure, particularly at lower levels.

The observed changes in soluble immune factors are similarly difficult to interpret. In addition to the evidence of increased IL-4 in the blood, multiple observations, primarily from allergen sensitization studies in rodents, suggest that IL-4 production in the lower respiratory tract (LRT) in response to antigen stimulation is further exacerbated by formaldehyde exposures ≥0.3 mg/m^3 (see Sections 3.2.2–3.2.3). Although the specific implications of cytokine changes for tumor development and progression is still emerging, IL-10 and IL-4 in particular are important cytokines in tumor immunology (Li et al., 2009), and the tendency of IL-4 and IL-10 to increase while IFN-γ decreases (see Section 3.2.3) is a pattern commonly observed in human cancer patients, including those diagnosed with some LHP cancer subtypes (Shurin et al., 1999). However, the relationships between cell signaling molecules and affected components of the immune system are complex, and an understanding of how these molecular changes might relate specifically to immune cell dysfunction, and further, to LHP carcinogenesis, is incomplete.

Evidence does not exist to describe how formaldehyde exposure might cause the observed systemic changes in immune system-related responses. While it is possible that these changes might result from disturbed bone marrow hematopoiesis resulting indirectly from formaldehyde exposure, studies specifically testing this possibility were not identified. Alternatively, it is possible that altered immune system responses are related to formaldehyde-induced toxicity at the URT. Interestingly, while peripheral blood CTL levels were generally decreased in individuals exposed to formaldehyde concentrations >0.5 mg/m^3, respiratory tract CTL levels (and total WBC counts) tended to increase in rodent studies, although the latter data are limited to short-term exposure at much higher formaldehyde levels (see Appendix C.7). It is possible that CTLs were preferentially recruited from the peripheral blood into the URT, thus explaining their depletion from the former and accumulation in the latter tissue; however, none of the identified human studies report WBC

counts from both peripheral blood and POE tissue compartments, and the available animal data likewise cannot adequately inform this hypothesis.

Overall, while several studies indicate effects on hematopoietic cell populations and secreted factors, for which exposure concentration may be an important determinant, the impact of these changes on leukemogenesis cannot be clearly discerned.

Evidence of formaldehyde-induced oxidative stress

Similar to observations in the airways, inhaled formaldehyde has been associated with biomarkers of oxidative stress in distal tissues (see Section 3.2.3 and Appendix C.7).

Some human studies have evaluated changes in markers of oxidative stress in blood or urine in relation to formaldehyde exposure, and also have attempted to determine whether the oxidation of lipid membrane components might be associated with the presence of formaldehyde-induced DNA damage. Two studies provide evidence of oxidative stress-related genotoxicity or mutagenicity, including elevations in malondialdehyde-deoxyguanosine (M1dG) adducts (i.e., exocyclic DNA adducts formed as byproducts of lipid peroxidation) in WBC DNA with exposure to an average formaldehyde concentration as low as 0.07 mg/m^3 (Bono et al., 2010). This finding is indirectly supported by an observed association between increases in malondialdehyde and p53 protein (a potential biomarker of carcinogenicity; see discussion of the potential for p53 to contribute to URT carcinogenesis in Section 3.2.5) in plasma with urinary formate levels (which may serve as an imprecise marker of formaldehyde exposure) among cosmetic workers (Attia et al., 2014). Additional evidence that formaldehyde exposure is associated with oxidative stress is provided by a study that reported increased urine levels of 15-F2t isoprostane (a sensitive, but nonspecific marker of oxidative stress) from formaldehyde-exposed workers (Romanazzi et al., 2013); although this marker is not specific to changes in a particular tissue, strong correlations between measurements from urine and plasma (Rodrigo et al., 2007; Morrow et al., 1995) suggest similarly elevated isoprostanes in the workers' blood. Somewhat in support of the observations in humans, several animal studies in two species observed increases in markers of oxidative stress following acute or short-term formaldehyde exposure to a range of formaldehyde concentrations including ≤1 mg/m^3; however, these studies had notable methodological limitations, and it is not clear whether these changes persist with long-term exposure (see Section 3.2.3). Suggestive evidence of elevated indicators of formaldehyde-induced oxidative stress and inflammation have been reported in bone marrow from exposed mice at ≥0.5 mg/m^3 formaldehyde; however, these animals were coexposed to methanol, drawing into question the validity of these findings (formalin was the formaldehyde source; (Zhang et al., 2013b; Yu et al., 2014; Ye et al., 2013b)). These limited studies also observed higher rates of DNA damage in bone marrow. Overall, together with the genotoxicity data, this evidence supports the likely presence of DNA damage and, possibly coincidentally, the likely presence of elevated oxidative stress in circulating leukocytes, although the data are insufficient to describe this potential relationship in terms of duration or concentration of exposure.

Studies of susceptibility to DNA damage conferred by polymorphisms in genes coding for enzymes with activity that either increases or decreases oxidative damage observed greater genotoxicity associated with formaldehyde exposure and polymorphic variation in genes encoding the ROS-inducer, CYP2E1 (more damage associated with wildtype), and the detoxifying enzyme, GSTP1 (more damage associated with variant) (Costa et al., 2015), although another study using a different measure of DNA damage found a marginal increase in susceptibility among exposed with the wildtype GSTP1 allele compared to the variant genotype (Jiang et al., 2010). However, DNA damage in human PBLs was not increased to a greater degree in formaldehyde-exposed human cohorts with increased susceptibility to oxidative damage due to glutathione-S transferase (GSTM1 or GSTT1) null genotype (Santovito et al., 2011; Jiang et al., 2010; Costa et al., 2008); therefore, these results remain inconclusive.

Relevance to LHP carcinogenesis

Together, the available data suggest that oxidative stress may be elevated at distal sites following formaldehyde exposure in humans, rats, and mice; however, available studies of genetic susceptibility in exposed workers are not adequate to draw conclusions. Considered alongside the evidence of oxidative stress in the airways (Sections 3.2.1–3.2.2), the data reporting oxidative stress at distal sites suggest that formaldehyde exposure might increase the production of potentially harmful factors throughout the body. If sufficiently severe or sustained for a prolonged duration, oxidative stress could perturb the function of circulating leukocyte populations including HSPCs, increasing lipid, protein, and DNA oxidation, causing DNA strand breakage, as well as altering cellular energetics and signaling pathways (Mikhed et al., 2015). Regarding any potential role in LHP carcinogenesis, the impact of oxidative stress-induced DNA damage on gene or chromosomal changes could be similar to the damage caused by a variety of directly DNA-reactive compounds (Mchale et al., 2012; DeMarini et al., 2000). The available evidence is inadequate to determine what role formaldehyde-associated oxidative stress may play in LHP carcinogenesis, although impacts on leukocyte genotoxicity, increased HSPC mobilization, or immunomodulation are all plausible consequences of systemically elevated oxidative stress.

Data are not available to describe how formaldehyde might cause oxidative stress outside of the airways. Similar to changes in leukocyte cell numbers, this may be secondarily due to sustained airway inflammation, which could cause the release of factors from the inflamed tissue(s) into the circulation that result in increased oxidative stress; however, no studies have examined this possibility. In summary, the potential relationship of increased systemic oxidative stress to LHP carcinogenesis is unknown.

Evidence of formaldehyde-induced changes in the bone marrow niche

As noted above, there is some evidence of pancytopenia in formaldehyde-exposed humans that may indicate disturbance of or cytotoxicity in the bone marrow niche at higher environmental exposures. In F344 rats, bone marrow hyperplasia was elevated following chronic exposure to

18 mg/m^3 formaldehyde (Battelle, 1982). In two chronic rat bioassays (Sellakumar et al., 1985; Kamata et al., 1997) and a short-term (8-week) study of p53 deficient mice (Morgan et al., 2017), the authors evaluating nonrespiratory tissues did not provide details regarding nonneoplastic histopathology in tissues outside the URT, and the incidence of hematopoietic neoplasms did not appear to be elevated in any of these studies. In female B6C3F1 mice exposed similarly to the F344 rats above, hyperplasia was not observed in the bone marrow, spleen or lymph nodes (Battelle, 1982). Evaluations of changes in numbers of bone marrow megakaryocytes were likewise fairly equivocal in mice exposed to 0.5–20 mg/m^3 formaldehyde (see Appendix C.7).

Two studies in mice suggest that cell subpopulations in the bone marrow niche might be differentially affected by formaldehyde exposure. Specifically, in a 20-week study, a dose-dependent decrease in the ratio of immature to mature RBCs (PCE/NCE ratio) in the bone marrow was observed after exposure to 1 and 10 mg/m^3 formaldehyde for 2 hours per day (Liu et al., 2017); however, there was no corresponding change in micronucleus rate. A short-term, 2-week study indicated that *in vivo* formaldehyde exposure of 3 mg/m^3 caused a decreased formation of BFU-E (erythroid progenitor) and CFU-GM (granulocyte/monocyte progenitor) colonies in cultures from bone marrow or spleen (Zhao et al., 2020b). However, in both of these studies the formaldehyde source is presumed to have been formalin, which prevents interpretation of these results at systemic sites as reliable and highlights this as an area deserving of additional research.

As noted above, a dose-related increase in bone marrow DPXs was observed in BALB/c mice exposed to 0.5–3.0 mg/m^3 formaldehyde generated from evaporating formalin (Ye et al., 2013a). However, the presence of methanol in the formalin confounds interpretation of the potential for systemic formaldehyde effects, as the co-administered methanol could be rapidly absorbed, distributed to the bone marrow, and locally metabolized to formaldehyde (see Appendix C.1 and C.3). Consistent with this hypothesized contribution of methanol, neither DPXs nor DNA mono adducts were elevated in rodent bone marrow exposed via paraformaldehyde (Lu et al., 2010a; Leng et al., 2019; Heck and Casanova, 2004; Casanova-Schmitz et al., 1984a; Casanova and Heck, 1987). While bone marrow has not been evaluated in exposed human cohorts, elevations in WBC DPX levels have been reported in some human workers chronically exposed to concentrations ≥0.5 mg/m^3 (Shaham et al., 1997; Shaham et al., 2003), but not consistently in others (Lin et al., 2013).

In general, the data relevant to potential formaldehyde-induced changes in the bone marrow niche were fairly weak and inconsistent across the available studies, although the minimal data available indicate that additional studies are warranted.

Relevance to LHP carcinogenesis

Bone marrow niches consist of bone marrow mesenchymal stem cells (BM-MSCs) and HSPC pairings under tight regulation by local input from the surrounding microenvironment, as well as long-distance cues from soluble signaling mediators (e.g., hormones, cytokines, eicosanoids) and the autonomic nervous system (Lo Celso and Scadden, 2011). Aberrant bone marrow stroma can

lead to HSPC dysfunction including MDS (Lo Celso and Scadden, 2011), a precursor to AML. Therefore, altered stromal behavior could affect HSPC quiescence and mobilization as well as directly induce the expansion of leukemic clones over normal cells.

Although inhaled formaldehyde does not likely reach the bone marrow to elicit direct effects analogous to exposure in the URT (see Appendix C.1), formaldehyde-induced effects in the URT could indirectly affect the bone marrow microenvironment or "niche" in several ways, including inflammation or induction of systemic immune responses (see Section 3.2.3), oxidative stress (see Sections 3.2.3), hormonal or cytokine changes that affect BM-MSC and HSPC interactions, and disrupted regulation of HSPC mobilization from the niche. However, evaluations of bone marrow following formaldehyde inhalation have been limited to histological or genotoxic endpoints in experimental systems, with no information available regarding either molecular changes in stromal cell function or HSPC activation, differentiation, or mobilization.

The sympathetic nervous system has some control over the mobilization and circulation rate of bone marrow progenitor cells including HSPCs (Elenkov et al., 2000). While formaldehyde exposure has been shown to activate the trigeminal nerve in the rodent URT via transient receptor potential channel stimulation at low concentrations ((Mcnamara et al., 2007); see Section 3.2.1), no studies have examined whether or how this might be indirectly related to regulation of HSPC mobilization or hematopoiesis; however, it is considered unrealistic that activation of neural pathways relaying irritant and pain information would convey excitatory or inhibitory signals to networks responsible for HSPC regulatory functions.

It is difficult to reconcile these disparate observations across the available data streams: the general lack of bone marrow toxicity in experimental model systems corresponds with no excess leukemia reported in chronic rodent bioassays, while the varied fluctuations in immune cell subpopulations, including some evidence of pancytopenia in the peripheral blood of chronically exposed humans (Section 3.2.3), is consistent with the evidence of leukemia induction in humans. It is possible that humans are more sensitive to the hematotoxic effects of formaldehyde than either rodents or nonhuman primates (Goldstein, 2011), as has been noted in the context of chromosomal damage resulting from direct leukemogens (e.g., benzene; (Mchale et al., 2012; IARC, 2012; French et al., 2015)). However, mechanism(s) responsible for any potential differential sensitivity remain to be elucidated. Based on the currently available data, no conclusions can be drawn regarding the potential involvement of formaldehyde exposure-induced indirect effects on the bone marrow niche in LHP carcinogenesis.

Evidence of formaldehyde-induced changes in gene expression or posttranscriptional regulation in peripheral blood leukocytes or bone marrow

Few studies have evaluated the effect of formaldehyde exposure on microRNA (miRNA) or messenger RNA (mRNA) levels from non-POE tissues in vivo, and none evaluated chronic exposures. In a small study where human volunteers (N = 21) were variably exposed to ≤1 mg/m^3 formaldehyde for 5 days, statistically significant changes in mRNA expression were observed in

cells from either nasal biopsies or whole blood samples; however, study limitations prevent interpretation of the changes to be a result of formaldehyde exposure (Zeller et al., 2011). In F344 rats, significant changes in both miRNA and mRNA expression were reported in the nasal epithelium and circulating white cells following inhalation exposure to 2.5 mg/m^3 formaldehyde for ≤4 weeks, primarily involving pathways related to immune/inflammatory response, apoptosis, and proliferation; no significant changes were observed in miRNA samples from the bone marrow, and mRNA transcript levels were not evaluated (Rager et al., 2014). A majority of the reported changes appeared to be tissue- and exposure duration-specific, and only expression of one transcript was consistently affected (miR-326 levels increased) in the WBCs across exposure conditions (Rager et al., 2014). As these endpoints have not been well-studied, conclusions cannot be made regarding the consistency and reproducibility of these data across studies.

Relevance to LHP carcinogenesis

Epigenetic mechanisms such as miRNA-mediated regulation of mRNA may play a role in the pathogenesis of LHP malignancies (Yendamuri and Calin, 2009). For example, differential miRNA expression profiles have been reported between normal and leukemia cells, and among LHP cancer subtypes such as AML and ALL (Mi et al., 2007; Marcucci et al., 2009). However, the bone marrow represents a heterogeneous population of cells, and in the context of variable and temporal responses induced following formaldehyde exposure, such gene expression array results can be difficult to assimilate and interpret (Weinberg, 2014).

Although the potential role of miR-326 in LHP carcinogenesis is unknown, increased serum miR-326 expression was associated with bone matrix turnover and positively correlated with lung cancer bone marrow metastasis (Valencia et al., 2013). Considering that WBCs are a highly heterogeneous population, of which only a small fraction is likely to contain target cells of interest in LHP carcinogenesis (i.e., HSPCs), the observation of altered miRNA and mRNA levels in WBCs from rats provides very limited evidence that supports the biological plausibility for other formaldehyde-induced effects, such as genotoxicity (Appendix C.3) in the peripheral blood cells of occupationally exposed humans. Additional studies examining potential epigenetic and transcriptional mechanisms related to LHP carcinogenesis in non-POE tissues following formaldehyde exposure are needed to confirm and expand the observations from this limited set of studies.

Discussion of mechanistic evidence relevant to LHP carcinogenesis.

While the mechanistic events evaluated in the context of formaldehyde-associated LHP cancer are similar to those described for well-described human leukemogens (Mchale et al., 2012; IARC, 2012), the specific mechanism(s) of LHP cancer induction are not understood, which complicates the construction of any simple, linear MOA (Mchale et al., 2012). Therefore, a network of plausible mechanistic events or pathways was discussed, including specific aspects of genotoxicity and mutagenicity, hematologic effects, oxidative stress, and changes in gene

expression or regulation, consistent with previous analytical frameworks employed in the evaluation of LHP carcinogenesis (NRC, 2014b). The most pertinent evidence and conclusions for potential mechanistic events associated with formaldehyde induction of LHP cancers are summarized in Table 3-69.

It is possible that potential LHP target cells (e.g., HSPCs) are affected in the URT tissue, via direct interactions with formaldehyde, given observations that stem cell precursors can traverse between the URT and bone marrow. However, the concentrations of inhaled formaldehyde reaching sites through which HSPCs might traverse (e.g., lymphatic URT tissue), as well as the population of HSPCs present in the URT at any one time, would both be expected to be quite low, although no specific data address these unknowns. Indirect toxicity to HSPCs in the URT also might result from inflammation or oxidative stress in these tissues. Furthermore, genotoxic effects on HSPCs, as well as immune cell toxicity and dysfunction, may occur in peripheral blood or bone marrow via indirect effects of formaldehyde-associated inflammation in the URT resulting in systemic oxidative stress and changes in gene expression or regulation. However, no studies of formaldehyde exposure investigating these hypotheses have been conducted.

Evidence from evaluation of respiratory tract and oral cells (nasal and buccal epithelium), and circulating leukocytes (e.g., HSPCs and PBLs) consistently demonstrates increased levels of Comet assay-detectable DNA damage, as well as MN, CAs, and SCEs associated with formaldehyde exposure from a variety of occupational cohorts. Some of the genotoxic endpoints observed in circulating blood cell progenitors from formaldehyde-exposed workers have also been specifically observed in patients with AML (Mchale et al., 2012; Bowen and Hannigan, 2006), while other endpoints observed in PBLs, such as MN and CA, are generally regarded as biomarkers associated with increased human risk for a variety of cancers, including LHP malignancies (Kirsch-Volders et al., 2014; Fenech et al., 2011; Bonassi et al., 2004b; Bonassi et al., 2007; Bonassi et al., 2008); see Section 3.2.5, *Evidence on Mode of Action*). Genotoxicity to circulating PBLs may also serve as a surrogate biomarker of genotoxicity in HSPCs, which may play a more direct role in LHP carcinogenesis. No information from the available formaldehyde studies exists to evaluate this potential association.

Following formaldehyde exposure, the available evidence supports the following observations: (a) elevated levels or severity of DNA or chromosomal damage in circulating human blood cells, including in both myeloblasts and mature lymphocyte populations; (b) the specific nature of DNA damage in circulating human leukocytes exhibits aneugenic characteristics similar to damage reported in humans with or at increased risk for AML; and (c) that the human immune system is impacted, possibly as a function of formaldehyde concentration, in a complex manner. Formaldehyde exposure is associated with reductions in immune cell populations, although other lines of evidence indicate stimulation of some immune cell populations, which might reflect a complex concentration or duration dependence in the pattern of effects. The observations of DNA or chromosomal damage in exposed humans, including aneuploidy, and reductions in immune cell

populations associated with comparable formaldehyde levels (≥0.5 mg/m^3) provide coherent evidence suggesting that these effects may be related.

Despite the internal consistency of many of the individual effects described above regarding formaldehyde-induced damage to target cells and biomarkers of genotoxicity in circulating mature PBLs in humans, there is a general lack of understanding regarding both how formaldehyde exposure might cause these changes, as well as how these mechanistic events may lead to LHP cancer. Regarding the latter, for example, any specific effects on the bone marrow niche have not been studied in exposed humans, and the evidence from the available animal studies is generally inconclusive.

The relationships between leukocyte responses in peripheral blood and formaldehyde exposure are complex; studies observed changes in different cell populations, which were both increased and decreased across studies, although some tentative patterns could be discerned, particularly at exposure concentrations >0.5 mg/m^3. The mechanisms responsible for these observations are unclear, as is any specific contribution of these mechanistic events to LHP carcinogenesis. Likewise, although some evidence exists to support increased systemic oxidative stress associated with formaldehyde exposure, its role in targets of LHP cancers is also unclear, and any specific impacts on immune function or tumor immunosurveillance remain to be determined.

Alternative hypotheses

A hypothesized scenario that does not require bone marrow cytotoxicity is that HSPCs damaged in the URT tissues do not return to the bone marrow but form local neoplastic foci. However, there is no evidence supporting this possibility. Collections of neoplastic myeloid cells localized in extramedullary tissues (myeloid or granulocytic sarcomas occurring outside of the medulla of the bone), are associated with MDS and AML but are not commonly reported in human nasal tissue (Yamamoto et al., 2010b; Prades et al., 2002; Paydas et al., 2006). Myeloid sarcomas have not been specifically associated with formaldehyde exposure, although these lesions are frequently misclassified as NHLs in patients without concurrent MDS or AML (Yamamoto et al., 2010a). However, HSPCs do not travel through the nasopharynx-associated lymphoid tissue (Massberg et al., 2007), and may not be the target cell population responsible for nasal myeloid sarcoma. This observation could suggest that the nasal tissue does not provide a suitable niche microenvironment for sustaining neoplastic myeloid cell expansion (Wilson et al., 2009; Granick et al., 2012).

Inferences can be made by extending the proposed hypothesis of circulating or nasal-resident HSPCs as LHP cancer target cells to the spectrum of effects commonly associated with leukemias induced by exposure to other agents (U.S. EPA, 2005a). Although the results of this exercise cannot dismiss the biological plausibility of the events evaluated with specific data from the formaldehyde exposure database, it may illustrate that the identified set of mechanistic events are incomplete. For example, if HSPCs are exposed to the genotoxic activity of formaldehyde as they transit through the URT tissues, and then proceed back to the bone marrow to progressively

become leukemogenic, then other genotoxic URT carcinogens could potentially have a similar effect and be associated with both URT and bone marrow cancers. Most agents associated with nasal cancer in humans have not also been associated with leukemia induction, despite displaying variable genotoxic activity, except for those agents that are also systemically available and hematotoxic (IARC, 2012). This suggests that genotoxicity and distribution to the URT alone may not be sufficient to induce LHP carcinogenesis. It has been proposed (IARC, 2012) that well-studied human leukemogens (e.g., ionizing radiation, benzene, chemotherapeutics) induce hematotoxicity more frequently or to a greater extent than neoplasia, which would be consistent with DNA damage more frequently resulting in bone marrow cell death than progenitor transformation. However, this observation cannot rule out leukemogenesis driven by mechanisms other than genotoxicity-induced bone marrow cytotoxicity.

Gaps in understanding of formaldehyde exposure-related LHP carcinogenesis

As discussed in this section, there appears to be a lack of concordance between evidence from chronic rodent bioassays and human epidemiological evidence regarding incidence of LHP cancers. Moreover, contrary to the consistent evidence supporting genetic damage to circulating leukocytes in formaldehyde-exposed humans, few positive associations have been reported in rodent bioassays. This MOA discussion evaluated the mechanistic database pertinent to leukemogenesis based on the fundamental assumption that exogenous formaldehyde is not distributed appreciably beyond POE tissues. Differences in physiology between humans and rodents, as well as the apparent relative insensitivity of rodent models to reflect the human pathogenesis of AML (Eastmond, 1997), may together contribute to the potential lack of concordance between the abundant human epidemiological data and the more limited results (e.g., most bioassays did not examine tissues relevant to LHP cancers in detail) from rodent bioassay data.

Conclusion

The available evidence supports some events that could contribute to plausible mechanistic pathways relating formaldehyde exposure to LHP carcinogenesis. However, the database was insufficient to support the evaluation or development of any specific MOA. Both temporal and exposure-response relationships have been demonstrated in studies of humans, and mechanistic pathways exist that support a biologically plausible relationship between formaldehyde exposure and cancer, even though the mechanistic pathways explaining such systemic effects are unclear (NRC, 2014b). Most notably, the available evidence for genotoxicity in circulating blood cells is strong and largely consistent. It is important to reemphasize that systemic delivery of formaldehyde is not a prerequisite for the observed mechanistic changes, as some of the reported systemic effects might result from direct interactions with formaldehyde in the URT, while others could plausibly result indirectly from events such as URT irritation, cytotoxicity, oxidative stress, and inflammation locally initiated at the POE. Further, the evidence for other effects at distal sites

was compelling. This evidence included increased female reproductive and developmental toxicity and male reproductive toxicity, based on studies of experimental animals and workers exposed to high formaldehyde levels, as well as LRT disease (i.e., current asthma symptoms and decreased asthma control in population-based epidemiology studies). It is plausible that these effects could result indirectly from events occurring in the URT. While the available mechanistic database has limitations, this does not detract from the strength of the association between formaldehyde exposure and myeloid leukemia in epidemiology studies.

Summary of Inferences Regarding Mode of Action

Support for the hypothesized mode of action in experimental animal models

While evidence for the several identified mechanistic events ranges from strong and consistent to inadequate (see Table 3-69), the supporting evidence was drawn primarily from studies of exposed humans; no single MOA could be assembled and evaluated from the limited relevant experimental animal data available.

Relevance of the hypothesized mode of action to humans

Due to the paucity of pertinent mechanistic information, no single, stochastic MOA was identified for LHP cancers associated with formaldehyde exposure. However, evidence supporting the identified mechanistic events was obtained primarily from studies of exposed human cohorts, and thus the mechanistic events are all relevant or of presumed relevance to human LHP cancer risk (see Table 3-69).

Table 3-69. Summary conclusions regarding plausible mechanistic events associated with formaldehyde induction of lymphohematopoietic cancers

Hypothesized mechanistic event	Evidence informing mechanistic event	Human relevance	Weight-of-evidence conclusion and biological plausibility
2.1 Formaldehyde-induced DNA damage to peripheral blood leukocytes	HSPC aneuploidy and structural chromosome damage in myeloid progenitors (CFU-GMs) from human workers occupationally exposed to median levels of 1.6 mg/m^3 (Zhang et al., 2010; Lan et al., 2015). • ↑ Monosomy and polysomy in multiple chromosomes (especially monosomy 1, 5, 7) consistent with damage observed in patients with MDS or AML (Lan et al., 2015) • ↑ Breaks, deletions, and translocations in chromosome 5 ↑ genotoxicity in circulating PBLs from inhalation-exposed humans, including increases in strand breaks, MN, CA (see Appendix A.4; (Kirsch-Volders et al., 2014) NBUDs, or SCE induction at ≥0.14 mg/m^3 (Jiang et al., 2010), and DPXs at higher exposures (Shaham et al., 2003; Lin et al., 2013). • ↑ DPXs in PBLs from mice after inhalation of formaldehyde generated from formalin (Ye et al., 2013b), although results may be confounded by methanol coexposure	Yes. Evidence comes primarily from exposed humans.	Strong and consistent human data exist associating formaldehyde exposure with various genotoxic outcomes in myeloid progenitors and PBLs, and exposure-response relationships demonstrated. Genotoxicity in circulating leukocytes shows concordance with similar endpoints in POE tissues. Aneugenic damage observed in CFU-GMs from formaldehyde-exposed human workers is associated with MDS or

Hypothesized mechanistic event	Evidence informing mechanistic event	Human relevance	Weight-of-evidence conclusion and biological plausibility
	• No increase in DPXs in peripheral blood or bone marrow of monkeys or rats exposed via paraformaldehyde (Lai et al., 2016; Casanova and Heck, 1987) • DNA damage in human PBLs is consistently associated with genotoxicity in human POE tissues (e.g., exfoliated buccal and nasal epithelial cells) in studies evaluating both tissues after longer-term exposures (see Appendix C.3; see Section 3.2.5)		AML in humans. Together this evidence constitutes the strongest support for the biological plausibility for LHP induction resulting from formaldehyde exposure.
2.2 Evidence of formaldehyde-induced impacts other than genotoxicity on circulating blood cell populations, including inflammatory changes and/or immune system dysfunction	↓ CFU-GM colony formation in human workers occupationally exposed to median levels 1.6 mg/m^3 (Zhang et al., 2010), which may reflect not only altered bone marrow progenitor cell viability, but also immune dysfunction or altered activation. • Numerous published studies reporting divergent changes in various peripheral blood cell populations from formaldehyde-exposed humans (see Section 3.2.3; Appendix C.7), including: - ↑ Pancytopenia and consistent decreases in total WBCs ↓ or ↑ in some lymphocyte populations, with decreased CD8 T cells likely at concentration >0.5 mg/m^3. Fluctuations in immune cell numbers and immune/inflammation markers show a complex pattern with concentration, with decreases in blood cell number and decreased cytotoxic response generally at higher concentrations, some of which are consistent with observations in AML patients (Kim et al., 2015). Other studies indicate immune cell activation generally observed at lower concentrations ≤0.36 mg/m^3.	Yes. Most of the available data comes from human studies.	The evidence supporting changes in populations or function of circulating blood leukocytes following human exposure to formaldehyde is strong in terms of a frequency of alterations, but different patterns in changes are reported (e.g., specific direction of changes in various lymphocyte subpopulations, or in blood levels of soluble signaling mediators). LHP cancer risk increases with loss of normal immune function.
2.3 Formaldehyde-induced systemic oxidative stress	• ↑ M1dG adducts in whole blood DNA from pathologists, compared to workers and students in other science labs (Bono et al., 2010), elevated plasma MDA and plasma p53 associated with each other and with urinary formate concentrations (an imprecise marker of formaldehyde exposure) among cosmetics workers (Attia et al., 2014), and ↑ 15-F2t isoprostane levels in the urine of formaldehyde-exposed workers (Romanazzi et al., 2013) • Inconclusive evidence for and against involvement by genes that regulate oxidative stress in formaldehyde associations with DNA damage risk in PBL in humans (see Appendix C.3) • ↓ GSH, ↑ ROS, ↑ MDA in bone marrow, peripheral blood mononuclear cells, liver, spleen, and testes (Ye et al., 2013b), although markers of oxidative stress were not correlated with DPXs and results may be confounded by methanol coexposure.	Yes. Some human data available, and results from experimental models are presumed relevant to humans.	Limited human and rodent evidence supports the association between formaldehyde exposure and induction of oxidative stress beyond the POE. While biologically plausible, the available evidence is inadequate to determine what role such oxidative stress may play in LHP carcinogenesis.
2.4 Formaldehyde-induced changes in the bone marrow niche	• ↑ Bone marrow hyperplasia in rats from one study (Kerns et al., 1983; Battelle, 1981), but unclear if other results were negative or null (Sellakumar et al., 1985; Kamata et al., 1997) due to imprecise reporting • Dose-related ↑ DPXs in the bone marrow of formalin-exposed mice (Ye et al., 2013b), although results may be confounded by methanol coexposure	Yes. Available data are from experimental models presumed	The limited evidence available is currently inadequate to evaluate any effect on bone marrow or stromal cells following formaldehyde exposure, although such

Hypothesized mechanistic event	Evidence informing mechanistic event	Human relevance	Weight-of-evidence conclusion and biological plausibility
	• HSPC mobilization and the BM-MSC niche is regulated by cytokines, hormones, and signals, which may be distributed through circulation as a result of inflammation although these effects have not been directly evaluated following formaldehyde exposure	relevant to humans.	an effect appears consistent with current understanding of hematopoiesis.
2.5 Evidence of formaldehyde-induced changes in gene expression or posttranscriptional regulation in peripheral blood leukocytes or bone marrow	Limited study reported some statistically significant differences in mRNA expression in either nasal or whole blood samples from human volunteers associated with 5-day exposures up to 1 mg/m^3 formaldehyde; however, study limitations prevent interpretation that results were related to formaldehyde exposure (Zeller et al., 2011). In F344 rats, significant changes in both miRNA and mRNA expression were reported in the nasal epithelium and circulating WBCs following inhalation exposure to 2.5 mg/m^3 formaldehyde for 1 or 4 weeks; no changes were observed in miRNA expression in the bone marrow, and mRNA was not evaluated (Rager et al., 2014). • "Immune system/inflammation" markers were enriched in both nasal tissue and WBCs at both time points • ↑ WBC miR-326 expression, associated with bone marrow metastasis in other models (Valencia et al., 2013)	Yes. Available data are from experimental models presumed relevant to humans.	Limited rodent evidence supports the association between formaldehyde exposure and epigenetic effects in circulating leukocytes; the available human evidence is inadequate. Insufficient evidence is available to determine what role epigenetics may play in LHP carcinogenesis.

Abbreviations: HSPC = hematopoietic stem and progenitor cell; MN = micronuclei; CA = chromosomal aberration; CFU-GM = colony-forming unit, granulocytes and macrophages; MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; PBL = peripheral blood lymphocytes; NBUD = nuclear budding; SCE = sister chromatid exchange; DPX = DNA-protein crosslink; GSH = glutathione; ROS = reactive oxygen species; MDA = malondialdehyde.

Evidence Integration Summary

The strength of the evidence from human studies is *robust* for myeloid leukemia (see *Lymphohematopoietic cancers in humans* above). The assessment of LHP cancers was based on epidemiology studies of groups with occupational formaldehyde levels either in specific work settings (e.g., cohort studies) or in case-control studies. Aneuploidy in chromosomes 1, 5, and 7 in circulating myeloid progenitor cells, considered a potential primary target for LHP carcinogenesis was associated with occupational formaldehyde exposure. The type of aneuploidies observed in the formaldehyde-exposed asymptomatic human workers are also found in patients with leukemia, specifically MDS and AML, as well as other worker cohorts at increased risk of developing leukemias, which provides support for the plausibility of an association between chronic formaldehyde exposure and leukemogenesis. Moreover, the strong and consistent evidence from a large set of studies that observed mutagenicity in circulating leukocytes of formaldehyde-exposed humans, specifically CAs, and MN formation, provides additional evidence of biological plausibility for these cancer types. Further support is provided by studies that observed perturbations to immune cell populations in peripheral blood associated with formaldehyde exposure. In particular, decreases in RBCs, WBCs, and platelets, along with a 20% decrease in CFU-GM colony formation in vitro were observed in the same exposed group (Zhang et al., 2010), suggesting both a decrease in

the circulating numbers of mature RBCs and WBCs as well as possible decreases in the replicative capacity of myeloblasts.

Increased LHP cancers have not been observed in a large, *medium* confidence, chronic rodent bioassay involving inhalation exposure of both rats and mice to formaldehyde, although routine histopathological evaluations were only performed at the highest exposure level (which caused high mortality in rats), nor in another *medium* confidence rat bioassay that failed to report the incidence of non-nasal neoplastic lesions. However, there are notable uncertainties in the available animal data, including increased bone marrow hyperplasia in rats, slight but uncertain increases in lymphoma in mice, and a general lack of rigorous evaluation of non-respiratory tissues. Mechanistic changes related to leukemia have not been consistently reported in well-conducted rodent studies. Thus, while uncertain and insufficient to inform the hazard judgment in either direction, there is a general lack of clear support for the human epidemiological evidence from rodent bioassays, noting that concordance across species is not necessarily expected (U.S. EPA, 2005a). The apparent lack of consistency in results raises uncertainties about the currently available research results on these diseases, including how formaldehyde exposure-induced LHP cancers might arise without substantial distribution to target sites. Notably, it is important to emphasize that the available animal evidence was judged as *indeterminate* and not *compelling evidence of no effect* (see evidence integration methods in Section 2.6), as there are important uncertainties that prevent such an interpretation. Thus, the animal evidence does not detract from the strength of the association between formaldehyde exposure and myeloid leukemia (and related mechanistic changes) in epidemiology studies (NRC, 2014b). Differences in physiology between humans and rodents, as well as the apparent relative insensitivity of rodent models to reflect the human pathogenesis of AML (Eastmond, 1997), may together contribute to the potential lack of concordance between the abundant human epidemiological data and the more limited results (e.g., most bioassays did not examine tissues relevant to LHP cancers in detail) from rodent bioassay data.

Taken together, based on the *robust* human evidence from studies of groups with occupational formaldehyde levels, the **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans (see Table 3-70). Separately, based on a limited number of epidemiological studies and potentially relevant mechanistic evidence in exposed humans, the integration of the evidence results in a judgment that the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple myeloma and Hodgkin lymphoma. While mechanisms for the induction of myeloid leukemia are yet to be elucidated, they do not appear to require direct interactions between formaldehyde and bone marrow constituents, and either are different in animals or the existing animal models tested thus far do not characterize the complex process leading to cancers in exposed humans.

Table 3-70. Evidence integration summary for effects of formaldehyde inhalation on LHP cancers

Evidence	Factor	Increasing Certainty	Decreasing Certainty	Synthesis Judgment	Hazard determination
Myeloid Leukemia					
Human	*Consistency and Study Confidence*	• Consistent increases in risk across a set of *high* and *medium* confidence, independent studies with varied study designs and populations.		*Robust* Based on consistent findings of increased risk in high and medium confidence studies of groups exposed to occupational formaldehyde levels, several of which demonstrated large and dose-dependent elevations. Although not necessary for this judgment, the strong and consistent evidence from a large set of studies that observed mutagenicity in circulating leukocytes of formaldehyde-exposed humans further supports the plausibility of the cancer findings.	The **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans This conclusion was primarily based on epidemiology studies of groups with occupational formaldehyde exposure. While evidence exists to suggest a lack of concordance between chronic rodent bioassays and human epidemiological evidence, notable uncertainties prevent an animal evidence judgment of *compelling evidence of no effect* *Potential susceptibilities:* There is no evidence to evaluate the potential risk to sensitive populations or lifestages
	Strength and Precision	• Several studies demonstrated strong associations (1.5- to 3-fold increase in risk)			
	Dose-Response	• Several studies demonstrated clear exposure-response relationships across multiple measures of increasing exposure			
	Coherence	• A temporal relationship consistent with causality (i.e., allowing for cancer induction, latency and mortality)			
	Biological Plausibility	• Evidence from *high* and *medium* confidence studies of exposed humans identifies relevant mechanistic changes for cancers of the blood such as myeloid leukemia, including impacts on peripheral immune cell populations (which seem to be affected in a complex manner), and elevated levels or severity of DNA or chromosomal damage in circulating myeloblasts and mature lymphocyte populations. The DNA damage exhibits aneugenic characteristics similar to that found in humans with, or at increased risk for, acute myeloid leukemia. (Note: potentially relevant to cancer types			

		below)			
Animal	*Consistency and Study Confidence*		• Overall, the available data do not provide evidence supporting the development of LHP cancers in a *medium* confidence chronic bioassay of rats and mice, a second *medium* confidence rat bioassay, and two other *low* confidence, long-term exposure studies.	*Indeterminate (for any LHP cancer type)* Based on the general lack of relevant cancers in two well-conducted studies and the lack of strong evidence supporting biological plausibility. Uncertainties in the available studies prevent a judgment of compelling evidence of no effect.	
	Strength and Precision	N/A			
	Dose-Response	N/A			
	Coherence	N/A			
	Biological Plausibility	Although some potentially relevant changes have been observed in mechanistic studies of exposed animals (e.g., inflammatory and immune changes in systemic tissues and bone marrow hyperplasia in rats), the evidence related to genotoxicity (i.e., in systemic tissues) or other more directly relevant changes were weak (e.g., only in *low* confidence studies) or not observed. Given the MOA inference (below), the mechanistic data do not suggest a judgment other than *indeterminate* for LHP cancers in animals.			
Other inferences	• *Relevance to humans:* The evidence is from studies in humans. • *MOA:* No MOA exists to explain how formaldehyde might cause LHP cancers without systemic distribution (i.e., without direct interactions of inhaled formaldehyde with constituents in bone marrow tissue); however, given the mechanistic changes in exposed humans, it is reasonable to infer that an undefined MOA is likely to involve modulatory effects on circulating immune cells.				
Multiple myeloma					

Human	*Consistency and Study Confidence*	• Increases in risk associated with peak exposure metrics across one *high*, one *medium*, and two *low* confidence studies.	• No associations with exposure metrics other than peak.	*Slight* Based primarily on increased risks with peak exposure in two well-conducted studies, with some mechanistic support (see description for myeloid leukemia).	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple myeloma [a]
	Strength and Precision	• Increases spanned an approximate 1.2- to 4-fold increase in risk, with the highest confidence evidence showing a 2-fold increase.	• Risks may have been driven by peak exposures as increases were limited to groups of people who experienced high peak exposures, and two low confidence studies reported inverse relationships with duration of exposure.		
	Dose-Response	• Very limited evidence of an exposure-response relationship in one *high* confidence study			
	Coherence	*N/A*			
	Biological Plausibility	[Description above for myeloid leukemia applies to human evidence for all LHP cancers]			
Animal	*Consistency and Study Confidence*	[Description above for myeloid leukemia applies to all LHP cancers]		*Indeterminate (for any LHP cancer type)* [see above explanation]	
	Strength and Precision				
	Dose-Response				
	Coherence				
	Biological Plausibility				
Other inferences	• *Relevance of the animal evidence to humans*: The evidence is from studies in humans.				

<table>
<tr><td></td><td colspan="3">• MOA: No MOA exists to explain how formaldehyde might cause LHP cancers without systemic distribution.</td><td></td></tr>
<tr><td colspan="5">Hodgkin lymphoma</td></tr>
<tr><td rowspan="5">Human</td><td>Consistency and Study Confidence</td><td>• Significantly increased risk in the highest peak exposure group alongside an exposure-response relationship in one medium confidence study of industrial workers.</td><td>• An inconsistent pattern of risks across 1 medium and the low confidence studies, many with <5 exposed cases, noting that the high survival rate for Hodgkin lymphoma may indicate that mortality data are not a good proxy for incidence.</td><td rowspan="5">Slight
Based primarily on suggestive findings from a single study in the absence of clearly conflicting evidence.</td><td rowspan="6">The evidence suggests, but is not sufficient to infer, that formaldehyde inhalation might cause Hodgkin lymphoma[a]</td></tr>
<tr><td>Strength and Precision</td><td colspan="2">N/A</td></tr>
<tr><td>Dose-Response</td><td colspan="2">N/A</td></tr>
<tr><td>Coherence</td><td colspan="2">N/A</td></tr>
<tr><td>Biological Plausibility</td><td colspan="2">[Description above for myeloid leukemia applies to human evidence for all LHP cancers]</td></tr>
<tr><td rowspan="5">Animal</td><td>Consistency and Study Confidence</td><td colspan="2" rowspan="5">[Description above for myeloid leukemia applies to all LHP cancers]</td><td rowspan="5">Indeterminate (for any LHP cancer type)
[see above explanation]</td></tr>
<tr><td>Strength and Precision</td></tr>
<tr><td>Dose-Response</td></tr>
<tr><td>Coherence</td></tr>
<tr><td>Biological Plausibility</td></tr>
<tr><td>Other inferences</td><td colspan="3">• Relevance to humans: The evidence is from studies in humans.
• MOA: No MOA exists to explain how formaldehyde might cause LHP cancers without systemic distribution</td><td></td></tr>
</table>

Lymphatic leukemia					
Human	*Consistency and Study Confidence*		• A consistent pattern of null results across eight *high*, *medium*, and *low* confidence studies, noting that the high survival rate for lymphatic leukemia may indicate that mortality data are not a good proxy for incidence.	*Indeterminate* Based on a general lack of associations for this cancer type.	There is **inadequate evidence** to determine whether formaldehyde inhalation may be capable of causing lymphatic leukemia in humans
	Strength and Precision	*N/A*			
	Dose-Response	*N/A*			
	Coherence	*N/A*			
	Biological Plausibility	[Description above for myeloid leukemia applies to human evidence for all LHP cancers]			
Animal	*Consistency and Study Confidence*	[Description above for myeloid leukemia applies to all LHP cancers]		*Indeterminate*, [see above explanation]	
	Strength and Precision				
	Dose-Response				
	Coherence				
	Biological Plausibility				
Other inferences	N/A: no signal exists across lines of evidence				

N/A = indicates the factor was not applicable to (i.e., did not influence) the judgment drawn

[a]Given the uncertainty in this judgment and the available evidence, this assessment does not attempt to define a quantitative estimate for this cancer type (see Section 5.2).

4. SUMMARY OF HAZARD IDENTIFICATION CONCLUSIONS

This section provides summaries of the available evidence on susceptible populations and life stages and on populations that may have heightened formaldehyde exposures compared to the general population (Section 4.1), the weight of evidence for effects other than cancer (Section 4.2), and the weight of evidence for carcinogenicity (Section 4.3).

4.1. SUSCEPTIBLE POPULATIONS AND LIFESTAGES

Susceptible populations and lifestages refer to groups of people who may be at increased risk for adverse health consequences following chemical exposures due to factors such as age, genetics, health status and disease, sex, lifestyle, and other coexposures. This discussion of susceptibility focuses on factors for which there are available formaldehyde exposure-specific data and on factors hypothesized to be important to formaldehyde. Vulnerable populations, defined as groups that may be at an increased risk for adverse health consequences due to heightened formaldehyde exposures, are also discussed.

4.1.1. Lifestage

Embryos, fetuses, infants, children, and the elderly may have differing levels of maturity and functioning of cellular and organ systems, and metabolizing enzymes, as well as unique activity patterns that may influence the toxicodynamics of chemicals in the body. Embryonic, fetal, neonatal, and juvenile periods, as well as reproductive lifestages in both men and women, are often periods of increased susceptibility to negative health consequences following chemical exposures.

Developmental and reproductive effects

The Developmental and Reproductive Toxicity (Section 3.3.2) provides a detailed analysis of human and animal studies evaluating susceptibility to formaldehyde toxicity while in utero and during infancy, childhood, and reproductive lifestages. Overall, it was judged that the available **evidence indicates** that formaldehyde inhalation exposure likely causes developmental or reproductive toxicity in humans. This hazard conclusion was primarily based on *moderate* evidence from epidemiological studies of women that reported decreased fecundity and increased spontaneous abortion risk at occupational exposure levels as high as 1.2 mg/m^3 (Taskinen et al., 1999; John et al., 1994) as well as effects on fetal growth among three pregnancy cohorts observed at indoor formaldehyde concentrations >0.04 mg/m^3, and possibly lower (Franklin et al., 2019; Chang et al., 2017; Amiri and Turner-Henson, 2017).

Further research is needed to determine if the increased spontaneous abortion risk and decreased fecundity in occupationally exposed women is due to toxicity to the reproductive system or to the developing fetus. Additionally, there is a need for more targeted evaluation of the female reproductive system following inhalation exposure to formaldehyde, including an assessment of female reproductive function, such as would be assessed in a two-generation reproductive study in animals. Further assessment of both female reproductive toxicity and developmental toxicity would benefit from the use of paraformaldehyde instead of formalin to avoid possible confounding exposures to methanol.

Several animal studies raise the possibility that formaldehyde exposure might also cause toxicity to the developing nervous system; however, due to methodological limitations, these data were considered inconclusive (i.e., **evidence suggests**). Three publications from one laboratory (Songur et al., 2003; Sarsilmaz et al., 2007; Aslan et al., 2006) reported changes in brain structure and neuron numbers following developmental exposure to formaldehyde. However, two of these studies were evaluations of the same animals, and all three studies possessed notable methodological limitations and tested formaldehyde levels >7 mg/m^3, which introduces uncertainties (e.g., differences in toxicokinetics; irritant effects not experienced by humans) in relating these data to the potential for effects in exposed humans. The changes in brain structure and neuron number were not tested using similarly sensitive protocols in adult animals, although less rigorous evaluations failed to observe effects, highlighting additional data gaps. Only *low* confidence studies evaluated other potential neurodevelopmental effects (i.e., the evidence is *indeterminate*).

Children

Lungs in children are underdeveloped at birth and are not fully functional until about 6 to 8 years of age (Bateson and Schwartz, 2008); therefore, children may be more susceptible to the respiratory effects of formaldehyde, compared to adults. In addition, formaldehyde exposure has been associated with airway inflammation (see Section 3.2.3), which could have a greater impact on children's airways because they are narrower than adult airways (OEHHA, 2003). This is supported by studies of other chemicals suggesting that human sensitivity to sensory irritation may also be dependent on age (Shusterman, 2007; Hummel et al., 2003). The distribution of inhaled formaldehyde may be different for children compared with adults as well. For example, population variability in distribution is influenced by differences in physical characteristics of the URT, breathing patterns (e.g., oral versus nasal), and ventilation rate. However, studies suggest that extrathoracic absorption of highly reactive and soluble gases, such as formaldehyde, is similar between children and adults (Ginsberg et al., 2005; Ginsberg et al., 2010), as is overall uptake efficiency, average flux, and maximum flux levels over the entire nasal lining (Garcia et al., 2009). Garcia et al. (2009) did find that local flux between the seven individuals (five adults and two children) in his study varied by a factor of three to five, which is important as formaldehyde toxicity is likely to be mediated by its point-of-contact effects along the URT. Because this study only

evaluated seven individuals who had normally shaped nasal cavities, it may not be generalizable to the entire population, including susceptible individuals. Notably, formaldehyde distribution to more distal parts of the airways could be substantial under conditions of higher activity and oral breathing, both of which occur with children.[39]

The expression of formaldehyde metabolizing enzymes may also be different in infants and children. The metabolism of formaldehyde is described in more detail in Appendix C.1. Briefly, expression of glutathione-dependent formaldehyde dehydrogenase, also called alcohol dehydrogenase class III, ADH3, or ADH5, the primary enzyme in formaldehyde metabolism, is developmentally regulated and thus may alter the toxicokinetics of formaldehyde in early life (Reviewed in (Thompson et al., 2009; Hines and McCarver, 2002)). ADH3 is critical to the detoxification of formaldehyde, as it is involved in the pathway leading to formaldehyde's conversion to formate, a metabolite that is excreted from the body. Therefore, if the concentration or activity of ADH3 is reduced, more formaldehyde is likely to remain in the body to react with cellular macromolecules. ADH3 mRNA expression levels are significantly lower in premature neonates and infants up to 5 months old compared with adults. Benedetti et al. (2007) reported that ADH activity reached adult levels by 2.5 to 5 years of age. Thus, neonates and very young children, in particular, may have a decreased ability to metabolize formaldehyde, increasing their susceptibility to formaldehyde toxicity; however, enzyme activity levels for ADH3 specifically, and the potential for alternate metabolic pathways in children, are not known.

Some epidemiological studies have found that children have an increased sensitivity to formaldehyde exposure-induced respiratory effects. One study reported a relationship between increased residential formaldehyde exposure and decreased PEFR (both bedtime and morning) among children exposed to levels averaging 0.032 mg/m^3 (Krzyzanowski et al., 1990). In adults, an association of smaller magnitude was observed, but only among smokers. Krzyzanowski et al. (1990) also reported an increase in the prevalence of physician-diagnosed asthma in children, but not in adults, who lived in homes with formaldehyde levels that were higher than 60 ppb (0.074 mg/m^3). Similarly, a study by Zhai et al. (2013) reported a higher prevalence of current asthma in children compared with adults at the same exposure levels in their homes. Although prevalence of current asthma (i.e., symptoms or use of medications in the past 12 months) does not appear to be increased among adults or children below exposure levels of approximately 0.05 mg/m^3, studies of the exacerbation of asthma symptoms (asthma control) among children suggest their greater susceptibility at lower average formaldehyde concentrations (e.g., 0.04 mg/m^3; (Venn et al., 2003; Dannemiller et al., 2013). Children younger than five years of age also may experience symptoms consistent with lower respiratory infections in association with

[39]For example, in the case of ozone concentrations of 0.1 ppm, a moderately reactive gas, Ginsberg (2008) predicted a five-fold variation in the dose to the deep lung between quiet and heavy breathing conditions for an 8-year-old child.

residential formaldehyde levels lower than those at which older individuals experience these symptoms (Rumchev et al., 2002; Roda et al., 2011).

Children are also likely to be more susceptible than adults to the mutagenic effects of formaldehyde. EPA has concluded that early-life exposure to chemicals that are carcinogenic through a mutagenic MOA might present a higher risk of cancer than exposure during adulthood (U.S. EPA, 2005b). Because formaldehyde-induced carcinogenicity of the URT is attributable, at least in part, to a mutagenic MOA (see Section 3.2.5), it is expected that children are at heightened risk of URT cancers following formaldehyde exposure. In contrast, because it is unknown whether myeloid leukemia resulting from formaldehyde exposure involves a mutagenic MOA, no assumption about increased early-life susceptibility is made for this type of cancer.

Pregnant women

Because pregnant women have increased sensitivity to the development and exacerbation of atopic eczema (Weatherhead et al., 2007; Kar et al., 2012; Cho et al., 2010), it is likely that they also have heightened susceptibility to this form of dermatitis following exposure to formaldehyde. To date, however, no studies are available that specifically evaluate the prevalence of atopic eczema in pregnant women compared to other populations following exposure to formaldehyde. In one study, Matsunaga et al. (2008) found a two-fold higher risk for atopic eczema in pregnant women with formaldehyde exposures of greater than approximately 0.05 mg/m^3 measured in their homes.

Later lifestages

In general, older adults may have greater susceptibility than younger adults to chemical exposures due to slower metabolisms and an increased incidence of altered health status (Ginsberg et al., 2005; Benedetti et al., 2007). One study (Bentayeb et al., 2015) indicated possible differential effects of formaldehyde exposure for elderly adults (>65 years old) compared with other age groups. Bentayeb et al. (2015) observed an elevated risk of decreased pulmonary function in nursing home residents at lower formaldehyde exposure levels than have been seen to cause effects in younger adults.

4.1.2. Health Status and Disease

Preexisting health conditions and diseases may predispose individuals to toxic effects following exposure to formaldehyde. Some epidemiological studies have suggested that asthmatics are more susceptible than nonasthmatics to declines in respiratory function following formaldehyde exposure. Krzyzanowski et al. (1990) found that asthmatic children showed a steeper decline in morning peak expiratory flow rate (PEFR) compared with nonasthmatic children at formaldehyde concentrations below 0.05 mg/m^3. Similarly, a study by Kriebel et al. (1993) reported a greater decrease in peak expiratory flow (PEF) in asthmatic, compared with nonasthmatic, medical students after formaldehyde exposures in an anatomy lab. However, this study (Kriebel et al., 1993) had a small sample size and the effect was not statistically significant.

Studies evaluating effect modification by existing allergies are inconsistent. Acute and short-term studies in two animal species demonstrate that formaldehyde increases responsiveness to allergens and bronchoconstrictors, particularly with prior sensitization, indicating that allergy status may modify an individual's sensitivity to bronchial hyperreactivity and other asthma symptoms due to formaldehyde exposure (Swiecichowski et al., 1993; Riedel et al., 1996; Leikauf, 1992; Larsen et al., 2013). However, studies of associations with eczema, prevalence of asthma or asthma control were inconsistent, reporting either an increased or decreased prevalence among groups with a positive atopy status in adults or children (Venn et al., 2003; Smedje and Norback, 2001; Matsunaga et al., 2008; Annesi-Maesano et al., 2012). The evidence, therefore, is inconclusive and additional research is needed to address the question of potential effect modification by atopy status. Separately, the swelling of the mucus membrane, which has been observed in humans exposed to <1 mg/m^3 formaldehyde (see Section 3.2.4), is expected to be highly influenced by the underlying respiratory status of the exposed individuals, such as allergy status or previous or current respiratory infections. Supporting this assumption, nasal lesions have been found to be more severe in formaldehyde-exposed rodents with prior nasal damage (Woutersen et al., 1989; Appelman et al., 1988), and similar observations have been made in exposed humans (Falk et al., 1994). Therefore, individuals with prior nasal damage might also have heightened subsceptibililty to the development of nasal cancer following formaldehyde exposure.

As discussed in Section 3.1, nasal anatomy and soluble factors in the URT play a major role in the uptake of a highly reactive gas like formaldehyde. There are considerable interindividual variations in nasal anatomy (ICRP, 1994). For example, the nasal volumes of 10 adult nonsmoking subjects between 18 and 50 years of age in a study in the United States varied between 15 and 60 mL (Santiago et al., 2001), and disease states can result in further variation (Singh et al., 1998). Therefore, population variability in the distribution of inhaled formaldehyde, and in the susceptibility to its health effects, could potentially be large.

To date, many other factors related to health, such as obesity, have not been investigated to determine if they affect susceptibility to formaldehyde-related adverse effects.

4.1.3. Sex

Males and females can differ greatly in body composition, organ function, and many other physiological parameters that may influence the toxicokinetics of chemicals and their metabolites in the body (Gochfeld, 2007; Gandhi et al., 2004). The human epidemiology data set does not support many specific sex susceptibilities for noncancer effects due to formaldehyde exposure. However, in general, data suggest that nonpregnant women, on a per kilogram body weight basis, may have slightly lower air intake than men, which would suggest that women may be less susceptible than men to inhaled pollutants like formaldehyde, but this has not been investigated to date.

Similar to age and allergy and respiratory infection status, studies of related chemicals suggest that human sensitivity to sensory irritation may also be dependent on sex (Shusterman, 2007; Hummel et al., 2003). It is likely that women may be more sensitive than men to the eye and URT irritant properties of formaldehyde. For example, a higher prevalence of burning or tearing eyes was observed among women compared to men in a study of residential exposure (Liu et al., 1991).

In contrast, several animal studies suggest that males may be more susceptible than females to histopathological lesions of the URT, although most studies only examined male animals. For example, one study in rats reported that males generally had more severe damage, including metaplasia, to the nasal respiratory and olfactory epithelium and larynx following formaldehyde exposure (Woutersen et al., 1987). Supportive findings of increased incidence or severity of lesions in males as compared to females was also reported in a second study of rats (Zwart et al., 1988), and in mouse studies of (Maronpot et al., 1986; Kerns et al., 1983). Male rats have a higher metabolic rate and oxygen demand than do female rats; therefore, these findings might reflect a greater inhaled dose of formaldehyde in males compared to females at similar exposure concentrations.

It is also concluded that the **evidence indicates** formaldehyde exposure likely causes sex-specific health effects related to reproduction, given sufficient exposure conditions. Specifically, a coherent spectrum of male reproductive effects was observed in experimental animal studies following exposure to high levels of formaldehyde, with supporting evidence in a well-conducted human study. In addition, epidemiological studies identified decreased fecundity and increased spontaneous abortion risk in women occupationally exposed to formaldehyde. This evidence could reflect developmental effects, or changes in the female reproductive system.

4.1.4. Race

Race may be a modifying factor of formaldehyde toxicity, for example, if specific polymorphisms in metabolizing enzymes affecting chemical toxicokinetics are more prevalent in specific races. Additionally, lifestyle factors that modify toxicity may be more or less prevalent in specific races. The only study to evaluate the potential role of race in carcinogenicity (Hayes et al., 1990) found significantly increased death rates from nasopharyngeal cancer and multiple myeloma in nonwhite embalmers and funeral directors; whereas no changes in death rates from nasopharyngeal cancer or in cases of multiple myeloma were found in white embalmers and funeral directors. Very few other studies have explored the role of race in formaldehyde susceptibility, preventing the interpretation and generalizability of this observation.

A more detailed description of the role of polymorphisms in susceptibility is provided below. Additional research is needed to confirm the findings in Hayes et al. (1990).

4.1.5. Genetic Polymorphisms

Genetic polymorphisms may affect the expression level of genes and resulting activity of important metabolizing enzymes, and this may lead to differential toxicity following chemical exposures. As discussed in Appendix C.1, the primary metabolizing enzyme of formaldehyde is ADH3 (referred to as ADH5 in recent papers). A secondary pathway involves mitochondrial aldehyde dehydrogenase 2 (ALDH2). Both ADH3 and ALDH2 are important in the detoxification of formaldehyde, converting it to formate, which is readily excreted from the body. ADH3 is also known to catalyze the NADP-dependent reduction of the endogenous nitrosylating agent S-nitrosoglutathione (GSNO) and, in this capacity, is referred to as S-nitrosoglutathione reductase (GSNOR) (Jensen et al., 1998). GSNOR participates in the oxidation of retinol and long-chain primary alcohols. It also contributes to nitric oxide (NO) signaling through its role in metabolizing GSNO an endogenous bronchodilator and reservoir of NO (Staab et al., 2008; Jensen et al., 1998; Hess et al., 2005), indicating ADH3's involvement in bronchial tone allergen-induced hyperresponsiveness (Que et al., 2005; Hess et al., 2005; Gerard, 2005).

Wu et al. (2007) found that carrying one or two copies of the minor allele rs1154404 for a single nucleotide polymorphism (SNP) of *ADH3* resulted in a decreased risk of asthma in Mexican children. For a different SNP (rs28730619), homozygotes for the minor allele had an increased risk of asthma. Although only speculative as their functional characteristics are unknown, these SNPs may affect the response of individuals to formaldehyde exposure by altering their metabolism. One study (Hedberg et al., 2001) identified four polymorphisms in the human *ADH3* gene promoter that resulted in reduced transcriptional activity. Because this would likely result in reduced levels of the ADH3 protein, individuals with this polymorphism may be at greater risk for formaldehyde toxicity compared with people with the wild-type gene. This is supported by a study in which deletion of the *ADH3* gene increased the sensitivity of mice to formaldehyde toxicity (Deltour et al., 1999).

Some studies have also suggested that CNS toxicity can result from reduced activity of the metabolizing enzymes responsible for clearing formaldehyde from relevant tissues (e.g., downregulated ALDH2 in Tan et al. (2018)). Therefore, it is plausible that individuals with polymorphisms in *ALDH2* or in other genes encoding detoxifying enzymes may be more susceptible to CNS toxicity caused by formaldehyde exposure compared to those with wild type alleles. This highlights another area of interest for future studies on potential susceptibility to inhaled formaldehyde exposure.

A few studies of genotoxicity among formaldehyde-exposed groups evaluated differences in response based on polymorphisms in genes coding for proteins involved in the metabolism of xenobiotics, including *CYP2E1*, glutathione-S-transferases (*GST*s), and *ADH3*. The X-ray repair cross-complementing gene 3 (*XRCC3*), which codes for a protein involved in DNA repair and chromosome stabilization, also was evaluated (Santovito et al., 2011; Ladeira et al., 2013; Jiang et al., 2010; Costa et al., 2015). The results of these studies were inconsistent and no conclusions regarding the impact

of these genetic polymorphisms on susceptibility can be drawn. (e.g., (Shen et al., 2016; Rager et al., 2014))

Studies of mice with knocked out *Aldh2* and *Aldh5*, which encode for enzymes that remove endogenous formaldehyde, have suggested that polymorphisms in *Aldh2* and *Aldh5*, may increase susceptibility to genotoxicity. These knockouts resulted in severely disrupted hematopoiesis and leukemia, including mutated and abnormal HSPCs, which is presumably linked to increased accumulation of endogenous formaldehyde (Pontel et al., 2015; Dingler et al., 2020; Burgos-Barragan et al., 2017b). Likewise, direct treatment of *Aldh5-/-* bone marrow cells with formaldehdye caused genotoxicity and reduced HSPC formation, effects which are further exacerbated by loss of *Fancd2* (this latter deficiency is associated with increased sensitivity to DNA damage) (García-Calderón et al., 2018; Burgos-Barragan et al., 2017b). As reviewed and tested by Dingler et al. (2020), genetic deficiencies in these Aldh family genes have been linked to bone marrow failure and related diseases in humans, including in children. Reduced ALDH2 or ALDH5 activity resulting in increased endogenous formaldehyde in mice and humans might also contribute to postnatal lethality, stunted growth, cognitive effects (see Section 1.3.1) and various cancers arising from DNA damage or deficient repair (Nakamura et al., 2020; Dingler et al., 2020). While formaldehyde inhalation does not seem to cause appreciable changes in formaldehyde levels in nonrespiratory regions (see Appendix C.1), HSPCs expressing these enzymes are known to exist in many tissues. However, no studies in any species have specifically examined these possible linkages in relation to inhaled formaldehyde. Therefore, while genetic differences may alter susceptibility to the cytogenetic effects of formaldehyde, more definitive research is needed. A few in vitro studies have suggested that epigenetic changes or loss of function of important genes might increase susceptibility to formaldehyde toxicity (e.g., (Shen et al., 2016; Rager et al., 2014)). However, additional studies are needed to clarify these preliminary observations.

4.1.6. Lifestyle Factors

Lifestyle factors may increase or decrease exposure to formaldehyde and may also affect the resulting health effects following formaldehyde exposure. These lifestyle factors may vary by race, ethnicity, socio-economic status, or geographic location. To date, specific studies do not exist to address the role of lifestyle factors on formaldehyde toxicity.

Nutritional status

Because formaldehyde appears to cause inflammation, particularly in the airways, it is plausible that a diet rich in antioxidants would protect against inflammation and one that lacks sufficient antioxidants would result in greater inflammation. Additional research is needed to specifically evaluate possible modification of formaldehyde toxicity by nutritional status.

Smoking

Smoking is considered a lifestyle factor, but it also introduces coexposures to the many chemicals in cigarette smoke, including additional formaldehyde. Thus, it is difficult to disentangle potential indirect contributions of smoking to the health effects of formaldehyde exposure from the possible direct effects of the formaldehyde in tobacco smoke (see additional discussion below under "coexposures").

Exercise

The possibility that more extensive distribution of formaldehyde (e.g., to the LRT) may occur when people are breathing through the mouth during exercise has not been investigated. However, some controlled human exposure studies observed pulmonary function deficits when a longer exercise component (15 minutes) was included that were not observed by other studies with shorter periods or no exercise (Green et al., 1987; Green et al., 1989), and another study observed an increase in bronchial hyperresponsiveness with an exposure protocol using nose clips necessitating mouth-only breathing (Casset et al., 2006). Clearly, further research is warranted to understand the role of exercise in formaldehyde susceptibility.

4.1.7. Coexposures

Coexposures to other pollutants, such as those that produce similar metabolites and health effects to formaldehyde and those that are mutagens, may exacerbate the effects of formaldehyde exposure. In addition, constituents in the diet, such as methanol and caffeine, contribute to the generation of endogenous formaldehyde in nonrespiratory tissues (Summers et al., 2012; Riess et al., 2010; Hohnloser et al., 1980), which are promptly detoxified (Burgos-Barragan et al., 2017a). Yet, it is not expected that variation in endogenous formaldehyde levels at sites distal to the URT would affect relative sensitivity to the effects of inhaled formaldehyde. These findings are inconclusive, however, so additional research is needed to investigate the role of these coexposures.

As described in Section 3.2.3, tobacco smoke may increase the incidence of hypersensitivity responses in formaldehyde-exposed individuals. Effect modification by environmental tobacco smoke (i.e., stronger associations, or associations seen at lower formaldehyde exposures, with this coexposure) were reported in two studies that examined asthma prevalence stratified by environmental tobacco smoke exposure among children and adults (nonsmokers) (Palczynski et al., 1999; Krzyzanowski et al., 1990). Additional studies are needed to establish if this interaction is seen only in children, in adults and children, or in neither group. One residential study by Krzyzanowski et al. (1990) indicated that smokers experienced a greater decline in morning PEFR compared to nonsmokers at formaldehyde concentrations above 0.050 mg/m^3. Smokers were not more responsive to formaldehyde exposures in most occupational studies that stratified by smoking behavior. Nonsmokers experienced 2- to 3.5-fold larger annual decreases in FEV_1, FEV_1/FVC, and FEF_{25-75} over 5 years (Alexandersson and Hedenstierna, 1989), as well as larger declines during a work shift (Alexandersson et al., 1982; Alexandersson and Hedenstierna, 1989).

In contrast, current smokers had an approximately two-fold larger OR for airway obstruction, defined as an FEV_1/FVC <75%, compared with nonsmokers (Herbert et al., 1994). The magnitude of the difference associated with formaldehyde exposure may have reflected the existing difference in baseline pulmonary function values between smokers and nonsmokers.

Although not a chemical coexposure, humidity also appears to modify the effects of formaldehyde exposure. For example, formaldehyde exposure-induced bronchoconstriction in mice housed only in humid, but not dry, environments indicating that the bronchoconstrictive effects of formaldehyde may be impacted by humidity (Larsen et al., 2013). The effects of formaldehyde on mucus flow patterns also appear to vary based on humidity.

In addition, it is possible that exposure to nonchemical stressors, such as poverty, violence, and other social factors, might make some populations more susceptible to formaldehyde-related health effects. However, at this time, studies evaluating the contribution of nonchemical stressors to formaldehyde susceptibility have not been published.

Additional research is needed to investigate whether coexposures to pollutants other than tobacco smoke and to nonchemical stressors confer additional susceptibility to formaldehyde toxicity.

4.1.8. Summary of Susceptible Populations and Lifestages

Epidemiological and toxicological studies identify reproductive or developmental toxicity as a human health hazard of formaldehyde exposure. At this time, it is not clear whether increased time-to-pregnancy (TTP) and spontaneous abortion rates seen in occupationally exposed women are due to reproductive system toxicity or to toxicity to the developing fetus.

Children also appear to be a susceptible population. Studies have indicated that they have an increased sensitivity to respiratory and immunological effects following formaldehyde exposure. In addition, younger age is likely to be associated with a higher risk of mutagenic effects and, therefore, to a higher risk of URT cancers. As age may be a modifying factor of the sensory irritant properties of formaldehyde, both children and the elderly may be at an either increased or decreased risk for sensory irritation.

Health status and disease are likely to be modifying factors of formaldehyde toxicity as well. Studies suggest that asthmatics are more susceptible than nonasthmatics to declines in respiratory function following formaldehyde exposure. Whether atopy and allergies can also influence the health effects of formaldehyde exposure remains to be determined; additional studies are needed to confirm this relationship. Individuals with prior nasal damage might also have heightened susceptibility to the development of nasal cancer following formaldehyde exposure.

Study findings on the role of genetic susceptibility in formaldehyde toxicity are inconclusive. Therefore, gene-environment interaction studies are needed to investigate the effects of polymorphisms in genes that encode formaldehyde metabolizing enzymes, as well as receptors (e.g., TRPA1) or other proteins that appear to be key components of the MOA for certain human health effects of formaldehyde exposure.

Coexposures appear to increase susceptibility to health effects following formaldehyde exposure as well. There is some evidence that cigarette smoking increases sensitivity to formaldehyde toxicity; however, it is not clear if this increased sensitivity is due to the additional formaldehyde to which smokers are exposed, to exposures to other chemicals that are present in cigarette smoke, or to compromised respiratory systems.

Although other factors are hypothesized to confer increased susceptibility to formaldehyde toxicity, the available data are limited. Overall, the most extensive research on the health effects of inhaled formaldehyde and susceptible groups indicates a greater susceptibility among children to respiratory disease, manifested as reduced pulmonary function, increased prevalence of current asthma, and greater asthma severity (reduced asthma control). More research is needed to investigate the role of sex, race, nutrition, exercise, and other coexposures that may modulate susceptibility to formaldehyde toxicity. In addition, these susceptibility factors might interact with one another. For example, lifestage, pre-existing health conditions, genetic polymorphisms and co-exposures to both chemical and nonchemical stressors could all contribute to heightened susceptibility to formaldehyde toxicity for some individuals.

4.1.9. Summary of Vulnerable Population

Groups that may receive disproportionally high levels of exposure to formaldehyde, and therefore might experience more frequent or severe formaldehyde-related health consequences, include people in occupations with workplace exposures. Some industries with the greatest potential for exposure include health services, business services, printing and publishing, chemical manufacturing, garment production, beauty salons, and furniture manufacturing (IARC, 1995). People who spend a significant amount of time in mobile homes and trailers, either as primary residences, classrooms, job sites or for other reasons, might also be vulnerable because these structures can have high formaldehyde levels (Murphy et al., 2013). Lastly, in addition to the potential of cigarette smoking to increase susceptibility to formaldehyde, it also can increase exposure to it (Fishbein, 1992). It should be noted that individuals who are both susceptible and highly exposed to formaldehyde are at the highest risk of suffering from formaldehyde-related health effects.

4.2. SUMMARY OF CONCLUSIONS FOR NONCANCER EFFECTS

Overall, the **evidence demonstrates** that inhalation of formaldehyde causes sensory irritation and respiratory pathology in humans, given sufficient exposure conditions, based on studies of the general population with residential exposure, controlled human exposure studies, and occupational studies. The **evidence indicates** that inhalation of formaldehyde likely causes decrements in pulmonary function, and an increased frequency of current asthma symptoms and allergic responses, given sufficient exposure conditions, based on studies of adults and children exposed in their homes or at school. In addition, the **evidence indicates** that inhalation of

formaldehyde likely causes female reproductive or developmental toxicity, and reproductive toxicity in males, given sufficient exposure conditions, based on studies involving residential and occupational exposure and toxicological studies. Lastly, while a number of studies reporting evidence of potential neurotoxic effects were available, including developmental neurotoxicity, multiple manifestations of behavioral toxicity, and an increased incidence of, or mortality from, the motor neuron disease, amyotrophic lateral sclerosis (ALS), due to limitations identified in the database (e.g., poor methodology; lack of consistency), the evidence integration analyses for these outcomes determined that the **evidence suggests**, but is not sufficient to infer, a human health hazard(s). The data on potential nervous system effects were considered insufficient for developing quantitative estimates of risk. Context on these decisions is provided below:

- Sensory Irritation:
    - The **evidence demonstrates** that inhalation of formaldehyde causes sensory irritation in humans, given sufficient exposure conditions, based on *robust* human evidence from controlled human exposure studies testing responses to concentrations 0.1 mg/m^3 and above and observational epidemiology studies of residential populations with mean formaldehyde concentrations >0.05 mg/m^3 (range of 0.01 to approximately 1.0 mg/m^3), *robust* evidence for an effect in animals (this phenomenon is well described and accepted across a range of experimental species), as well as an established MOA based on mechanistic evidence in animals (the identified MOA is interpreted to be operant in humans). The irritant response occurs within minutes to hours depending on concentration, and severity is concentration dependent. Potentially large variations in sensitivity are expected, depending primarily on differences in nasal health (including allergy or inflammatory status) and physiology.
- Pulmonary Function:
    - The **evidence indicates** that long-term (chronic) inhalation of formaldehyde likely causes decrements in pulmonary function, given sufficient exposure conditions, based on *moderate* human evidence primarily from observational epidemiology studies among occupational cohorts with long-term exposure to >0.2 mg/m^3 and a study of children and adults with residential exposure (mean, 0.03 mg/m^3, maximum 0.17 mg/m^3), as well as *slight* evidence for an effect in animals involving inflammatory airway changes in mechanistic studies (it is expected that related mechanistic changes can occur in exposed humans, and some indirect confirmatory evidence from exposed humans exists).
- Respiratory Tract Pathology:
    - The **evidence demonstrates** that inhalation of formaldehyde causes increased respiratory tract pathology in humans, including hyperplasia and squamous metaplasia, given sufficient exposure conditions, based on *robust* evidence from animal studies involving multiple species with increases in severity and frequency of lesions with increasing concentration or longer exposure duration. The primary support for this conclusion is based on rat bioassays of chronic exposure which

consistently observed squamous metaplasia at formaldehyde exposure levels ≥2.5 mg/m^3. There is *moderate* human evidence from occupational epidemiology studies supported by more limited findings in mechanistic studies of exposed humans, and strong support for a plausible MOA based largely on mechanistic evidence in animals (supported by coherent findings in human studies). Variation in sensitivity may depend on differences in URT immunity and nasal structure or past injury, but few studies exist that specifically evaluate these possibilities.

- Immune-mediated Conditions, including Allergies and Asthma:

    - The **evidence indicates** that inhalation of formaldehyde likely causes increases in the prevalence of allergic conditions in humans**,** given sufficient exposure conditions, based on *moderate* evidence of an enhanced immune hypersensitivity response to allergens (i.e., allergic rhinitis or rhinoconjunctivitis; eczema) in general population studies of adults and children at average exposures between 0.04 and <0.1 mg/m^3 formaldehyde, and *slight* evidence of effects relevant to immune-mediated respiratory conditions in animals from mechanistic studies of airway hyperresponsiveness and some more limited data relevant to systemic inflammatory changes in both human and animal mechanistic studies; however, the proposed, incomplete MOA(s) are not established and have not been experimentally verified.

    - The **evidence indicates** that inhalation of formaldehyde also likely causes increases in the prevalence of asthma symptoms in humans, given sufficient exposure conditions, based on *moderate* evidence of an increased risk of prevalent current asthma in occupational settings (>0.1 mg/m^3) and population studies in adults and children, or poor asthma control in children at exposures above 0.05 mg/m^3 formaldehyde and *slight* evidence for effects in animals from mechanistic studies; however, an MOA explaining this association is not available. Specifically, regarding the animal evidence, although several events typically associated with asthma are not well supported by the available data, the animal mechanistic data support that formaldehyde inhalation induces bronchoconstriction with and without allergen sensitization and stimulates a number of immunological and neurological processes that would be expected to augment or drive asthmatic responses. Variation in sensitivity is anticipated depending on respiratory health, age, and exposure to tobacco smoke.

- Developmental and Reproductive Toxicity:

    - The **evidence indicates** that inhalation of formaldehyde likely causes developmental or female reproductive toxicity in humans given sufficient exposure conditions, based on *moderate* evidence in observational studies finding effects on fetal growth among pregnancy cohorts observed at indoor formaldehyde concentrations >0.04 mg/m^3, and possibly lower, as well as increases in TTP and spontaneous abortion risk among occupationally exposed women (average formaldehyde concentrations >0.1 mg/m^3); the evidence in animals is *indeterminate*, and a plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde is lacking.

- The **evidence indicates** that inhalation of formaldehyde also likely causes reproductive toxicity in men, given sufficient exposure conditions, based on *robust* evidence in animals that presents a coherent array of adverse effects in two species, and *slight* evidence from observational studies of occupational exposure. Uncertainties include a lack of well-conducted animal studies testing formaldehyde exposure levels below 6 mg/m^3 and no plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde; however, some support for indirect effects in rodents is provided by relevant mechanistic changes in male reproductive organs.

- Nervous System Effects

  - The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause an increase in incidence or mortality from the motor neuron disease, ALS, given sufficient exposure conditions, based on *slight* epidemiological evidence. No relevant animal studies (i.e., *indeterminate* evidence) or mechanistic information were identified, and additional studies are warranted.

  - Likewise, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause increases in multiple manifestations of neurobehavioral toxicity, given sufficient exposure conditions, based primarily on *slight* evidence of effects in animals of two species across several behavioral domains (i.e., neural sensitization; tests of learning and memory; and tests of motor-related behaviors), and supported by *slight* evidence in human observational and controlled exposure studies. An experimentally verified MOA explaining such effects without systemic distribution of formaldehyde is lacking; however, some mechanistic findings support the potential for indirect effects on relevant brain regions. Well-conducted studies of these potential effects are currently unavailable.

  - The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause developmental neurotoxicity, given sufficient exposure conditions, based on *slight* evidence in animals for neuropathology and potentially supportive mechanistic findings in relevant brain regions. However, as neither an experimentally verified MOA nor relevant studies in children were identified, this is an area in need of further research.

4.3. SUMMARY OF CONCLUSIONS FOR CANCER

"Formaldehyde Is Carcinogenic to Humans by the Inhalation Route of Exposure"[40]

[40]Although not influential to the independent evaluation in this assessment, the hazard conclusion for cancer is consistent with those drawn by other expert review panels (see Appendix G). Formaldehyde was classified as a known carcinogen by the (NTP, 2011) and a Group 1 carcinogen by (IARC, 2006, 2012), both based on evidence for nasal cancers in humans and animals and myeloid leukemia in humans. For nasal cancers, these classifications were also supported by mechanistic evidence sufficient to identify genotoxicity as contributing to cancer development independent of cellular damage and proliferation. In addition, an expert committee convened by the NAS NRC confirmed the conclusions of the NTP 12th RoC and conducted an independent review of the literature through 2013, concluding that formaldehyde is a known carcinogen. The European Union and Health Canada concluded that formaldehyde is a genotoxic carcinogen with a cytotoxic MOA based on nasal cancer evidence (SCOEL, 2017; Health Canada, 2001, 2006; ECHA, 2012).

Several lines of evidence support this conclusion. Specifically, the hazard descriptor ***carcinogenic to humans*** is independently substantiated by three lines of evidence, namely evidence integration judgments that the **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer, sinonasal cancer and, myeloid leukemia, in exposed humans.

These overall confidence conclusions, as well as the strength of the human and animal evidence (i.e., *robust, moderate, slight, indeterminate*), were based on the currently available evidence using the approaches described in the description of methods in Section 2 of this report, which included a consideration of mechanistic evidence when drawing each conclusion. Note that, as the site-specific relationship of the animal data to the specific human cancer types involved additional considerations, the inference regarding the relevance of the animal data to each specific human cancer is presented herein as a component of the animal evidence judgments.

Conclusion: Carcinogenic to Humans

Three separate evidence integration judgments independently substantiate this conclusion:

- Nasopharyngeal cancer—The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer (NPC) in humans. This is based primarily on observations of increased risk of NPC in groups exposed to occupational formaldehyde levels and nasal cancers in mice and several strains of rats, with strong, reliable, and consistent mechanistic evidence in both animals and humans (i.e., *robust* evidence for both the human and animal evidence, and strong mechanistic support for the human relevance of the animal data). The nasopharynx, although not typically specified in animal studies, is the region adjacent to the nasal cavity, where the animal evidence was predominantly observed (thus, the animal evidence is judged as *robust*). In addition, the evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced nasopharyngeal carcinogenicity.

- Sinonasal cancer—The **evidence demonstrates** that formaldehyde inhalation causes sinonasal cancer (SNC) in humans. This is based primarily on observations of increased risk of SNC in groups exposed to occupational formaldehyde levels (i.e., *robust* human evidence) and supported by apical and mechanistic evidence for nasal cancers across multiple animal species. Some uncertainties remain in the interpretation of the animal nasal cavity data as wholly applicable to interpreting human sinonasal cancer (thus, the animal evidence is judged as *moderate*). While uncertainties remain, the evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced sinonasal carcinogenicity.

- Myeloid leukemia—The **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans. This is based primarily on *robust* human evidence of an increased risk of the occurrence of myeloid leukemia in epidemiological studies among different populations exposed to occupational formaldehyde levels representing diverse exposure settings. The findings from the occupational cohorts are further supported by other studies of human occupational exposure providing strong and coherent mechanistic evidence that formaldehyde exposure is associated with the detection of additional endpoints relevant to LHP cancers, including an increased prevalence of multiple markers of genotoxicity in peripheral blood and myeloid progenitors. Indirect support is also

provided by evidence of other systemic health effects (e.g., reproductive or developmental toxicity) and mechanistic evidence indicating changes in immune cell populations and markers of inflammation (e.g., oxidative stress) in the peripheral blood of exposed humans and animals, although the exact pattern of immune-related changes across studies and species was difficult to interpret. Notably, leukemia has not been observed in the two available rodent bioassays of chronic exposure, including one testing both sexes of rats and mice, and the evidence for genotoxicity in the peripheral tissues of exposed rodents is weak, providing *indeterminate* evidence of LHP cancers in animals. Taken together, it appears that mechanisms yet to be elucidated that do not involve direct interactions of formaldehyde in the bone marrow need to be considered, and that either the mechanistic pathways stimulated by formaldehyde are different in animals or that the existing animal models tested thus far do not characterize the disease process in humans for these cancers. The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown.

The remaining evidence relevant to evaluating the potential for formaldehyde inhalation to cause cancer did not contribute to the overall hazard conclusion above, including formal evaluations of the following cancer types:

- Oropharyngeal/hypopharyngeal cancer—The available **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause oropharyngeal/ hypopharyngeal cancer in humans. This is based primarily on *slight* human evidence from epidemiological findings and potentially relevant mechanistic changes (e.g., in buccal cells) and supporting *slight* animal evidence of preneoplastic lesions and mechanistic changes. While cancer site concordance is not required for hazard determination (U.S. EPA, 2005a), given the known reactivity and distribution of inhaled formaldehyde, a lesser level of confidence in the applicability of the animal nasal findings is inferred for this cancer type as compared to NPC or SNC and the evidence overall is not interpreted to provide reasonable support for a MOA.

- Multiple myeloma—The available **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple myeloma. This is primarily based on *slight* human evidence from epidemiological findings. The animal evidence is *indeterminate*, and the available mechanistic information was not interpreted to be influential, indicating a need for additional study.

- Hodgkin lymphoma— The available **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause Hodgkin lymphoma. This is primarily based on *slight* human evidence from epidemiological findings. The animal evidence is *indeterminate*, and the available mechanistic information was not interpreted to be influential, indicating a need for additional study.

- Laryngeal cancer— All the evidence related to laryngeal cancer was judged as *indeterminate*; thus, the **evidence** was **inadequate** to determine whether formaldehyde inhalation exposure may be capable of causing this cancer type.

- Lymphatic leukemia—All the evidence related to lymphatic leukemia was judged as *indeterminate*; thus, the **evidence** was **inadequate** to determine whether formaldehyde inhalation exposure may be capable of causing this cancer type.

5. DERIVATION OF TOXICITY VALUES

5.1. INHALATION REFERENCE CONCENTRATION FOR EFFECTS OTHER THAN CANCER

This section describes analyses that better characterize the "sufficient exposure conditions" necessary for formaldehyde inhalation exposure to cause the identified noncancer human health hazards (see Sections 3.2.1 to 3.2.4 and 3.3.1 to 3.3.2, as summarized in Section 4.2), culminating in selection of a reference concentration (RfC). The RfC (expressed in units of mg/m^3) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or the 95% (typically) lower bound on the benchmark concentration (BMCL), with uncertainty factors (UFs) generally applied to reflect limitations of the data used. The approach for deriving an overall RfC involves the following steps, specific methods and considerations which are outlined within each of the subsequent sections:

1) Identify studies and endpoints for each health effect that are sufficient (i.e., with one of the two strongest evidence integration judgments for hazard, namely of **evidence demonstrates** or **evidence indicates,** and *high* or *medium* confidence in the study methods and results, as well as data considered to be most amenable for dose-response analysis to represent the identified hazards)

2) Calculate points of departure (PODs) from the studies

3) Derive candidate RfCs (cRfCs) by applying UFs to the PODs

4) Select organ- or system-specific RfCs (osRfCs) based on the cRfCs

5) Select an overall RfC based on the osRfCs

Candidate RfCs (cRfCs) were derived from studies supporting several health hazards, including sensory irritation (eye irritation symptoms), pulmonary function (peak expiratory flow rate), allergies (rhinoconjunctivitis, atopic eczema), current asthma (i.e., symptoms or medication in the previous 12 months), degree of asthma control, respiratory tract pathology (squamous metaplasia), developmental toxicity (delayed time to pregnancy), and male reproductive toxicity (testes weight, serum testosterone). Based on the hazard synthesis conclusions (see Section 3), for many health effects, specific endpoints were prioritized for use in dose-response evaluation (e.g., squamous metaplasia rather than hyperplasia for respiratory tract pathology). The cRfCs for

sensory irritation, pulmonary function, immune effects including allergies and current asthma, and female and developmental toxicity were derived using data from human epidemiology and controlled exposure studies, while the cRfCs for respiratory tract pathology and male reproductive toxicity were derived using data from experimental animals. cRfCs were not derived for nervous system effects, as the available evidence was deemed to be too uncertain, and thus insufficient, to support quantitative dose-response assessment. In this case, the primary sources of uncertainty in the data included study-specific methodological limitations[41] and a lack of reproducibility across well-conducted studies within the databases for the individual outcomes evaluated.

As documented in Section 5.1.1, the studies considered to be most applicable to formaldehyde exposure settings in the general population were preferred for use in dose-response analyses. The strengths and limitations of the available studies (i.e., for use in dose-response, as documented in Section 5.1.1) were considered alongside uncertainties in deriving PODs for the studies which were advanced (see Section 5.1.2) to determine a level of confidence in each derived cRfC (Section 5.1.3). This level of confidence in the cRfCs was incorporated into the derivation of the organ- or system- specific RfCs (osRfCs; see Section 5.1.4). An overall RfC for formaldehyde of 0.007 mg/m^3 was selected. This value is the midpoint of the three osRfCs with the highest confidence and least uncertainty (0.006, 0.007, and 0.008 mg/m^3) representing a group of respiratory system-related hazards (i.e., pulmonary function, allergy-related conditions, and current asthma prevalence or degree of control). The RfC is interpreted with *high confidence*. Uncertainties in the RfC are discussed with the rationale for the RfC selection in Section 5.1.5.

While the RfC is interpreted to be a concentration associated with negligible risk over a lifetime of exposure, a few of the hazards or outcomes for which cRfCs are derived, including sensory irritation symptoms and the degree of asthma control, could be relevant to a shorter exposure time-frame. The applicability of such cRfCs to shorter exposure periods is noted for the relevant hazards.

5.1.1. Choice of Studies

Data sufficient to support dose-response analyses were available for all of the health systems for which the integration of all the evidence resulted in judgments of **evidence demonstrates** or **evidence indicates** that inhalation of formaldehyde can cause adverse human health effects. Rationales for study selection are detailed in this section using tables within each health effect-specific section that apply the criteria from Section 2.7 to the available *high* or *medium* confidence studies to identify those amenable to dose-response analysis and select those most appropriate for use in POD derivation (Section 5.1.2), with an explanatory rationale.

[41]For example, the reported formaldehyde exposure data in epidemiology studies demonstrating associations were generally not amenable to use in quantitative dose-response analysis. In the available animal studies, there were prominent methodological limitations including poor exposure quality; an inability to rule out nonspecific effects due to irritant or odorant responses, or due to conditions unlikely to be relevant to human exposure scenarios; and deficiencies in the reporting of quantitative results important to quantitative analyses (e.g., litter information).

Methods of Analysis

From among the body of evidence used for the hazard identification assessment, selection of the studies for dose-response assessment used information from the study confidence evaluations, with particular emphasis on conclusions regarding the characteristics of the study population and the accuracy of formaldehyde exposure, the severity of the observed effects, and the exposure levels analyzed. Section 2.7 outlines the specific considerations for selecting studies for dose-response analysis. The application of these considerations and the rationale for selecting specific studies over others is outlined in tables within each health effect-specific section below. Generally, human studies were preferred over laboratory animal studies if quantitative measures of exposure were analyzed in relation to health endpoints. Epidemiological studies that evaluated groups most representative of the general population (i.e., residential or school-based study populations) were preferred if exposure-response analyses were presented. These criteria emphasize the use of *high* or *medium* confidence studies with appropriate study designs, complete reporting of results, and results that would not be reasonably explained by selection bias or information bias or altered by adjustment for confounding. Studies with risk estimates for multiple exposure levels or regression coefficients per unit of formaldehyde concentration were preferred because they provided information about the concentration-response trend. The presence of an exposure-response gradient and analyses of data at lower exposure levels were considered.

If there were no adequate studies of human exposure for exposure-response analysis, then studies of experimental animals were evaluated. Using similar criteria as described for human studies (above), the overall quality of the experimental animal studies was considered (e.g., preference was given to studies with less likelihood of bias, confounding, etc.). As described in Section 2.7 and as documented in each health effect-specific section below, experimental animal studies were generally preferred if they were from models that respond most like humans; tested the effects of formaldehyde inhalation exposure using paraformaldehyde as the test article; were of longer exposure duration and follow-up, evaluated across multiple exposure levels; and were adequately powered to detect effects at lower exposure levels.

Sensory Irritation

The effects of formaldehyde on sensory irritation are understood to occur as a result of direct interactions of formaldehyde with cellular macromolecules leading directly or indirectly to stimulation of trigeminal nerve endings; branches of the trigeminal nerve responsible for chemosensation innervate the oral, ocular, and nasal cavities. However, the most notable and well-studied of these is activation within the nasal mucosa (i.e., in the respiratory epithelium) and stimulation in the oral cavity is unlikely to lead to eye irritation or similar symptoms. Such stimulation results in the rapid detection of a burning sensation (see Section 3.2.1). It is not clear if desensitization occurs over time or the concentrations or timeframes over which this might occur. Because of the rapid nature of the irritant response generated by inhalation of formaldehyde, the

studies that were considered to be the most informative for derivation of a cRfC were those where the exposure assessment was concurrent with the outcome assessment.

Data from studies in humans involving residential populations with continuous exposure, as well as controlled human exposure studies evaluating acute effects were determined to be pertinent to the derivation of cRfCs. The studies of anatomy students and formaldehyde-exposed workers assessed exposure settings with high formaldehyde concentrations and with frequent peaks. Thus, average formaldehyde concentrations or TWAs, the exposure metrics used by these studies, could not capture the variation inherent in these types of settings. Therefore, the large uncertainty in deriving a POD based on results of studies in these high and variable exposure settings was considered to have been a critical concern and PODs were not derived for these exposure scenarios. After evaluating the available *medium* and *high* confidence studies on sensory irritation for their utility in dose-response analysis (see Table 5-1), four studies (two controlled exposure and two epidemiology studies) were advanced for POD derivation (Liu et al., 1991; Kulle, 1993; Hanrahan et al., 1984; Andersen and Molhave, 1983).

Table 5-1. Studies selected for POD derivation and rationale for decisions to not select specific studies for sensory irritation

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation[a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Residential Studies						
(Zhai et al., 2013) Nose and throat irritation	[n] *Medium* confidence [+] Selection bias and confounding unlikely	N/A	Some concern: [-] Potential information bias (exposure sampling time-frame)	N/A	**Critical concern:** [--] Analyses of formalde-hyde using a dichotomous variable	No POD derived. Critical concern with results utility for POD derivation.
(Liu et al., 1991), Eye irritation prevalence	[n] *Medium* confidence [+] Information bias unlikely [n] Selection bias possible due to low participation rate, but unlikely due to formaldehyde exposure [+] Confounding unlikely	[+] Diverse population	[+] 7-d passive sampling [n] 2 area samples per home [+] Continuous exposure [+] Wide exposure range [+] Lowest indoor exposure level = 0.01 ppm	[n] Self-report [n] Survey not described [+] symptoms were reported for the week during the monitoring period	[+] N = 836 homes [n] Logistic regression (dose-response data can be estimated from results presented graphically) *Some concern*: [-] Model parameters not reported	POD estimated in combination with (Hanrahan et al., 1984), limitations noted.
(Hanrahan et al., 1984),	[n] *Medium* confidence	[+] Diverse population	[+] Method matched NIOSH 3500[f] including	[n] Self-report	[n] N = 61	POD estimated in combination with

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation[a]	**Population or subjects**	**Exposure**	**Outcome measure(s)**	**Result(s) utility**	
Eye irritation prevalence	[+] Selection bias and confounding unlikely	(including teens)	sampling time of 1 hr [n] 2 area samples per home [+] Continuous exposure [+] QC showed no issues [+] Wide exposure range [n] Lowest indoor exposure level = 0.1 ppm	[n] Survey not described	[n] Logistic regression (dose-response data can be estimated from results presented graphically)	(Liu et al., 1991), limitations noted.
			Some concern: [-] Potential information bias (exposure sampling time-frame)	*Some concern*: [-] Symptoms recalled for any time in residence: sampling time-frame does not match outcome ascertainment time-frame	*Some concern*: [-] Model parameters not reported	
(Olsen and Dossing, 1982) Eye, nose, and throat irritation	[n] *Medium* confidence [+] Selection bias and confounding unlikely	N/A	*Some concern*: [-] Potential information bias (exposure sampling time-frame)	N/A	**Critical concern:** [--] Compared symptoms in exposed to referent group	No POD derived. Critical concern with results utility for POD derivation
Controlled Exposure Studies						
(Mueller et al., 2013)[b], Eye irritation scaled score, nasal flow, blinking frequency, conjunctival redness, tear film break-up time	[+] *High* confidence [+] Selection bias and confounding unlikely [+] Good exposure quality	*Some concern*: [-] Healthy volunteers only	[n] Acute exposure appropriate for endpoint [+] Lowest indoor exposure level = 0.01 ppm	[+] Self-report plus objective measures	[n] N = 41	No POD derived. Data less sensitive or not dose-dependent, in addition to some concerns with the population and outcome measures. No dose-response trend was observed and difficult to determine adversity cutoff. Less preferred exposure metric.
			Some concern: [-] Exposure protocol less relevant to RfC derivation (included peak concentrations over a	*Some concern*: [-] Large interindividual variability and difficult to	*Some concern*: [-] Within person comparisons with correlated responses	

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation[a]	**Population or subjects**	**Exposure**	**Outcome measure(s)**	**Result(s) utility**	
			continuous background)	determine adversity cutoff	across dose levels [-] Dose-response trend not observed [-] Several effects null or not significant	Studies with more robust analyses available.
Berglund et al. (2012), detection of odor and nasal irritation	[+] *Medium* confidence [+] Selection bias and confounding unlikely [+] Good exposure quality	*Some concern*: [-] Healthy volunteers	[n] Acute exposure appropriate for endpoint *Some concern*: [-] Exposure protocol less relevant to RfC derivation (series of 3 second sniffs)	*Some concern*: [-] Large interindividual variability in detections at same concentration. [-] Difficult to interpret the measure (% of presentations with correct detection) to define adversity cutoff.	[n] N = 31	No POD derived. Difficult to interpret the measure used, in addition to some concerns with the population and outcome measures. Studies with more robust analyses available.
(Lang et al., 2008)[b], Eye irritation score, blinking frequency, conjunctival redness	[+] *High* confidence [+] Selection bias and confounding unlikely [n] Adequate exposure quality	*Some concern:* [-] Healthy volunteers	[n] Acute exposure appropriate for endpoint [n] "Quasi-static" chamber (dynamic chamber preferred) *Some concern*: [-] Experimental issues with lingering exposures from previous day	[+] Self-report plus objective measures *Some concern*: [-] Difficult to determine adversity cutoff for objective measures	[n] N = 21 *Some concern:* [-] Effects only at higher levels for these endpoints (note: other endpoints in this study more sensitive)	No POD derived. Data less sensitive, in addition to some concerns with the population and outcome measures. Issues with adequacy of exposure quality. Studies with more robust analyses available.

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation[a]	**Population or subjects**	**Exposure**	**Outcome measure(s)**	**Result(s) utility**	
(Kulle, 1993)[b], Eye irritation prevalence	[n] *Medium* confidence [+] Selection bias and confounding unlikely [+] Good exposure quality	*Some concern*: [-] Healthy volunteers	[n] Acute exposure appropriate for endpoint	[n] Self-report symptom scores	*Some concern*: [-] Irritation in controls NR [-] Regression coefficients NR [-] Within person comparisons with correlated responses across dose levels. [-] Small N (N = 9-10)	POD derived, limitations noted.
(Andersen and Molhave, 1983)[b], Eye irritation prevalence	[n] *Medium* confidence [+] Selection bias and confounding unlikely [n] Adequate exposure quality	*Some concern*: [-] Healthy volunteers [-] > 30% smokers	[n] Acute exposure appropriate for endpoint	[n] Self-report symptom scores	[n] N = 16	POD derived, limitations noted.
			Some concern: [-] Variable exposure levels, with analytical concentrations within 20% of target		*Some concern*: [-] Irritation during clean air exposure NR [-] Within person comparisons with correlated responses across dose levels.	
Other high/ medium confidence studies [c]	N/A	N/A	**Critical concern:** [--] only one exposure level	N/A	N/A	No POD derived. Critical exposure concern.
Other Studies						
Studies of laboratory students[d]	N/A	N/A	**Critical concern:** [--] Episodic (1–2x/ week for 1–4 hr) [--] High exposures compared to other designs	N/A	N/A	No POD derived Critical exposure concern.

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation[a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Studies of workers[e]	N/A	N/A	**Critical concern:** [--] High exposures compared to other designs	N/A	N/A	No POD derived Critical exposure concern.

Representing the impact of each factor on the inferred utility of the study for dose-response analysis for this outcome: [+] = increases utility; [n] = neutral effect on utility; [-] decreases utility; [--] critical concern that greatly inhibits utility (gray shading)
NR = not reported
N/A = not applicable = consideration was not influential to the decision (e.g., because a critical concern was identified).
[a] Select features of the study evaluations that may have the most impact on quantification may be highlighted (if not otherwise highlighted in other columns), but the bullets in this column do not represent a full synopsis (see Appendix B for details).
[b] EPA's Human Studies Review Board review of this intentional exposure study determined the ethical conduct to be adequate for use.
[c] See Appendix C.3.3. *High* confidence: (Green et al., 1987; Green et al., 1989); *Medium* confidence: (Witek et al., 1986; Witek et al., 1987; Schachter et al., 1986; Schachter et al., 1987).
[d] See Appendix C.4. *High* confidence: (Uba et al., 1989; Mori et al., 2016; Kriebel et al., 1993); *Medium* confidence: (Wantke et al., 2000; Takigawa et al., 2005; Takahashi et al., 2007; Kriebel et al., 2001).
[e] See Appendix C.4. *Medium* confidence: (Neghab et al., 2011; Horvath et al., 1988; Holness and Nethercott, 1989).
[f] "The working range is 0.02 to 4 ppm (0.025 to 4.6 mg/m^3) for an 80-L air sample. This is the most sensitive formaldehyde method in the NIOSH Manual of Analytical Methods and is able to measure ceiling levels as low as 0.1 ppm (1 5-L sample). It is best suited for the determination of formaldehyde in area samples." (https://www.cdc.gov/niosh/docs/2003-154/chaps.html); NIOSH Manual of Analytical Methods, 4th Edition (NMAM 3500) (NIOSH, 1994).

Pulmonary Function

As described in Section 3.2.2, the synthesis judgments were based on human studies of long-term formaldehyde exposure and effects on pulmonary function; these studies were considered in dose-response analysis. Most studies in residential settings either did not provide quantitative results needed for dose-response analysis, used dichotomized concentration data, or compared exposed groups to a referent group. The studies of effects among anatomy lab students involved episodic and high-level exposures compared to other available study designs. The occupational studies also involved high exposure levels, some with periodic peaks. Overall, after evaluating the available *medium* and *high* confidence studies on pulmonary function for their utility in dose-response analysis (see Table 5-2), one epidemiology study was advanced for POD derivation (Krzyzanowski et al., 1990).

Strengths of the Krzyzanowski et al. (1990) study include a large sample size in a residential population, with a comprehensive exposure assessment protocol (i.e., three locations in the home; two 1-week periods in each location) reasonably representing exposures in the homes during the previous weeks and months (i.e., the etiologically relevant exposure window for pulmonary function status). Additionally, the use of multiple exposures per day (morning and evening) for each child over the 12 days of exposure measurements and the twice-daily repeated measurements of PEFR enhanced the sensitivity of this study for detecting an effect on pulmonary function.

Table 5-2. Eligible studies for POD derivation and rationale for decisions to not select specific studies for pulmonary function

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Residential Studies						
(Krzyzanowski et al., 1990), Peak expiratory Flow Rate (PEFR)	[+] High confidence [+] Information bias unlikely [+] Selection bias and confounding unlikely	[+] Diverse population with wide spectrum of SES, ethnicity, and ages (including children 6-15 years)	[+] Two one-week samples measured in bedroom, living area and kitchen. [+] Continuous exposure [+] Average exposure 26 ppb (32 µg/m^3) [+] Wide exposure range	[+] Subjects were trained in use of the mini-Wright peak flow meter [+] PEFR was measured for up to 4 times/day [+] To eliminate any training effect, first 2 days measurements were excluded [n] Self-report	[+] N = 298 children [+] Regression parameters were provided that allowed for the dose-response to be estimated in all children and in asthmatic children	POD derived
(Wallner et al., 2012) Forced Flow volume (MEF_{75}, MEF_{50})	N/A	N/A	N/A	N/A	[+] N=433 [n] Regression of % change in pulmonary function per 1 SD change in formaldehyde **Critical concern**: [--] Required concentration data for regression not reported.	No POD derived. Critical concern with results utility for POD derivation.
Broder et al. (1988b, 1988c); Broder et al. (1988a) Spirometry measures	N/A	N/A	N/A	N/A	**Critical concern**: [--] No quantitative results provided for within group regression models and formaldehyde	No POD derived. Critical concern with results utility for POD derivation.

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Residential studies with analyses inadequate for dose-response [b]	N/A	N/A	N/A	N/A	**Critical concern**: [--] only dichotomous analyses or comparisons of exposed to a referent group	No POD derived. Critical concern with results utility for POD derivation.
Studies of anatomy lab students [c]	N/A	N/A	**Critical concern**: [--] Episodic (1–2x/ week for 1–4 hr) [--] High exposures compared to other designs	N/A	**Critical concern**: [--] Analyzed changes in pulmonary function with time as the independent variable or regression parameters that complicated dose-response evaluation	No POD derived. Critical concerns with exposure and results utility for POD derivation.
Occupational exposure studies [d]	N/A	N/A	**Critical concern**: [--] High exposure compared to other designs	N/A	N/A	No POD derived. Critical concern with exposure as compared to other available studies.

Representing the impact of each factor on the inferred utility of the study for dose-response analysis for this outcome: [+] = increases utility; [n] = neutral effect on utility; [-] decreases utility; [--] critical concern that greatly inhibits utility (gray shading)
NR = not reported
N/A = not applicable = consideration was not influential to the decision (e.g., because a critical concern was identified).
[a] Select features of the study evaluations that may have the most impact on quantification may be highlighted (if not otherwise highlighted in other columns), but the bullets in this column do not represent a full synopsis (see Appendix B for details).
[b] See Appendix B.3.3. *Medium* (Franklin et al., 2000; Bentayeb et al., 2015).
[c] See Appendix B.3.3. *High* confidence: (Uba et al., 1989); *Medium* confidence: (Kriebel et al., 1993; Kriebel et al., 2001; Akbar-Khanzadeh et al., 1994).
[d] See Appendix B.3.3. *High* confidence: (Horvath et al., 1988); *Medium* confidence: (Schoenberg and Mitchell, 1975; Nunn et al., 1990; Neghab et al., 2011; Malaka and Kodama, 1990; Löfstedt et al., 2009; Löfstedt et al., 2011; Levine et al., 1984b; Khamgaonkar and Fulare, 1991; Holness and Nethercott, 1989; Holmström and Wilhelmsson, 1988; Herbert et al., 1994; Alexandersson et al., 1982; Alexandersson, 1988; Alexandersson and Hedenstierna, 1988, 1989).

Immune-mediated Conditions, Focusing on Allergies and Current Asthma

As described in Section 3.2.3, the synthesis judgments were based on human studies of long-term formaldehyde exposure and effects on allergic conditions and asthma; acute exposure studies did not contribute to the evidence integration judgments. The long-term human studies on these outcomes were considered separately in dose-response analysis.

Allergic conditions

Seven *high* or *medium* confidence epidemiology studies in children or adults provide data on measures of allergy-related symptoms (Yon et al., 2019; Norbäck et al., 2017; Neamtiu et al., 2019; Matsunaga et al., 2008; Huang et al., 2017; Billionnet et al., 2011; Annesi-Maesano et al., 2012). As discussed in Section 3.2.3, effect sizes were around 1.2 in children for rhinitis and rhinoconjunctivitis at exposures around 0.04 mg/m^3 and above (Yon et al., 2019; Annesi-Maesano et al., 2012). Two studies in children did not observe an association with rhinitis at lower exposure levels (Norbäck et al., 2017; Huang et al., 2017). The point estimates of the relative risks in two studies of rhinitis in adults covering a higher exposure range were also around 1.2, but these estimates were highly imprecise and so cannot be interpreted as strong support for an association in this older population (Matsunaga et al., 2008; Billionnet et al., 2011). Stronger associations (approximate RR 2 to 3) were seen in the only study of eczema in adults (Matsunaga, 2008) and in a study in children of a combination of symptoms relating to eye, nose, and skin (Neamtiu et al., 2019). Two of the studies presented exposure-response analyses using formaldehyde exposure categorized in three levels (Annesi-Maesano et al., 2012) or four levels (Matsunaga et al., 2008).

In addition, two *medium* confidence epidemiology studies in children provide data on exposure and skin prick tests (SPTs) needed to conduct a quantitative analysis (Palczynski et al., 1999; Garrett et al., 1999). However, because of the limitations with respect to the timing of the exposure measure in relation to SPT testing, and the interpretation of SPTs as less informative to the identified hazard than other allergy-related effects (Section 3.2.3), these studies are not considered further as a basis for quantitation.

Thus, after evaluating the available *medium* and *high* confidence studies on allergic conditions for their utility in dose-response analysis (see Table 5-3), two epidemiology studies were advanced for POD derivation (Matsunaga et al., 2008; Annesi-Maesano et al., 2012). A specific strength of the (Annesi-Maesano et al., 2012) study was the 5-day exposure measurement period, which was taken to be a good estimate of the chronic, on-going exposure that would be seen in this non-occupational (i.e., school-based) setting.

Table 5-3. Eligible studies for POD derivation and rationale for decisions to not select specific studies for allergic conditions

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
(Annesi-Maesano et al., 2012), France Rhinoconjunctivitis prevalence	[+] *High* confidence [+] Information bias unlikely [+] Selection bias and confounding unlikely	[+] Children ages 9–10 [n] Participation rate 69%	[+] 5-day sampling in classrooms [+] Continuous exposure [+] Low median exposure 0.027 mg/m^3 [n] Exposure range up to 95th% of 0.055 mg/m^3	[+] ISAAC questionnaire administered by parents (sneezing and runny nose accompanied by itchy eyes out of cold in the past year)	[+] N = 6,683 children 10.7% of girls and 13.1% of boys with rhinoconjunctivitis [+] Logistic regression, OR (95% CI) by tertiles of exposure [+] No other pollutants were associated with rhino-conjunctivitis	POD derived for rhinoconjunctivitis, with no notable concerns.
Other ***medium*** or ***high*** confidence studies supporting the NOAEL derived from Annesi-Maesano 2012 at relatively low exposures (≤0.04 mg/m^3) [b]	N/A	N/A	N/A	N/A	[n] General lack of effects at these exposure levels in the general population support the NOAEL derived from (Annesi-Maesano et al., 2012) **Critical concern:** [--] Smaller studies or more limited analysis compared to (Annesi-Maesano et al., 2012)	Specific PODs not derived from these studies with similar exposure levels and findings, but more limited study designs, compared to (Annesi-Maesano et al., 2012)
(Matsunaga et al., 2008), Japan Allergy: Self-report medication use for atopic eczema in past 12 months.	[n] *Medium* confidence [-] Potential information bias (Some uncertainty due to lack of data pertaining to	[n] Pregnant women median age ~30 years	[n] 24-hr personal sample [+] Continuous exposure	[n] Self-report of medication use for atopic eczema without clarification of type of medicine	[+] N=998 pregnant women; N=57 eczema cases [+] Logistic regression, OR (95% CI) by 4	POD derived for eczema, concerns noted

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
	sensitivity and specificity of outcome assessments) [n] Selection bias possible but differential participation (by formaldehyde exposure and disease status) uncertain [+] Confounding unlikely	*Some concern*: [-] Low participation rate 17%	[+] Low median exposure: 30th% 0.022 mg/m^3; 60th% 0.033 mg/m^3 [+] Wide exposure range (up to 0.161 mg/m$^{3)}$		exposure categories (<30th, 30th-59th, 60th-89th, and ≥90th %-tiles) *Some concern*: [-] No estimate of mid-point in highest exposure category	
High or *medium* confidence studies of skin prick tests[c]	N/A	**Critical concern**: [--] Uncertainty regarding timing of the exposure measure in relation to SPT testing	N/A	**Critical concern**: [--] Endpoint far less informative to the identified hazard than other allergy-related effects	N/A	No PODs derived. Critical concerns regarding exposure and outcome as compared to other allergy-related endpoints.

Representing the impact of each factor on the inferred utility of the study for dose-response analysis for this outcome: [+] = increases utility; [n] = neutral effect on utility; [-] decreases utility; [--] critical concern that greatly inhibits utility (gray shading)
NR = not reported
N/A = not applicable = consideration was not influential to the decision (e.g., because a critical concern was identified).
[a] Select features of the study evaluations that may have the most impact on quantification may be highlighted (if not otherwise highlighted in other columns), but the bullets in this column do not represent a full synopsis (see Appendix B.3.4 for details).
[b] Other ***medium*** or ***high*** confidence studies of rhinitis, rhinoconjuctivitis, or combined eye, nose, and skin symptoms in children (Yon et al., 2019; Norbäck et al., 2017; Neamtiu et al., 2019; Huang et al., 2017); or adults (Matsunaga et al., 2008; Billionnet et al., 2011).
[c] (Palczynski et al., 1999; Garrett et al., 1999)

Asthma prevalence or degree of asthma control

Residential and school-based exposure studies have examined the prevalence of current asthma in relation to formaldehyde exposure in adults and children in relatively low exposure settings. As discussed in Section 3.2.3, five *medium* or *high* confidence studies at exposures of ≤ approximately 0.050 mg/m^3 do not indicate risk at these lower exposure levels. Several of the RR estimates from these individual studies at these exposure levels were limited by low statistical power. The large sample size (N = 6,683 children, ages 9–10 years), relatively long sampling period (5 days), and detailed analytic strategy, including addressing within-city correlations among participants, other pollutants (NO_x, $PM_{2.5}$, acetaldehyde, acrolein), and stratification by atopy status

in (Annesi-Maesano et al., 2012) study are strengths that support its use to derive a NOAEL to represent the set of studies in this relatively low exposure range.

Prevalence of current asthma was also examined in five *medium* confidence studies in children at higher residential or school exposure levels (> approximately 0.05 mg/m^3), three of these reported relative risks 2.0 and 3.0, with a wider range seen in the other two studies (RR 1.19 and 12.4). The Krzyzanowski et al. (1990) results for children (5–15 years of age) are based on a relatively large sample size, with a comprehensive exposure assessment protocol (i.e., three locations in the home; two 1-week periods covering two seasons) and categorical analysis using three exposure groups; a limitation is the relatively small number of participants at the higher exposure levels. Other studies in children (Zhai et al., 2013; Neamtiu et al., 2019; Branco et al., 2020) are supportive of the results in of Krzyzanowski et al. (1990) but presented only a dichotomized exposure-response analysis, and so were not used for quantitation. (Liu et al., 2018) was not considered for quantitation because of uncertainty regarding the interpretation of formaldehyde as a single variable representing 4 quartiles.

One of the four *medium* confidence studies of prevalence of current asthma in adults in higher exposure residential settings (>0.05 mg/m^3) did not provide quantitative results (Krzyzanowski et al., 1990). Of the remaining two studies, Billionnet et al. (2011), presented only a dichotomized exposure-response analysis, and so was not used for quantitation. The lower three levels of the -level categorical analysis from Matsunaga et al. (2008) contributed to the evaluation of the NOAEL for studies with exposures <0.05 mg/m^3, while the highest exposure group 0.058–0.161 compared to <0.022 mg/m^3) was considered as supportive of the POD derived from Krzyzanowski et al. (1990).

The collection of occupational studies (see Section 3.2.3) provides a strong basis for inferences regarding asthma risk at relatively high exposures (e.g., 0.1 to >0.5 mg/m^3) (Malaka and Kodama, 1990; Herbert et al., 1994; Fransman et al., 2003). However, there would be considerable uncertainty in a POD derived from these studies, identified as a LOAEL, given the dichotomous analyses used to examine associations and the wide variability in exposure measures within each of these studies. Therefore, PODs were not determined using the occupational studies.

EPA identified two studies that examined degree of asthma control in children with asthma in relation to formaldehyde measures in the home (Venn et al., 2003; Dannemiller et al., 2013). Analysis was conducted using four categories of exposure in Venn et al. (2003), based on 3-day exposure measures taken in the home and daily symptom diaries kept for one month among children with persistent wheeze; this 3-day sample was taken to be a good estimate of the ongoing exposure relevant to the symptom diary. Dannemiller et al. (2013) compared mean exposure levels (based on 30 minute samples) in two groups (those with very poor control and all others, based on a five-question survey about symptom control in the past 4 weeks). The larger sample size, longer sampling period, and more detailed exposure-response analysis makes Venn et al. (2003) a stronger basis for providing a POD. Additional adjustment of regression models for dampness or

other exposures including visible mold, total VOCs, or NO_2, did not affect formaldehyde results, reducing the likelihood of residual confounding by coexposures.

Thus, after evaluating the available *medium* and *high* confidence studies on prevalence of current asthma or control of asthma symptoms for their utility in dose-response analysis (see Table 5-4), three epidemiology studies were advanced for POD derivation (Venn et al., 2003; Krzyzanowski et al., 1990; Annesi-Maesano et al., 2012).

Table 5-4. Eligible studies for POD derivation and rationale for decisions to not select specific studies for current asthma prevalence and asthma control

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Prevalence of Current Asthma						
(Annesi-Maesano et al., 2012), Allergy: Rhinoconjunctivitis prevalence Supported by other residential or school studies with relatively low exposures (≤ approximately 0.05 mg/m^3)[b]	[+] *High* confidence [+] Information bias unlikely [+] Selection bias and confounding unlikely	[+] Children ages 9–10 years [n] Participation rate 69%	[+] 5-day sampling in classrooms [+] Continuous exposure [+] Low median exposure 0.027 mg/m^3 [+] Wide exposure range	[+] ISAAC questionnaire Asthma: asthma in past year (wheezing or whistling in the chest or wheezing or whistling in the chest at night-time or taken asthma treatment in the past year)	[+] N = 6,683 children [+] Logistic regression, OR (95% CI) by tertiles of exposure with consideration of several other pollutants	POD derived, no notable concerns.
(Krzyzanowski et al., 1990), United States Asthma prevalence Supported by other residential or school studies with relatively high exposures (> approximately 0.05 mg/m^3)[c]	[n] *Medium* confidence [+] Information bias unlikely [+] Selection bias and confounding unlikely	[+] Diverse population with wide spectrum of SES, ethnicity, and ages (including children 6-15 years)	[+] Two 1-week samplings from kitchen, living area, and bedroom [+] Continuous exposure [+] Average exposure 26 ppb (32 µg/m^3) [+] Wide exposure range	[+] American Thoracic Society questionnaire; Doctor-diagnosed asthma	[+] N = 298 children [+] Increased prevalence of asthma in highest exposure category *Some concern*: [-] N = 21 cases of asthma	POD derived. Concern regarding small number of asthma cases noted.
Liu et al. (2018) (China) Asthma prevalence	[n] *Medium* confidence [+] Information bias unlikely	[+] Children, mean age 10 years	[+] 2-month sampling period in bedroom and living room	[+] Hospital diagnosis of asthma; current asthma symptoms based	[+] N=180 cases, 180 controls **Critical concern**:	POD not derived. Critical concern with results utility regarding interpretation of formaldehyde as a

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
	[n] Uncertainty regarding selection bias – participation rate not provided, but the "pass rate" of the questionnaire was 100% and equal number of cases and controls. [+] Confounding unlikely		[+] Wide range of exposure Median, 75th percentile, maximum: 0.0384, 0.057, 0.142 0 mg/m^3	on ISAAC questionnaire; responses (2 or more incidents of cough, wheezing, and dyspnea for ≥ 3 consecutive days)	[--] Logistic regression, with quartiles of formaldehyde used as a single variable	single variable representing 4 quartiles.
Occupational studies (exposures > 0.1 mg/m^3) [d,e] Asthma prevalence	N/A	**Critical concern**: [--] Worker population does not include susceptible children and "healthy worker" effect likely to be relevant for this outcome.	**Critical concern**: [--] High exposures compared to other available study designs	N/A	N/A	POD not derived. Critical concerns regarding population and exposure as compared to available residential- and school-based studies.
Asthma Control						
Dannemiller et al. (2013) United States Asthma symptom control	[n] *Medium* confidence [+] Information bias unlikely [n] Selection bias possible but differential participation (by formaldehyde exposure and disease status) uncertain	[+] Children mean age 10.5 years [n] Participation rate 79% but population not defined	[+] Concurrent with data collection on outcomes [+] Median 0.044 mg/m^3 *Some concern*: [-] 30 minute sample	[n] 5 questions on symptom control in past 4 weeks??	*Some Concerns*: [-] small sample size (37 cases) [-] dichotomized exposure analysis	POD not derived. Studies with more robust design and analyses available given concerns with sampling and dichotomized exposure analysis.

Study, endpoint	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
(Venn et al., 2003), United Kingdom Asthma symptom control	[+] *High* confidence [+] Information bias unlikely [+] Selection bias and confounding unlikely	[+] Children ages 9-11 years [+] Initial participation rate 85% [n] Follow-up participation rate 54%	[+]3-d sample in bedroom [+] Concurrent with data collection on outcomes [+] Median 0.022 mg/m^3; 75th percentile 0.032 mg/m^3	[+] Symptom frequency: One month daily diaries recording symptoms, including daytime and nighttime wheezing, chest tightness, breathlessness, and cough, each measured on 0 to 5 scale.	[+] N=193 cases [+] Logistic regression, OR (95% CI) by quartile of exposure	POD derived, no notable concerns.

Representing the impact of each factor on the inferred utility of the study for dose-response analysis for this outcome: [+] = increases utility; [n] = neutral effect on utility; [-] decreases utility; [--] critical concern that greatly inhibits utility (gray shading)
NR = not reported
N/A = not applicable = consideration was not influential to the decision (e.g., because a critical concern was identified).
[a] Select features of the study evaluations that may have the most impact on quantification may be highlighted (if not otherwise highlighted in other columns), but the bullets in this column do not represent a full synopsis (see Appendix B.3.4 for details).
[b] Other supportive *high* and *medium* confidence studies with low (≤ approximately 0.05 mg/m^3) residential or school exposure levels: (Venn et al., 2003; Palczynski et al., 1999; Kim et al., 2011); and the lower three exposure groups in Matsunaga et al. (2008).
[c] Other supportive *medium* confidence studies with high (> approximately 0.05 mg/m^3) residential or school exposure levels: (Zhai et al., 2013; Neamtiu et al., 2019; Branco et al., 2020; Billionnet et al., 2011); and the highest exposure group in Matsunaga et al. (2008).
[d] (Malaka and Kodama, 1990; Herbert et al., 1994; Fransman et al., 2003).

Respiratory Tract Pathology

The four *medium* confidence occupational studies in humans provide support for the larger evidence base from the experimental studies in animals (Holmstrom et al., 1989c; Edling et al., 1988; Boysen et al., 1990; Ballarin et al., 1992). However, there would be considerable uncertainty in a POD derived from these studies, identified as a LOAEL, given the dichotomous analyses used to examine associations and the wide variability in exposure concentrations within each of these studies (e.g., 0.1 to >0.5 mg/m^3). Therefore, PODs were not determined using the occupational studies.

Given the abundance of animal studies examining respiratory tract pathology (see Section 3.2.4), the available long-term exposure studies were prioritized for POD derivation. From amongst the *medium* or *high* confidence studies with longer formaldehyde exposure durations, preference was given to those studies without significant concerns about the exposure quality or the sensitivity of the outcome measures.

After evaluating the available *medium* and *high* confidence studies on respiratory tract pathology for their utility in dose-response analysis (see Table 5-5), two experimental animal studies were advanced for POD derivation (Woutersen et al., 1989; Kerns et al., 1983).

Table 5-5. Eligible studies for POD derivation and rationale for decisions to not select specific studies for respiratory tract pathology

Study, species	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation[a]	Population or subjects[b]	Exposure	Outcome measure(s)	Result(s) utility	
Studies in Humans						
Occupational Studies[c]	N/A	N/A	**Critical concern**: [--] Wide within study variability in exposure levels	N/A	**Critical concern**: [--] Dichotomous analyses (N/LOAEL approach only)	No POD derived. Critical concerns with exposure and results utility for POD derivation. Far more certain estimates available using animal data.
Animal Studies[d]						
(Kerns et al., 1983); (Battelle, 1982); rats	[+] *High* confidence [+] Good exposure quality	[n] Rats appropriate for outcome	[+] 2-year exposure	[+] Good tissue sampling	[+] Large N (N = 119-121) [+] Detailed data (severity; lesion level)	POD derived, no notable limitations.
(Kerns et al., 1983); (Battelle, 1982); mice	[n] *Medium* confidence [+] *Good* exposure quality	[n] Mice appropriate for outcome *Some concern*: [-] Survival to 18 mo. < 33%	[+] 2-year exposure	*Some concern*: [-] Limited tissue sampling	[+] Large N (N = 119-121) **Critical concern**: [--] Lesion incidence or severity NR	No POD derived. Critical concern with results reporting for POD derivation.
(Woutersen et al., 1989), rats	[+] *High* confidence [+] Good exposure quality	[n] Rats appropriate for outcome	[+] 2-year exposure	[+] Good tissue sampling	[n] N = 30 *Some concern*: [-] Limited severity data [-] High baseline incidence	POD derived, limitations noted.
(Appelman et al., 1988), rats	[n] *Medium* confidence [+] Good exposure quality	[n] Rats appropriate for outcome	*Some concern*: [-] 2-month exposure [-] Wide dose spacing (0, 0.1, 1.2, 12 mg/m3)	[+] Good tissue sampling	*Some concern*: [-] Small N (10-20) [-] Limited data (on severity)	No POD derived. More limited than other available studies given concerns with results and exposure.
(Kamata et al., 1997), rats	[n] *Medium* confidence [n] Adequate exposure quality	[n] Rats appropriate for outcome	[+] 2-year exposure *Some concern*:	[+] Good tissue sampling	*Some concern*: [-] Small N (<10) for some data [-] Limited severity data	No POD derived. More limited than other available studies given concerns

Study, species	Dose-response considerations (see methods in Section 2.7)					Decision
	Study evaluation[a]	Population or subjects[b]	Exposure	Outcome measure(s)	Result(s) utility	
			[-] Methanol co-exposure		[-] Neoplastic lesions present	with results and exposure.
(Sellakumar et al., 1985), rats	[n] *Medium* confidence [n] Adequate exposure quality	[n] Rats appropriate for outcome [n] Males only considered okay for this outcome	[+] Lifetime exposure *Some concern*: [-] Likely co-exposure to kerosene [-] Single exposure level	[+] Good tissue sampling	[+] Large N (N = 100) *Some concern*: [-] Limited severity data	No POD derived. More limited than other available studies given concerns with results and exposure.
(Dalbey, 1982), hamsters	[n] *Medium* confidence [+] Good exposure quality	**Critical concern:** [--] Hamsters less sensitive than other animal models	[+] Chronic exposure **Critical concern:** [--] Single, high exposure level (12 mg/m^3)	[n] Adequate tissue sampling (note: only two nasal sections)	*Some concern*: [-] Limited severity data	No POD derived. Critical concerns with animals and exposure used.
(Feron et al., 1988), rats	[+] *High* confidence [+] Good exposure quality	[n] Rats appropriate for outcome	**Critical concern**: [--] High levels and wide spacing (0, 11, and 24 mg/m3) [--] 3-week exposure	[+] 2-year follow-up measures [+] Good tissue sampling	*Some concern*: [-] No interim sacrifice data (only recovery data)	No POD derived. Critical concern with exposure.
(Rusch et al., 1983), rats, hamsters, or monkeys	[n] *Medium* confidence [+] Good exposure quality	[+] Monkeys better represent human anatomy	[+] 22 hr/d exposure *Some concern*: [-] Narrow, low exposure range [-] 6-week exposure [-] Controls differ for different exposures	*Some concern*: [-] Limited tissue sampling (data only presented for one nasal section)	**Critical concern**: [-] Effects only at highest dose [--] Combined lesions only [-] Limited severity data	No POD derived. Critical concern with results utility for POD derivation.

NR = not reported

N/A = not applicable = consideration was not influential to the decision (e.g., because a critical concern was identified).

[a] Select features of the study evaluations that may have the most impact on quantification may be highlighted (if not otherwise highlighted in other columns), but the bullets in this column do not represent a full synopsis (see Appendix B.3.4 for details).

[b] Testing of males only in experimental animal studies was not considered a limitation for this endpoint. Although not definitive, male animals routinely exhibited increased sensitivity and severity of pathology, with potential physiological explanations for this observed sex difference discussed in Section 3.2.4.

[c] See Section 3.2.4. All are *medium* confidence*:* (Ballarin et al., 1992); (Boysen et al., 1990); (Edling et al., 1988); (Holmstrom et al., 1989c).

[d] Focusing on the study designs most informative for use in identifying more sensitive and reliable PODs for long-term toxicity values. Specifically, *medium* or *high* confidence studies with formaldehyde exposure longer than 13 weeks or of exposure for 13 weeks but with long-term follow-up examinations (see Section 3.2.4).

Reproductive and Developmental Toxicity

Female reproductive or developmental toxicity

Of the epidemiology studies that evaluated effects on fecundity or spontaneous abortion (see Section 3.3.2), only one study developed individual exposure estimates suitable for dose-response evaluation.

No animal studies of *high* or *medium* confidence evaluated these health effects. Thus, after evaluating the available *medium* and *high* confidence studies on female reproductive or developmental toxicity for their utility in dose-response analysis (see Table 5-6), only one occupational epidemiology study was advanced for POD derivation (Taskinen et al., 1999).

Table 5-6. Studies for POD derivation and rationale for decisions to not select specific studies for female reproductive or developmental toxicity

Study, species	Dose-Response Considerations (see methods in Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Studies in Humans						
Taskinen et al. (1999); Time to pregnancy; Fecundity	[n] *Medium* confidence	[n] Population appropriate for outcome	[n] Detailed exposure assessment *Some concern*: [-] Likely some error in exposure assignments and dermal exposure may contribute [-] Sampling protocol not described	[n] No notable limitations	[+] Large N = 3772	POD derived for time to pregnancy. Concern noted about potential exposure inaccuracy
Taskinen et al. (1999); Spontaneous abortion	[n] *Medium* confidence	[n] Population appropriate for outcome *Some concern*: [-] Excluded women with no live birth	[n] Detailed exposure assessment *Some concern*: [-] Likely some error in exposure assignments and dermal exposure may contribute [-] Sampling protocol not described	**Critical Concern**: [-] Uncertain applicability of temporal window for exposure data with respect to reported spontaneous abortions	[+] Large N = 3772	No POD derived. Critical concern with timing of outcome measure.

Study, species	Dose-Response Considerations (see methods in Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Franklin et al. (2019); Birth weight, head circumference	[n] *Medium* confidence	N/A	**Critical concern**: [--] Large uncertainties in exposure distribution due to large % < LOD and impact on quantitative results	N/A	N/A	No POD derived. Critical concern with exposure accuracy.
Chang et al. (2017); Birth weight	[n] *Medium* confidence	N/A	**Critical concern**: [--] Evidence of confounding by co-exposure	N/A	*Some concern*: [-] Log transformed formaldehyde concentration	No POD derived. Critical concern with potential co-exposure.
(John et al., 1994); spontaneous abortion	[n] *Medium* confidence	[n] Population appropriate for outcome	**Critical Concern**: [--] No specific formaldehyde levels reported	*Some Concern*: [-] Potential biases in evaluating spontaneous abortion	[+] Large N = 6202	No POD derived. Critical concern with exposure reporting.
Animal Studies						
No *Medium* or *High* confidence studies in animals were identified. *Low* confidence studies are typically not used in quantitative analyses when higher confidence studies within a health system are available.						

NR = not reported
N/A = not applicable = consideration was not influential to the decision (e.g., because a critical concern was identified).

Male reproductive toxicity

While two *medium* confidence, well conducted human occupational studies reporting on male reproductive system effects were available, the data were not amenable to dose-response analyses. Five *medium* or *high* confidence studies in experimental animals were available, all only testing high formaldehyde levels (> 6 mg/m^3). Three of these studies were not advanced for POD derivation, primarily due to critical concerns regarding exposure.

Overall, after evaluating the available *medium* and *high* confidence studies on male reproductive toxicity for their utility in dose-response analysis (see Table 5-7), two experimental animal studies were advanced for POD derivation (Ozen et al., 2002; Ozen et al., 2005).

Table 5-7. Eligible studies for POD derivation and rationale for decisions to not select specific studies for male reproductive toxicity

Study, species	Dose-response Considerations (see methods in Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Studies in Humans						
Wang et al. (2015); sperm parameters in woodworkers	[n] *Medium* confidence	[n] Population appropriate for outcomes	[+] Detailed exposure assessment [+] Highly exposed (good exposure contrast) *Some Concern*: [-] Concern for confounding (solvents)	[n] No notable limitations	[+] Evaluation of exposure-response [n] N = 124 **Critical concern**: [--] Unable to determine formaldehyde concentration from exposure index metric, so data not amenable to quantitative analyses	No POD derived. Critical concern with use of results in quantitative analyses.
Wang et al. (2012); spontaneous abortion and time-to-pregnancy	[n] *Medium* confidence	[n] Population appropriate for outcomes	[+] Detailed exposure assessment **Critical concern**: [--] Exposure levels not provided [-] Concern for confounding (solvents)	*Some concern*: [-] Potential biases in evaluating spontaneous abortion	[n] N = 302 **Critical concern**: [--] Unable to determine formaldehyde concentration from exposure index metric, so data not amenable to quantitative analyses	No POD derived. Critical concern with use of results in quantitative analyses.
Animal Studies						
Ozen et al. (2002); Wistar rat Relative testes weight, 13-week exposure	[n] *Medium* confidence [+] Good exposure quality	[n] Rats appropriate for outcome [n] Body weight decreases unlikely to affect outcome	[n] 13-week exposure *Some concern*: [-] Lowest tested exposure level of 12.2 mg/m^3	*Some concern*: [-] Relative weight only (for testes, absolute weight is preferred)	*Some concern*: [-] Small N = 7	POD derived; multiple concerns noted.
Ozen et al. (2005); Serum testosterone, Wistar rat, 13- and 4-week exposure	[n] *Medium* confidence [+] Good exposure quality	[n] Rats appropriate for outcome *Some concern*:	[n] 13-week exposure *Some concern*:	[n] No notable concerns	*Some concern*: [-] Small N = 6	POD derived for 13-week exposure; multiple concerns noted.

Study, species	Dose-response Considerations (see methods in Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
		[-] Although such effects are expected to be towards the null for this endpoint, uncertain if body weight decreases contributed to magnitude of response	[-] Lowest tested exposure level of 6.15 m/m^3 [--] For 4-week exposure experiment, duration is a critical concern.			No POD derived for 4-week exposure. Critical concern with exposure duration.
Ozen et al. (2005); Seminiferous tubule diameter, Wistar rats, 13-week exposure	[n] *Medium* confidence [+] Good exposure quality	[n] Rats appropriate for outcome	[n] 13-week exposure *Some concern*: [-] Lowest tested exposure level of 12.2 m/m^3	**Critical concern:** [--] Sampling insufficiently reported (randomly selected tubules may be oversampled from individual animals within a group)	**Critical concern:** [--] Unclear experimental unit (linked to sampling concern) [-] Small N = 7	No POD derived. Critical concerns with reporting of outcome measures and results.
Vosoughi et al. (2012); Vosoughi et al. (2013); Seminiferous tubule diameter, sperm abnormalities, serum T, testes weight, NMRI mice, 10-day exposure	[n] *Medium* confidence [+] Good exposure quality	[n] Mice appropriate for outcome	**Critical concern**: [--] 10-day exposure [-] Lowest tested exposure level of 12.3 mg/m^3	*Some concern*: [-] Concern for overt toxicity potentially contributing to responses for some endpoints	[n] N = 12	No POD derived. Critical concern with exposure.
Sarsilmaz et al. (1999); Leydig cell quantity or nuclear damage, relative testes weight Wistar rat, 4-week exposure	[n] *Medium* confidence [n] Adequate exposure quality	[n] Rats appropriate for outcome	**Critical concern**: [--] 4-week exposure [-] Lowest tested exposure level of 12.3 mg/m^3	*Some concern*: [-] Relative weight only (for testes, absolute weight is preferred)	[n] N = 10 *Some concern*: [-] Unclear reporting for Leydig cell measures	No POD derived. Critical concern with exposure duration
Sapmaz et al. (2018); Seminiferous tubule measures, Sprague-Dawley rats, 4- and 13-week exposure	[n] *Medium* confidence [+] Good exposure quality	[n] Rats appropriate for outcome *Some concern*: [-] Unreported source of rats	[n] 13-week exposure **Critical concern**: [--] single exposure level [-] Lowest tested exposure level of 6.15 mg/m^3	[n] No notable concerns	*Some concern*: [-] Small N = 7	No POD derived. Critical concerns with exposure.

NR = not reported

N/A = not applicable = consideration was not influential to the decision (e.g., because a critical concern was identified).

[a] Select features of the study evaluations that may have the most impact on quantification may be highlighted (if not otherwise highlighted in other columns), but the bullets in this column do not represent a full synopsis (see Appendix B.3.8 for details).

5.1.2. Calculation of PODs

The methods for determining PODs as well as the characterization of the resultant PODs, are detailed in this section.

Methods of Analysis

Once the preferred studies and effect(s) were identified within each health domain, PODs are derived for each chosen endpoint using a NOAEL, LOAEL, or BMCL. These PODs are then adjusted (POD_{ADJ}), if appropriate, to extrapolate from the estimated or measured exposures to a continuous exposure scenario. For laboratory animal studies, as applicable (U.S. EPA, 1994), this POD_{ADJ} was then converted to a human equivalent concentration (POD_{HEC}) using a mathematical calibration. Each of the following organ/health system discussions includes a summary analysis of the strengths and weaknesses for the PODs derived from the individual studies.

Sensory Irritation

Human residential studies

Table 5-1 provides the rationales for selecting the combination of two complementary sensory irritation studies of formaldehyde exposures in mobile homes (Liu et al., 1991; Hanrahan et al., 1984) for POD derivation, with study details in Table 5-8 below. Hanrahan et al. (1984), a *medium* confidence study, assessed exposure using two 1-hour average formaldehyde measurements[42] taken in two rooms in the mobile homes of a group including teenagers and adults and predicted the exposure-response for prevalence of "burning eyes" experienced by the participants since moving into the homes from a logistic regression model that adjusted for age, sex, and smoking. Hanrahan et al. (1984) reported that prevalent symptoms[43] of burning eyes and eye irritation were significantly associated with in-home formaldehyde exposures, and the authors provided a graphical representation of the best-fitting logistic regression model results of predicted prevalence of "burning eyes" for exposures at 100 ppb increments from 100 to 800 ppb (0.12–0.98 mg/m^3). The data points were estimated from the published graph (see Appendix D.1.1 for details).

Liu et al. (1991), a *medium* confidence study, collected data on symptoms during the exposure assessment using a sampling protocol that captured average formaldehyde concentrations in the mobile homes (7-day mean concentration from two rooms). The range of 7-day average formaldehyde concentrations measured by Liu et al. (1991) was comparable to the air concentrations in the homes studied by Hanrahan et al. (1984) (10–460 ppb [0.012–0.57 mg/m^3]) although this study had a lower LOD of 0.01 ppm (0.0123 mg/m^3). Although Liu et al. (1991)

[42] Exposure assessment methodology methods was consistent with NIOSH method 3500 (NIOSH, 1994) and were considered to have high accuracy for the 1-hour samples, however there was a concern that the symptom sampling timeframe did not match the exposure ascertainment time-frame.
[43]Hanrahan et al. (1984) reported on the "prevalence" of symptoms that had occurred since moving into the home.

estimated an exposure-response relation using logistic regression and reported that the effects of formaldehyde exposure were statistically significant, the regression coefficients estimated by the model were not reported. Liu et al. (1991) did report the prevalence of burning eyes for three categorical exposure groups for two seasons (Summer and Winter). More granular exposure data from the same study was published in (Sexton et al., 1986) which provided graphical data for the two seasons when homes were sampled: Summer (Jul/Aug) and Winter (Feb/Mar) and this information was used to refine the exposure estimates corresponding to what was reported in Liu (1991) (see Appendix D.1.1).

EPA extracted the main effect data from both studies (Liu et al., 1991; Hanrahan et al., 1984), transformed the prevalence data to "prevalence odds"[44] and combined the eight points estimated from the dose-response data from Hanrahan et al. (1984) with the six additional points from Liu et al. (1991) in Figure 5-1 which shows that the two sets of reconstructed dose-response data overlapped between 0.1 and 0.2 ppm formaldehyde concentration (see Appendix D.1.1 for details).

Assuming a background prevalence of "burning eyes" of 3%, EPA fit a cubic polynomial function with the intercept fixed at the log-odds of 0.03 (0.0309), to the combined prevalence odds data and found that a third-degree polynomial function fit with an R^2 value of 0.998. The following formula describes the functional form for the prevalence odds:

$$\frac{p}{1-p} = 7.8077 * (exposure)^3 + 1.6517 * (exposure)^2 + 0.7104 * (exposure) + 0.0309 \quad \text{(Eq. 5-1)}$$

[44] The dependent variable in both studies was displayed as a predicted percentage prevalence of burning eyes. However, the general epidemiologic method used to model prevalence data is logistic regression, which predicts the log odds of prevalence, which the authors then transformed to prevalence for graphing. In order to describe the underlying functional form of the results displayed, EPA converted the prevalence data back to prevalence odds. Prevalence odds = [Prevalence/(1-Prevalence)].

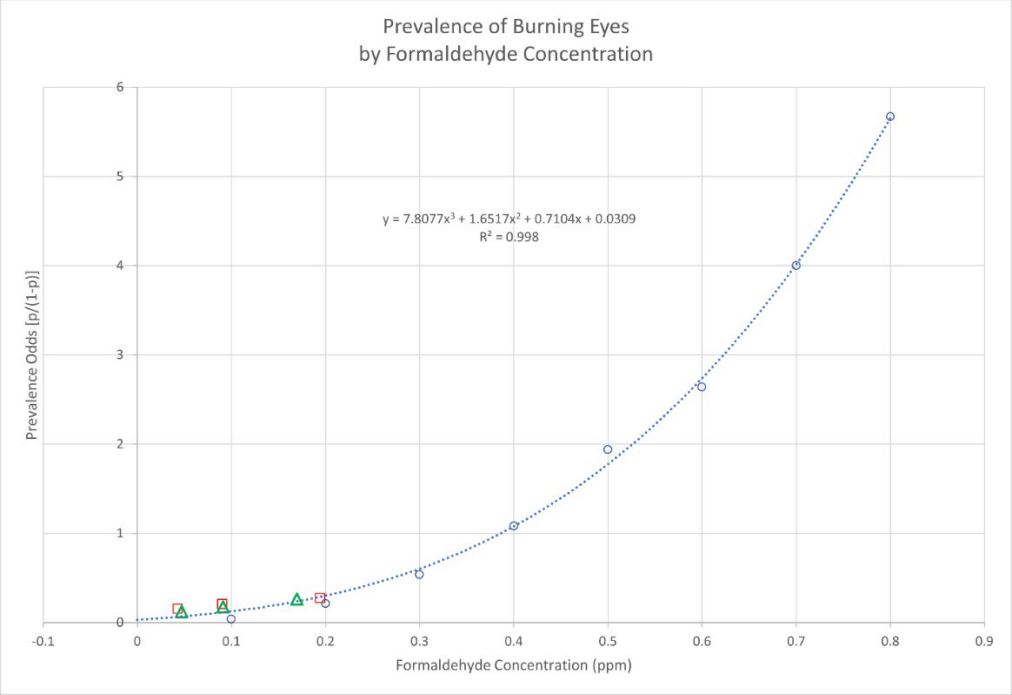


Figure 5-1. Plot of the prevalence odds by residential concentration-response information from the central estimate of from Hanrahan et al. (1984) combined with complementary information from the central estimate of from Liu et al. (1991).

Blue circles (**Hanrahan et al., 1984**); Red squares 'Summer' Liu et al. (**1991**); Green triangles 'Winter' Liu et al. (**1991**).

A parallel set of analyses was conducted using the upper bound effect estimates on prevalence from (Hanrahan et al., 1984) and (Liu et al., 1991) to derive a polynomial function of the upper bound prevalence of burning eyes. Assuming a background prevalence of "burning eyes" of 3%, EPA fit a cubic polynomial function with the intercept fixed at the log-odds of 0.03 (0.0309), to the combined prevalence odds data and found that a third-degree polynomial function fit with an R^2 value of 0.9996. The following formula describes the functional form for the prevalence odds:

$$\frac{p}{1-p} = 57.862 * (exposure)^3 - 11.934 * (exposure)^2 + 2.4996 * (exposure) + 0.0309 \quad \text{(Eq. 5-2)}$$

A BMR representing an extra risk of 10% is generally recommended as a standard reporting level for quantal data. Biological considerations may warrant the use of a BMR of 5% or lower for some types of effects (e.g., frank effects), or a BMR greater than 10% (e.g., for early precursor effects) as the basis of the point of departure (POD) for a reference value (U.S. EPA, 2012). EPA selected a BMR of 10% extra risks of eye irritation and assumed a background prevalence eye irritation of 3% (in the absence of formaldehyde exposure). Farrand (2017) reported that the prevalence of dry eye disease (eye irritation) was 3.4% among those aged 18-49 years and was higher in older groups and lower in younger groups (Farrand et al., 2017). The formaldehyde

concentration corresponding to a 13% prevalence of "burning eyes" was calculated from the exposure-response model (see Appendix D.1.1). The 13% prevalence represents a 10% extra risk of sensory irritation as a result of formaldehyde exposure in addition to an assumed background prevalence of 3%. These data were used to derive a BMC_{10} of 0.1403 mg/m^3 and a $BMCL_{10}$ of 0.070 mg/m^3 and the $BMCL_{10}$ serves as the POD for the combination of the two studies (see Appendix D.1.1 for details). A background prevalence of 3% was considered to be a reasonable estimate, but the impact of using lower and higher alternative estimates was evaluated.[45]

As noted by others (NASEM, 2023), this combined study analysis takes advantage of the greater range of exposure across the two studies for formaldehyde exposure in mobile homes, different exposure assessment methods (active and passive) with different limits of detection (0.1 ppm and 0.01 ppm), and different time periods of exposure assessment and symptom assessment.

Controlled human exposure studies

Based on the rationale for study selection provided in Table 5-1, PODs were determined using two controlled human exposure studies of formaldehyde for which there was *medium* confidence that evaluated multiple levels of exposure, one by Kulle et al. (Kulle et al., 1987; Kulle, 1993) and another by Andersen and Molhave (Andersen, 1979; Andersen and Molhave, 1983) (see study descriptions in Table 5-8). The selected points of departure (PODs) and most informative comparisons are described below, with additional details in Appendix D.1.1. Overall, the POD of 0.44 mg/m^3 (0.36 ppm) based on the study by Kulle et al. (Kulle et al., 1987; Kulle, 1993) was selected as the most reliable quantitative estimate of the sensory irritant responses from these two studies of intentionally exposed human volunteers. Although the POD from Anderson and Molhave of 0.12 mg/m^3 (0.10 ppm) was lower, this POD was associated with lower confidence due to the lack of information on background symptoms without formaldehyde exposure, lack of reporting on symptom severity and incidence of individual irritant symptoms, and other uncertainties (e.g., approximately one-third of participants were smokers) in the reported results.

Kulle et al. (1993) reanalyzed results of a study of eye, nose, and throat irritation among participants exposed to 0, 0.5, 1.0, 2.0, and 3.0 ppm for 3 hours once a week with exposure order randomly assigned (Kulle et al., 1987). The healthy volunteers (19 nonsmokers averaging approximately 26 years of age, including 10 males and 9 females total [note: only 6 females and 4 males were exposed at 0.5 ppm and only 5 males and 3 females were exposed at 3.0 ppm]) all served as their own controls. The sensory irritation symptoms reported by the authors were prevalence of eye irritation or prevalence of nose/throat irritation. The severity of the irritation symptoms was scored using a 4-point scale for none, mild, moderate, and severe effects. For this *medium* confidence study, two characteristics (one limitation, one strength) of the data were addressed in deriving the POD.

[45] A background of 1% yields a BMC_{10} of 0.174 mg/m^3; 2% yields 0.182 mg/m^3; 6% yields 0.213 mg/m^3; A background of 1% yields a $BMCL_{10}$ of 0.060 mg/m^3; 2% yields 0.066 mg/m^3; 6% yields 0.088 mg/m^3.

As a limitation of this study design, the same volunteers were exposed to multiple formaldehyde concentrations; thus, responses from individual volunteers were correlated across different exposure concentrations. Typical BMD approaches do not account for such data dependence and the standard BMDL (i.e., at the 95th percentile lower bound) is interpreted as unlikely to reasonably reflect the true variability in these measurements. To address the data dependence and underestimated variation in the BMC, the 99th percentile on the selected model is presented and ultimately selected. This widened confidence interval provides a transparent means of approximating the increased variability expected if independent data measurements were available. The 95th percentile lower bound is provided for all evaluated models for comparative purposes (see Appendix D.1.1 for additional details).

Several approaches were taken to address the presentation of symptoms of varying severity and different sensory irritation symptoms, a strength of this study. The current BMD modeling software is applicable for analysis of a single outcome, but it does not account for differences in outcome severity, and it does not allow for the inclusion of multiple related outcomes in a single analysis. EPA's categorical regression (CatReg; https://www.epa.gov/bmds/about-catreg) software allows for greater incorporation of these different components of the evidence in the modeling. CatReg provides two basic models to relate the probabilities of the different severity categories to exposure level and exposure duration, taking user-defined covariates into account (e.g., species, gender, target organ, etc.) (U.S. EPA, 2017). The parameters in the models are an intercept term and coefficients of dose and time. [46]

Thus, CatReg was used in dose-response analyses to incorporate information on severity and combine data across different sensory irritation endpoints, to the extent possible. These results were compared with results of modeling using current BMD software for comparative purposes (see additional details, including additional information on CatReg, in Appendix D.1.1). A POD of 0.44 mg/m^3 (0.36 ppm) was selected for this study based on the 99th percentile BMCL and CatReg modeling of the combination of eye irritation and nose/throat irritation symptoms. Importantly, this POD was interpreted with less uncertainty than the other POD options or incorporated more study-specific information on the subjects' responses; thus, this was considered to be the most reliable estimate available for this study.

Another experimental study exposed a group of 16 subjects (5 females and 11 males averaging 23 years old, 5 of which were smokers, with one being a heavy smoker) to 0.3, 0.5, 1.0, and 2.0 mg/m^3 formaldehyde for 5-hour periods with a 2-hour clean air exposure prior to each trial (Andersen, 1979; Andersen and Molhave, 1983). The healthy volunteers all served as their own controls and the order of exposure concentrations was randomized. The sensory irritation symptoms reported by the authors were prevalence of conjunctival redness and/or nose or throat

[46] Model 1, the cumulative odds model, allows the intercept term to vary with severity level, but not the coefficients of dose and time. Model 2, the unrestricted cumulative model, allows any of the parameters to vary with severity level. For details, see the CatReg User Guide (U.S. EPA, 2017).

dryness. For this *medium* confidence study, two limitations in the quantitative use of the reported data needed to be addressed in deriving the POD.

First, the occurrence of irritation symptoms during the clean air exposure was not reported. The background incidence of sensory irritation in the general population, or within healthy adult volunteers such as those participating in this study, is uncertain. An indirect comparison to the population prevalence of dry, irritated, or burning eyes may be a reasonable surrogate for estimating such a background. Although estimates vary, an estimate of the overall background prevalence of diagnosed dry eye disease in U.S. adults is 6.8% (Farrand et al., 2017). When this is restricted to 18–49-year-olds, the authors estimated a background prevalence of 3.4%. This is at the lower end of the background prevalence for such symptoms, which increase with age and vary by gender (with a higher prevalence in females). Thus, BMD modeling was performed assuming different background prevalence. The PODs derived using these different estimates of background varied less than 2-fold (see Appendix D.1.1). Ultimately, use of the lower end (i.e., 3%) of the estimates on the background prevalence of dry eye, is considered appropriate for modeling the broadly healthy populations (20–33-year-old healthy adults in (Andersen, 1979; Andersen and Molhave, 1983)) and variably severe irritation symptoms reported in the available controlled human exposure studies of formaldehyde. Thus, paralleling what was decided for the human residential studies discussed in the prior section, an estimate of 3% background prevalence of irritation during the clean air exposure was selected.

Second, the same volunteers were exposed to multiple formaldehyde concentrations; thus, responses from individual volunteers were correlated across different exposure concentrations. Typical BMD approaches do not account for such data dependence and the standard BMDL (i.e., at the 95th percentile lower bound) is interpreted as unlikely to reasonably reflect the true variability in these measurements. To address the data dependence and underestimated variation in the BMC, the 99th percentile on the selected model is presented and ultimately selected. As discussed for modeling of sensory irritation data reported by Kulle et al. (1993), this widened confidence interval provides a transparent means of approximating the increased variability expected if independent data measurements were available. The 95th percentile lower bound is shown for all evaluated models for comparative purposes.

Thus, BMD software was used to identify both the 95th and 99th percentile lower bounds assuming different levels of background symptoms in the clean-air exposures. A POD of 0.12 mg/m^3 (0.10 ppm) was selected for this study based on the 99th percentile BMCL assuming a 3% background prevalence (see additional details in Appendix D.1.1).

Analysis and Summary of the PODs

Table 5-8 presents the studies used to calculate PODs (bolded) for sensory irritation based on human residential studies and controlled human exposure studies.

Table 5-8. Summary of derivation of PODs for sensory irritation

Study and endpoint	Population	Observed effects by exposure level[a]	POD_{ADJ}[b] (mg/m^3)
Human Residential Studies			
Symptom prevalence Hanrahan et al. (1984) combined with Liu et al. (1991) *Medium* confidence (both studies)	Teenage and adults (M and F) n = 61, mean age 48 years + Adult (M and F), n = 739, Adults 20-64 years in Summer overlapping with n = 587, Adults 20-64 years of in Winter (M and F)	Prevalence data from Liu et al. combined with prevalence data points from Hanrahan et al. Prevalence data transformed to "Prevalence odds" [p/(1-p)] and fit with a third-degree polynomial model using graphically presented results of logistic regression analysis. BMC_{10}: concentration where an increased prevalence of 10% (BMR) over a 3% background prevalence. Upper bound on prevalence data points from Liu et al. combined with upper bound prevalence data from Hanrahan et al. and fit with a third-degree polynomial model. See Appendix D.1.1 for details. $BMCL_{10}$: concentration where an increased upper bound prevalence of 10% (BMR) over a 3% background prevalence.	BMC_{10}[c] = 0.14 **$BMCL_{10}$[c] =0.070**
Controlled Human Exposure Studies			
Symptom prevalence (combined eye irritation and nose or throat irritation) (Kulle et al., 1987; Kulle, 1993) *Medium* confidence	Nonsmoking, healthy, *n* = 10–19, mean age 26.3 years (M and F)	Exposure and proportion (and %) responding (M+F) *mg/m³*: 0 / 0.62 / 1.2 / 2.5 / 3.7 Eye irritation[d]: 1/19 / 0/10 / 5/19 / 10/19 / 10/10 %: 5 / 0 / 26 / 53 / 100 Nose or throat irritation: 3/19 / 1/10 / 1/19 / 7/19 / 9/10 %: 16 / 10 / 5 / 37 / 90 trend, $p < 0.05$ CatReg[e], analysis, combined endpoints and Probit model selected (both CatReg and standard BMDS modeling were used, with multiple endpoints individually or in combination; see Appendix D.1.1): CatReg, combined eye irritation and nose or throat irritation (probit) BMC = 0.69 mg/m^3 CatReg, eye irritation (CLogLog) BMC = 0.98 mg/m^3 CatReg, nose/throat irritation BMC= model fit unacceptable BMDS, eye irritation (Probit) BMC = 0.85 mg/m^3 BMDS, nose/throat irritation (Multistage 3°) BMC = 1.56 mg/m^3	BMC_{10} = 0.69 $BMCL_{10}$ (95th percentile) = 0.52 **$BMCL_{10}$ (99th percentile[f]) = 0.44**
Symptom prevalence (conjunctival redness and nose or throat dryness) (Andersen, 1979; Andersen and Molhave, 1983) *Medium* confidence	Healthy students, *n* = 16, age 20–33 years, 31.2% smokers (M and F)	Exposure and proportion (and %) responding (prevalence at the end of exposure) (M+F) *mg/m³*: 0 / 0.3 / 0.5 / 1.0 / 2.0 Symptom prevalence: Not reported / 3/16 / 5/16 / 15/16 / 15/16 %: 19 / 31 / 94 / 94 BMDS modeling assuming different (background) prevalence for clean air dose (see Appendix D.1.1[g]):	BMC_{10} = 0.28 $BMCL_{10}$ (95th percentile) = 0.17 **$BMCL_{10}$ (99th percentile[f]) = 0.12**

Study and endpoint	Population	Observed effects by exposure level[a]	POD_{ADJ}[b] (mg/m^3)
		0% Log-logistic model BMC = 0.26 mg/m^3 3% Log-logistic model BMC = 0.28 mg/m^3 6% Log-logistic model BMC = 0.30 mg/m^3 9% Hill model BMC = 0.45 mg/m^3	

[a]Any concentrations reported in publications as ppm have been converted to mg/m^3.
[b]These PODs were not adjusted for a 24-hour equivalent concentration because the timing of formaldehyde measurements was concluded to be appropriate to the time frame of reported symptoms. The selected POD for each study is bolded.
[c]BMC_{10} benchmark concentration at 10% increase in prevalence over an estimated 3% background prevalence. An increase of 10% was selected consistent with EPA guidelines (U.S. EPA, 2012) because the endpoint, burning eyes with mild to moderate severity, was considered a minimally adverse outcome.
[d]The study reported results in males and females across a 4-scale symptom rating system (none, mild, moderate, severe). The data here reflect pooled findings of any symptom incidence other than none in both males and females from the (Kulle, 1993) publication; the unpooled results are presented in Appendix D.1.1. Note that the authors also report results for a "symptom score difference" (pre- and post-exposure), pooling results across severity levels in the (Kulle et al., 1987) publication; however, these pooled data were not selected for use quantitatively as there was no information on either the underlying within-subject severity information at both timepoints (pre- and post-exposure) or the score calculations.
[e]EPA's categorical regression (CatReg; https://www.epa.gov/bmds/about-catreg) software was used in addition to standard BMDS modeling. The selected model used eye irritation data to predict the slope and combined eye and nose/throat irritation data for the intercept. A second modeling combination using nose/throat irritation for the slope and combined irritation data for the intercept yielded a slightly higher POD of 0.59 mg/m^3 (0.48 ppm) at the 99^{th} percentile. The selected CatReg model results for the combined endpoints were chosen primarily due to the lower POD, although the BMC/BMCL ratio for these results was also lower, indicating a narrower confidence interval and a lower level of uncertainty. See Appendix D.1.1 for additional details.
[f]The BMD models did not account for the correlated measures between concentration levels (each participant was exposed to each concentration). Therefore, the 95% confidence limit for the BMC estimated by the model is too narrow to use as the POD. A wider confidence interval (i.e., the 99% lower confidence limit) was used as the POD.
[g]Note: data for males and females were not reported separately.

The BMC_{10} based on the combination of two studies of sensory irritation in mobile homes (Hanrahan et al., 1984) combined with Liu et al. (1991) is 0.140 mg/m^3 and the $BMCL_{10}$ is 0.070 mg/m^3. Potential concerns regarding this POD include the short, 1-hour, duration of the measurement of formaldehyde to represent the average exposure, the lack of concurrence of the exposure and outcome ascertainment from (Hanrahan et al., 1984) which accounted for less than 10% of the combined population, and the graphical nature of the results from both studies. However, the combined study population from Hanrahan et al. (1984) and (Liu et al., 1991) is pertinent to the U.S. general population because: (1) the populations were randomly selected from the general population in the study area; (2) the exposure levels were concluded to reflect the usual, relatively constant formaldehyde concentrations in the residences; and (3) exposed individuals included a range of ages (teenagers and adults), men and women, and some with chronic disease. The impact of potential confounding by the presence of coexposures is likely to be minimal. The regression models in both studies adjusted for age, sex, and smoking. The presence of smokers or gas appliances in the home, sources that might contribute to variability in formaldehyde concentrations, were not associated with indoor formaldehyde concentrations. Other emissions released from the same sources as formaldehyde that also might contribute to eye irritation, such as phenols from resins in floor or wall coverings or pinene and terpenes from wood products, were not analyzed. However, a strong exposure-response relationship with formaldehyde concentration

was observed by this study, which argues against a large effect by residual confounding by other coexposures.

The PODs based on the two controlled human exposure studies were 0.12 mg/m^3 (Andersen, 1979; Andersen and Molhave, 1983) and 0.44 mg/m^3 (Kulle et al., 1987; Kulle, 1993), less than an order of magnitude greater than the POD estimated from residential exposure. The POD based on Kulle et al. (Kulle et al., 1987; Kulle, 1993) is preferred to the estimate based on Andersen and Molhave (Andersen, 1979; Andersen and Molhave, 1983), as explained above. In the context of deriving an RfC for lifetime formaldehyde inhalation, the PODs based on these intentional exposure studies possess several notable limitations as compared to the residential exposure POD because: (1) the study participants were young, healthy volunteers not representative of the age distribution and health status in the general population; (2) the PODs are based on small sample sizes, more subject to random variation; and (3) formaldehyde concentrations were high, imposing substantial uncertainty regarding responses at the low tail of the exposure distribution. However, the utility of the PODs from these two controlled exposure studies may be greater for other, less than chronic, exposure durations (e.g., derivation of an acute RfC).

Pulmonary Function

Table 5-2 provides the rationales for selecting the epidemiology study of residential formaldehyde exposure (Krzyzanowski et al., 1990) for POD derivation, which is summarized in Table 5-9 below. Declines in peak expiratory flow rate (PEFR) were associated with increases in 2-week average indoor residential formaldehyde concentrations, with greater declines observed in children (5–15 years of age) compared to adults (Krzyzanowski et al., 1990). This study of effects in a residential population used the most thorough exposure assessment protocol representing the etiologically relevant exposure window and repeated measurements of PEFR, thus enhancing the sensitivity of this study for detecting an effect on pulmonary function. Mean formaldehyde levels were 26 ppb (0.032 mg/m^3), and more than 84% of the homes had concentrations 40 ppb (0.049 mg/m^3) and lower. A BMC_{10} of 0.033 mg/m^3 and $BMCL_{10}$ of 0.021 mg/m^3 were determined from the regression coefficient from a random effects model of PEFR among children reported (and presented graphically) by the study authors (for details, see Appendix D.1.2). Table 5-9 presents the study used to calculate a POD with the epidemiology data and sequence of calculations leading to the derivation of a POD relating to pulmonary function.

Table 5-9. Summary of derivation of PODs for pulmonary function

Endpoint and reference	Population	Results by exposure level[a]	BMC and BMCL (mg/m^3)	POD_{ADJ}[b] (mg/m^3)
PEFR Krzyzanowski et al. (1990) Residential, prevalence	202 households, 298 children aged 5–15 years, current asthma prevalence 15.8%; 613 adults and adolescents > 15 years,	Random effects model; decreased PEFR, children -1.28 ± 0.46 L/minute-ppb (95% upper bound −2.04 L/minute-ppb)	BMC_{10}[c] 0.033 $BMCL_{10}$[c] 0.021	0.021

Endpoint and reference	Population	Results by exposure level[a]	BMC and BMCL (mg/m^3)	POD_{ADJ}[b] (mg/m^3)
High confidence	24.4% current smokers, current asthma prevalence 12.9%	Formaldehyde concentrations: Mean 0.032 mg/m^3, maximum 0.172 mg/m^3		

[a]Concentrations reported in publication converted to mg/m^3.

[b]The POD was not adjusted for a 24-hour equivalent concentration because formaldehyde is present in all indoor environments and time-activity information for participants was not reported.

[c]BMC_{10} benchmark concentration associated with a 10% decrease in pulmonary function. A BMR of 10% reduction in PEFR was selected as a cut-off point for adversity, based on rationales articulated by the American Thoracic Society (ATS, 2000). The American Thoracic Society (ATS, 2000) recommended that "a small, transient loss of lung function, by itself, should not automatically be designated as adverse" and ATS cited EPA's 1989 review of ozone, which offered a graded classification of lung function changes in persons with asthma as "mild," "moderate," or "severe" for reductions of less than 10, 10–20, and more than 20%, respectively (U.S. EPA, 1989). ATS (2000) concluded that, in evaluating the adverse health effects of air pollution at the level of population health (compared to individual risk), "[a]ssuming that the relationship between the risk factor and the disease is causal, the committee considered that such a shift in the risk factor distribution, and hence the risk profile of the exposed population, should be considered adverse." This was specifically considered by ATS (2000) even when "[e]xposure to air pollution could shift the distribution toward lower levels without bringing any individual child to a level that is associated with clinically relevant consequences." A moderate adverse effect at functional decrements of 10–20% was considered the best indicator of adverse effects in the study population.

Analysis and Summary of the POD

The adjusted POD estimated using the results of Krzyzanowski et al. (1990) (0.021 mg/m^3) was derived from the responses of a randomly selected population of adults and children continuously exposed to formaldehyde in their homes. In this large, population-based sample, the investigators observed a linear relationship between increased formaldehyde exposure and decreased peak expiratory flow rate (PEFR) among children exposed to average concentrations of 0.032 mg/m^3 (26 ppb), and a stronger response was observed among children with asthma. Krzyzanowski et al. (1990) adjusted for smoking status, environmental tobacco smoke and NO_2 levels in their analyses; thus, confounding by these coexposures can be ruled out. Further, a strong exposure-response relationship with formaldehyde concentration was observed by this study, which argues against a large effect by residual confounding by other coexposures. This study was able to evaluate associations with relatively constant, low formaldehyde concentrations and used a high-quality exposure measurement protocol, thus, reducing uncertainties for low-dose extrapolation (0.012 to 0.172 mg/m^3 (Quackenboss et al., 1989c). The average formaldehyde concentrations measured using two one-week sampling periods, some of which were separated by one to several weeks and in different seasons represent the average levels present in the homes during the previous year, and therefore the analysis used the etiologically relevant exposure window for average pulmonary function status in this study population. Average formaldehyde concentrations in these studies were pertinent to those experienced by the general population (the authors reported that more than 84% of the homes had concentrations 40 ppb [0.049 mg/m^3] and lower). The POD is based on the findings among children and was derived from a regression model that adjusted for important potential confounders including smoking status, environmental tobacco smoke, socioeconomic status, NO_2 levels, episodes of acute respiratory illness, and the time of day and estimated the interaction between formaldehyde exposure and asthma status.

Immune-mediated Conditions, Focusing on Allergies and Current Asthma

Allergic conditions

Table 5-3 provides the rationales for selecting the two epidemiology studies of residential- or school-based formaldehyde exposure (Matsunaga et al., 2008; Annesi-Maesano et al., 2012) for POD derivation. NOAELs were identified in each of the two studies selected for POD derivation based on the pattern of risk seen across the exposure groups; the PODs were based on these NOAELs. The study by Annesi-Maesano et al. (2012) used a relatively long exposure period (5 days), and was a very large study in a school-based sample of children in France (n = 6,683) with analysis presented by tertile. Matsunaga et al. (2008) used 24-hour personal samples in a study of 998 pregnant women in Japan. The primary limitation of the Matsunaga et al. (2008) study is that it is conducted only among adults, and so is less able to address the variability in susceptibility that would be anticipated within a population.

Current asthma

Table 5-4 provides the rationales for selecting the three epidemiology studies of residential- or school-based formaldehyde exposure (Venn et al., 2003; Krzyzanowski et al., 1990; Annesi-Maesano et al., 2012) for POD derivation. The consistency of the results in the available residential- and school-based exposure studies, and the absence of an increased risk in the study by Annesi-Maesano et al. (2012), a large school-based study (n = 6,683) that used a 5-day sampling period for formaldehyde measurement, strengthens the basis for interpreting this set of studies as indicating an absence of risk of current asthma below 0.05 mg/m^3. Based on both the study by Annesi-Maesano et al. (2012) and the support from this collection of studies as a whole, EPA selected a NOAEL of 0.042 mg/m^3 for risk of current asthma in Annesi-Maesano et al. (2012).

The Krzyzanowski et al. (1990) results for children (5–15 years of age) are based on a relatively large sample size, with a comprehensive exposure assessment protocol (i.e., three locations in the home; two 1-week periods covering two seasons). An increased prevalence of current asthma was seen in the highest exposure group in a categorical analysis. The exposure range in this group was 0.075–0.172 mg/m^3, but the study also notes that few values were above 0.11 mg/m^3. Based on this information, EPA selected a LOAEL based on the midpoint of this exposure category using a range estimated as 0.075 to 0.11 mg/m^3 (midpoint of 0.092 mg/m^3). The estimate for the middle category of exposure was selected as a NOAEL, although there is greater uncertainty in the NOAEL, given the imprecision of the estimate (n with asthma = 1 for this category).

For the selected study on the degree of asthma control in children with asthma by Venn et al. (2003), EPA selected a NOAEL of 0.027 mg/m^3 (median exposure in the third quartile; no or weak RRs seen below this value) and a LOAEL of 0.041 mg/m^3 (median exposure in top quartile, for which a two- to three-fold increased risk of symptoms was seen). Venn et al. (2003) did identify an exposure-response relationship for both nighttime symptoms of poor asthma control as OR = 1.40

(95% CI 1.06–1.98) and for daytime symptoms of poor asthma control as OR = 1.45 (95% CI 1.00–1.94). Using the reported OR per quartile exposure from the regression results, and the median exposure values for each quartile (personal communication to EPA (Venn, 2012)), EPA calculated the concentration associated with a 5% increase in prevalence of symptoms above the prevalence observed in the referent group (for details of BMCL calculations, see Appendix D.1.3). A BMR of 5% was selected because asthma attacks are overt effects, generally requiring the use of drugs to control symptoms (i.e., a notably adverse effect) (U.S. EPA, 2012).

Analysis and Summary of the PODs

Table 5-10 presents the studies with the epidemiology data and sequence of calculations leading to the derivation of a POD for each data set with effects relating to allergies and asthma.

Table 5-10. Summary of derivation of PODs for allergies and current asthma based on observational epidemiology studies

Endpoint and reference	Population	Observed effects by exposure level	POD_{ADJ} (mg/m^3)
Allergic conditions			
Rhinoconjunctivitis (prevalence); school-based exposure (5 days) Annesi-Maesano et al. (2012) *High* confidence	Children ages 9–10 years (M and F) *N* = 6,683	Prevalence 12.1%, OR (95% CI) (adjusted) ≤0.0191 mg/m^3 1.0 (referent) >0.0191–0.0284 1.11 (0.94, 1.37) >0.0284– ~0.055 1.19 (1.03, 1.39) NOAEL selection: 0.024 mg/m^3, midpoint of second exposure category (corresponding to RR 1.11) LOAEL selection: 0.040 mg/m^3, midpoint of third exposure category (corresponding to RR 1.19)	NOAEL: 0.024 LOAEL: 0.040
Atopic eczema (prevalence); personal monitor-based exposure (24 hours) Matsunaga et al. (2008) *Medium* confidence	Adult women (pregnancy cohort) with median age 30 years *N* = 998	Atopic eczema (5.7% prevalence); Allergic rhinitis (14.0% prevalence) mg/m^3 / *n* / OR / (95% CI) / OR / (95% CI) <0.022 / 298 / 1.0 / (referent) / 1.0 / (referent) 0.023–0.033 / 299 / 1.03 / (0.47, 2.29) / 1.06 / (0.65, 1.73) 0.034–0.057 / 301 / 1.11 / (0.50, 2.42) / 0.85 / (0.51, 1.40) 0.058–0.161 / 100 / 2.36 / (0.92, 6.09) / 1.17 / (0.60, 2.28) (trend *p*-value) / / / (0.08) / / (0.91) 0.058 to 0.161 vs. <0.058 / / 2.25 / (1.01, 5.01) / 1.22 / (0.68, 2.20) per 0.0123 mg/m^3 / / 1.16 / (0.99, 1.35) / / [Stronger associations seen for atopic eczema in women with no family history of atopy] For atopic eczema NOAEL selection: 0.046 mg/m^3, midpoint for third exposure category (corresponding to RR 1.11).	Atopic eczema NOAEL: 0.046 LOAEL: not identified (data too uncertain) [a]
Prevalence of current asthma/degree of asthma control			

Endpoint and reference	Population	Observed effects by exposure level	POD_{ADJ} (mg/m^3)
Current asthma (prevalence); school-based exposure (5 days) *Annesi-Maesano et al. (2012)* *High* confidence	Children ages 9–10 years (M and F) *N* = 6,683	Exposure (mg/m^3) / *n*[a] / OR / (95% CI) ≤0.0191 / 2,200 / 1.0 / (referent) >0.0191–0.0284 / 2,200 / 1.10 / (0.85, 1.39) >0.0284– ~0.055 / 2,200 / 0.90 / (0.78, 1.07) [a]Approximation, based on tertiles, with total *n* = 6,590 NOAEL selection: 0.042 mg/m^3, midpoint of third exposure category (corresponding to RR 0.90)	NOAEL: 0.042 No LOAEL
Current asthma (prevalence); residence-based exposure (two 1-week periods) Krzyzanowski et al. (1990) *Medium* confidence	Children ages 5-15 years (M and F) *N* = 298	Exposure (mg/m^3) / *N* / Proportion with asthma <0.049 / 248 / 0.12 0.049–0.074 / 24 / 0.04 0.075–0.172 / 21 / 0.24 (trend *p*-value) / (0.03) Only a few values were reported to be above 0.11 mg/m^3. NOAEL selection: 0.062 mg/m^3, midpoint of second exposure category LOAEL selection: 0.092 mg/m^3, based on report that only a few values were above 0.11 mg/m^3, so estimated midpoint of third category was based on range from 0.075 to 0.11, with midpoint of 0.092 mg/m^3	NOAEL: 0.062 LOAEL: 0.092
Asthma control among people with asthma, residence-based exposure (3 days) Venn et al. (2003) *High* confidence	Children (M and F) ages 9–11 years *N* = 194	Exposure (mg/m^3) / *N* / Proportion / OR / (95% CI) Frequent nighttime symptoms <0.016 / 39 / 0.41 / 1.0 / (referent) 0.016–0.022 / 35 / 0.49 / 1.40 / (0.54, 3.62) 0.022–0.032 / 36 / 0.53 / 1.61 / (0.62, 4.19 0.032–0.083 / 33 / 0.67 / 3.33 / (1.23, 9.01) (trend *p*-value) / (0.02) per quartile increase / 1.45 / (1.06, 1.98) Frequent daytime symptoms <0.016 / 37 / 0.62 / 1.0 / (referent) 0.020–0.022 / 34 / 0.47 / 0.47 / (0.47, 1.25) 0.022–0.032 / 37 / 0.73 / 2.00 / (0.71, 5.65) 0.032–0.083 / 32 / 0.73 / 2.08 / (0.71, 6.11) (trend *p*-value) / (0.05) per quartile increase / 1.40 / (1.00, 1.94) NOAEL selection: 0.027 mg/m^3, median of third exposure category LOAEL selection: 0.041 mg/m^3, median of fourth exposure category (based on correspondence with Dr. Venn)	NOAEL: 0.027 LOAEL: 0.041 From regression results: $BMCL_5$: 0.013

[a] Matsunaga (2008) reported a clear effect in the highest exposure group (0.058–0.161 mg/m^3), but EPA was not able to estimate a measure of central tendency for this interval so the next lower exposure interval was judged to be a NOAEL.

For allergy-related conditions (rhinoconjunctivitis), EPA selected NOAEL and LOAEL values of 0.024 and 0.040 mg/m^3, respectively, in the Annesi-Maesano et al. (2012) study. A higher NOAEL value (NOAEL = 0.046) was selected based on the study in adults by Matsunaga et al. (2008). The classification of rhinoconjunctivitis by Annesi-Maesano et al. (2012) was the most sensitive and specific of the available measures, and the narrower confidence intervals in this study reflected the larger sample size. No other pollutants (e.g., NO_X, $PM_{2.5}$, acetaldehyde, acrolein, ETS) analyzed by this study were associated with rhinoconjunctivitis.

For the analysis of prevalence of current asthma, EPA selected a NOAEL of 0.042 mg/m^3 using the data from Annesi-Maesano et al. (2012) (and supported by other studies examining exposures at <0.05 mg/m^3), and a NOAEL of 0.062 mg/m^3 based on the data for children in the

study by Krzyzanowski et al. (1990). The NOAEL identified from Krzyzanowski et al. (1990) is less reliable because it was based on only one case and a small number of participants in the selected exposure group. A $BMCL_5$ of 0.013 mg/m^3 was selected based on the data for degree of asthma control among children with asthma (Venn et al., 2003). Venn et al. (2003) used a strong study design, observed an exposure-related trend in response and adjusted the statistical analyses for key confounders, including other indoor exposures (e.g., visible mold, total VOCs, NO_2, cotinine levels). All three studies were well conducted and are interpreted with *high* or *medium* confidence. The study by Annesi-Maesano et al. (2012) is a large study with a relatively long exposure measurement period and is supported by a collection of several other smaller studies (with more imprecise effect estimates) at exposures of <0.050 mg/m^3, which also indicate no increased risk of current asthma at these lower levels (see Section 3.2.3). The analyses by Annesi-Maesano et al. (2012) were adjusted for age, gender, passive smoking, and paternal or maternal history of asthma or allergic disease; thus, confounding is unlikely. The lower NOAEL for degree of asthma control in children with asthma compared with the NOAELs for increased prevalence of current asthma is interpreted to reflect a greater sensitivity of this more susceptible population.

Respiratory Tract Pathology

Table 5-5 provides the rationales for deriving PODs based on exposure-response data from two animal studies on histopathological changes (squamous metaplasia[47]) observed in the nasal passages of F344 rats (Kerns et al., 1983) and Wistar rats (Woutersen et al., 1989).

Squamous metaplasia in F344 rat (Kerns et al., 1983)

The results of a large, 2-year bioassay in F344 rats was reported in Kerns et al. (1983) and the supporting Battelle report (Battelle, 1982). In this study, male and female rats were exposed to 2.5, 6.9, and 17.6 mg/m^3 with interim sacrifices at 6, 12, and 18 months. While Kerns et al. (1983) reported squamous cell metaplasia after inhaled formaldehyde exposure, detailed information on lesion incidence by concentration, duration, and cross-section level was provided in the report (Battelle, 1982). The lesions occurred only in the most anterior region (cross-section Level I) at low concentrations but progressed to more distal parts of the nose (cross-section Levels II–V) at higher concentrations. Additionally, the incidence of squamous metaplasia increased with exposure duration. Section 1.2.4 discusses the incidence of squamous metaplasia in the first five nasal sagittal cross sections of the F344 rat, as reported by Kerns et al. (1983) and Battelle (1982).[48]

[47]Although a cRfC for hyperplasia was not estimated (see Section 3.2.4 for rationale), a human POD_{ADJ} that can be estimated based on the basal cell hyperplasia end point is roughly two-fold greater than that obtained from the squamous metaplasia data from Woutersen et al. (1989) study. This estimate of hyperplasia provides context to the development of unit risk estimates for nasal cancer (see Section 5.2.1)

[48]The data for 27 and 30 mos represent incidence after 3 and 6 mos of nonexposure, respectively, following 24 mos of exposure.

The POD presented in Table 5-11 is based on lesions at Level 1 of the rat nasal passages. Extrapolation of the rat BMCL to the human is based on the available dosimetric simulations of formaldehyde flux[49] to the nasal lining in rats and humans. This assessment uses dosimetry derived from (Kimbell et al., 2001b; Kimbell and Subramaniam, 2001) and Overton et al. (2001) when extrapolating risk-related dose from the rat to the human (discussed in detail in Appendix C.1, particularly C.1.12, and Appendix D.1.4), and estimates the impact on the dosimetry modeling using Schroeter et al. (2014).[50] A POD based on lesions reported at Level 2 in Battelle (1982) can also be modeled. However, formaldehyde flux to the nasal lining on Level 2 was not available and could only be crudely estimated based on the locations of the nasal regions tabulated in Kimbell et al. (2001a), as elaborated further in Appendix C.1. For this reason, only a POD based on the Level 1 data is presented.

In determining the BMR level for the POD, severity scores for the squamous metaplasia data in Battelle (1982) were examined, where provided.[51] The average severity score was in the range of minimal-to-mild at the lowest dose for both the 18- and 24-month durations for Level 1. This finding supports a BMR of 0.1 extra risk, representing a minimal level of adversity. The 24-month data for Level 1 cannot be modeled because the dose-response relationship rises too steeply (for example, the Weibull model fit rises so steeply that the error on the Weibull model power cannot be bounded). Therefore, the 18-month data, for which incidence rises more gradually, were chosen even though these data would be less preferred over the 24-month exposure data. The fact that the lesion incidences are substantially higher with the longer duration (i.e., 24-month) data indicate that a lower POD would be associated with the 24-month exposure, were those data amenable to modeling.

Interspecies extrapolation of the rat BMCL level to humans was carried out in two steps. First, average flux values in the Level 1 region of the rat corresponding to the rat BMCL derived from the incidence of squamous metaplasia were estimated. Next, the exposure concentration at which any region in the human nose (see Appendix C.1) is exposed to this same level of formaldehyde flux at the inspiratory rate of 15 L/min was estimated from the flux tabulations in

[49]Flux (in units of mass/area-time) expresses the net transport of formaldehyde from the inspired air to the air-mucus interface of the nasal lining (prior to disposition within the tissue).

[50]As discussed in the Appendix C.1, Schroeter et al. (2014) revised the dosimetry model of (Kimbell et al., 2001b; Kimbell and Subramaniam, 2001) used for the flux estimates presented in Table 5-11, to include endogenous formaldehyde production and to explicitly model formaldehyde pharmacokinetics in the respiratory mucosa. EPA estimated the extent to which the results in Table 5-11 change if flux estimates from Schroeter et al. (2014) are used. The average flux over nonsquamous regions of the rat nose is roughly one-third of that in the human based on the dosimetry in Schroeter et al. (2014) in which endogenous formaldehyde is taken into account compared to a ratio of roughly one-half based on the dosimetry in (Kimbell et al., 2001b; Kimbell and Subramaniam, 2001). Thus, the POD is not altered appreciably (changing only by roughly a factor of 1.4) if the revised dosimetry model by Schroeter et al. (2014) is applied.

[51]The individual rat data generally allowed for assigning average severity scores for a given nasal level, concentration, and time point. In several cases (as with the 24-month, Level 2), the nasal level was not clear (i.e., the individual rat data could have come from Level 1, 2, or 3).

Kimbell et al. (2001a), table 3). These estimates are provided in the Table 5-11 below. The flux-based extrapolation results in a value similar to that obtained by applying the principle of ppm equivalence[52] (see table footnote). The benchmark dose model fits and such details and further elaboration of the human extrapolation are provided in Appendix D.1.4.

Table 5-11. Summary of derivation of POD for squamous metaplasia based on observations in F344 rats (Kerns et al., 1983)

Rat sagittal section	BMR	Rat $BMCL_{10}$ (mg/m^3)	Flux[a] ($pmol/mm^2$-hr)	Human exposure conc (mg/m^3)	Adjusted[b] human exposure conc (mg/m^3)
Level 1	0.10	0.448	685	0.484	0.086 [c]

[a]Approximate average flux over nasal lining at this level corresponding to the BMCL using estimates in Kimbell et al. (2001a).
[b]Adjusted for continuous exposure, (6 hours/24 hours) × (5 days/7 days).
[c]If extrapolation is based on ppm equivalence instead, value increases by 1.14-fold.

Squamous metaplasia Wistar rats (Woutersen et al., 1989)

Woutersen et al. (1989) reported on the nasal histopathology for male Wistar rats exposed to 0.1, 1.2, and 12.1 mg/m^3 for 28 months. Incidence of squamous metaplasia was reported by concentration and cross-section level (i.e., Level 1–2, 3, 4, and 5–6), with Level 1 as the most anterior region.

Following the determination for squamous metaplasia in F344 rats (Kerns et al., 1983), the same minimal adversity was considered for this effect in Wistar rats and a BMR of 0.10 extra risk was used. A dosimetry model for flux to the nasal lining of the Wistar rat is not available. EPA (U.S. EPA, 2012) concluded that internal dose equivalency in the extrathoracic region for rats and humans is in general achieved through similar external exposure concentrations (i.e., even for highly soluble and reactive gases ppm equivalence is a more appropriate default method for extrapolation than an approach based on adjustment by the ratio of surface area to minute volume). This concept is supported by the analysis described above of data from the squamous metaplasia occurring at Level 1 of the F344 rat nose. In that analysis, the extrapolation was based on site-specific flux in the rat and human and differs from an extrapolation based on ppm equivalence by only a factor of 1.14. Level 1 in that study was in the anterior portion of the nose, and the section levels in the Woutersen et al. (1989) study (see Table 5-12) are even more anteriorly located in the nose; therefore, there is even stronger support in this case for using ppm equivalence as the basis for extrapolation across species. Additional details on the benchmark dose modeling are provided in Appendix D.1.4.

[52]Also, see further discussion below in the analysis of squamous metaplasia in Wistar rats. "PPM equivalence" refers to toxicological equivalence across species when exposures are expressed in "ppm" and are suffered over equal durations expressed in units of the species lifetime. This originates from general allometric principles, wherein tissue exposure is equivalent when scaled by $BW^{3/4}$ while inhalation rates scale as $BW^{3/4}$; these factors cancel each other out when exposure is expressed in ppm.

Analysis and Summary of the PODs

The POD derivations are summarized in Table 5-12.

Table 5-12. Summary of derivation of PODs for squamous metaplasia based on studies in F344 and Wistar rats (Woutersen et al., 1989; Kerns et al., 1983)

Endpoint and reference	Species/ sex	Model	BMR	Rat BMC (mg/m^3)	Rat BMCL (mg/m^3)	Human POD^a_{ADJ} (mg/m^3)
Squamous metaplasia Kerns et al. (1983); Battelle (1982) *High* confidence	F344 rat, M and F	Log-probit	0.10[b]	0.576	0.448	0.086[c]
Squamous metaplasia Woutersen et al. (1989) *High* confidence	Wistar rat, M	Log-probit	0.10[b]	0.821	0.459	0.082[d]

[a]POD_{ADJ} is the human equivalent of the rat BMCL duration adjusted (6/24) × (5/7) for continuous daily exposure.
[b]BMR = 0.10 because the severity of squamous metaplasia, as indicated by the severity scores, was considered minimally adverse.
[c]Human extrapolation was based on estimates of regional formaldehyde tissue flux modeled in Kimbell et al. (2001a), table 3.
[d]Human extrapolation was based on ppm equivalence derived from pharmacokinetic principles.

Confidence is *high* in the two studies used to derive PODs, as both studies were well designed and executed with adequate reporting of data. Kerns et al. (1983; Battelle, 1982) was conducted under Good Laboratory Practice conditions, and the inhalation exposure protocols in both studies were adequately documented and well conducted. The POD from Kerns et al. (1983) is more uncertain, primarily because the calculation involved an extrapolation well below the tested formaldehyde concentrations and the BMCL was based on the 18-month exposure although the response was greater in magnitude after 24 months. Studies with various durations and in multiple species/strains have consistently reported histopathological effects after inhaled formaldehyde exposure. Squamous metaplasia was also observed in humans exposed to formaldehyde levels between 0.1 and 2.5 mg/m^3 (see Section 3.2.4).

Reproductive and Developmental Toxicity

Female reproductive or developmental toxicity

Table 5-6 provides the rationales for selecting a single occupational exposure study in humans for POD derivation (Taskinen et al., 1999). Taskinen et al. (1999) presented risk estimates for increased TTP for index pregnancies of women in three exposure categories. The exposure assignments were made for jobs held beginning at least 6 months prior to the index pregnancy to evaluate TTP, the primary endpoint of interest. Taskinen et al. (1999) calculated a fecundity density ratio for the three exposure categories based on 8-hour (time-weighted average) TWA (TWA8)

formaldehyde concentrations composed of measured concentrations associated with specific work tasks and reported time spent conducting those tasks in the workplace. TTP was elevated in the high exposure group relative to the unexposed group. EPA selected the middle TWA8 exposure level as a NOAEL.

The mean TWA concentrations for each exposure category needed to be adjusted for background formaldehyde exposures experienced by the employees when they were not conducting work tasks with identified formaldehyde exposure. Notably, the mean exposure (18 ppb TWA8) and lowest reported concentration measured in a work area (10 ppb) in the "low exposed" category were less than the reported average ambient exposures for Finland (21.4 ppb) (Jurvelin et al., 2001). The investigators in Taskinen et al. (1999) appear to have assumed that, while the women were away from their "exposed" work area, their exposure to formaldehyde was zero, not accounting for background occupational exposures and ambient levels of formaldehyde. Therefore, EPA recalculated the mean TWA8 concentrations. These calculations are presented in Table 5-13.

Normally, exposures from occupational studies are adjusted to account for the daily breathing volume appropriate to an environmental (versus occupational) setting and for exposure every day of the year (U.S. EPA, 1994). However, with formaldehyde, there is potential for exposure outside of work from in-home and environmental sources of formaldehyde. Therefore, the POD represents exposure during an 8-hour workday.

Table 5-13. Adjusted time-weighted average formaldehyde exposures for Taskinen et al. (1999)

(A) Proportion of work shift corresponding to the exposure group mean task-level formaldehyde exposure (ppb) and the exposure group daily exposure index (8-hour time-weighted average, TWA8). (B) Recalculation of daily exposure index (TWA8) where background formaldehyde exposure is estimated for work time spent on tasks considered unrelated to occupational use of formaldehyde.

A

Exposure group (*n*)	Reported mean exposure (TWA8)		Measured average task-level concentrations (ppb)		Estimate of work time for formaldehyde-related tasks assuming mean exposure levels	
	Mean (ppb)	Range	Mean	Range	Percentage of work time[a]	Hours per 8-hr work shift
Low (119)	18	1–39	70	10–300	26%	2
Medium (77)	76	40–129	140	50–400	54%	4.3
High (39)	219	130–630	330	150–1,000	66%	5.3

[a]Calculated as mean exposure (ppb, TWA8) divided by mean task-level exposures for the exposure group.

B

Exposure group (*n*)	Estimate of formaldehyde exposure during formaldehyde-related work tasks		Estimate of formaldehyde xposure from background levels during the work shift		Alternative daily exposure index (ppb, TWA8)
	Mean (mg/m^3)[a]	Percentage of work time in formaldehyde task	Background formaldehyde (ppb)	Percentage of time in tasks unrelated to formaldehyde	
Low (119)	0.086	26%	0.026	74%	0.042
Medium (77)	0.172	54%	0.026	46%	0.106
High (39)	0.406	66%	0.026	34%	0.278

[a]Converted from units of ppb reported in paper.

Male reproductive toxicity

Table 5-7 provides the rationales for selecting two studies reporting effects on the male reproductive system in rats for POD derivation (Ozen et al., 2002; Ozen et al., 2005). Both studies exposed the animals to paraformaldehyde via inhalation; thus, the interpretation of the results from these studies was not compromised by possible methanol coexposure as with many other studies that evaluated male reproductive toxicity endpoints. Although the (Ozen et al., 2002; Ozen et al., 2005) studies evaluated a small number of animals (seven and six male rats per group, respectively), the studies were able to detect statistically significant effects and the results did not demonstrate excessive variability. In Ozen et al. (2002), small but statistically significant and dose-dependent decreases (8 to 10% reductions from controls) in testis weight (relative to body weight)

were observed after 13 weeks of formaldehyde exposure. Although absolute organ weights are preferred for this measure because testis weights are generally conserved when body weight is decreased, mean body weights were also significantly decreased with exposure; thus, this response pattern suggests that the organ weight decreases were likely due to a direct effect on the testis (note: in this case, decreased relative testis weight is likely an underestimate of the more appropriate decrease in absolute testis weight). In addition, this effect increased with duration of treatment (from 4 to 13 weeks of exposure; (Ozen et al., 2002) and was associated with alterations in testicular zinc, copper, and iron levels (measured in the same study), thus reducing concerns about the small magnitude of effect. For the decreased testis weight at week 13 (Ozen et al., 2002), a LOAEL of 24.4 mg/m^3 was adjusted for continuous exposure based upon the experimental paradigm to yield a POD_{ADJ} of 5.81 mg/m^3 (POD_{ADJ} = 24.4 mg/m^3 × 8 hour exposed per day/24 hours per day × 5 days exposed per week/7 days per week).

In Ozen et al. (2005), statistically significant and dose-dependent decreases in serum testosterone levels (40 to 65% decreases from control values) were observed following 13 weeks of inhalation exposure. At the same exposure levels, significant decreases of 23 to 26% from control were noted in mean seminiferous tubule diameters, an effect that could have been directly related to testosterone decreases. For the decreased serum testosterone at 13 weeks (Ozen et al., 2005), a $BMCL_{1SD}$ of 1.465 mg/m^3 was calculated. A BMR of 1SD was used in the absence of information to support an alternative BMR, consistent with EPA guidelines (U.S. EPA, 2000). This value was adjusted for continuous exposure based upon the experimental paradigm to yield a POD_{ADJ} of 0.349 mg/m^3 (POD_{ADJ} = 1.465 mg/m^3 × 8 hour exposed per day/24 hours per day × 5 days exposed per week/7 days per week).

EPA (U.S. EPA, 2012) indicates that for highly soluble and reactive gases that interact with tissue at the portal of entry or for gases with systemic penetration ppm equivalence is likely to be the most appropriate default method for extrapolation. Accordingly, the human equivalent concentrations (HECs) were thus determined to be 5.81 and 0.349 mg/m^3 for the PODs from Ozen et al. (2002) and Ozen et al. (2005), respectively.

Analysis and Summary of the PODs

The POD for female reproductive or developmental toxicity is described in Table 5-14 and the PODs for male reproductive toxicity are described in Table 5-15.

Table 5-14. Summary of derivation of PODs for reproductive toxicity in females

Endpoint and reference	Population	Observed effects by exposure level	POD (mg/m^3)
Time-to-Pregnancy in Females			

Endpoint and reference	Population	Observed effects by exposure level	POD (mg/m³)
Occupational prevalence Taskinen et al. (1999) *Medium* confidence	Adult women, *n* = 602	**Time-to-Pregnancy by Formaldehyde Category** Fecundability density ratio (FDR)[a] Mean TWA8 (mg/m³) / # / FDR[b] / 95% CI Not exposed / 367 / 1.00 / - 0.042 / 119 / 1.09 / 0.86–1.37 0.106 / 77 / 0.96 / 0.72–1.26 0.278 / 39 / 0.64 / 0.43–0.92 FDR = ratio of average incidence densities of pregnancies in exposed compared to employed unexposed women Discrete proportional hazards regression; adjusted for employment, smoking, alcohol consumption, irregular menstrual cycles and # children Comparison: index pregnancies that occurred when participants were not employed in exposed workplace	NOAEL = 0.106 LOAEL = 0.278

Abbreviations: TWA8 = 8-hour time-weighted average; FDR = false discovery rate; NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level.

[a]Concentrations converted to mg/m³.

[b]TWA8 reported by authors was recalculated by EPA to account for background formaldehyde exposure while working in "nonexposed" work areas.

Table 5-15. Summary of derivation of PODs for reproductive toxicity in males

Endpoint and reference	Species/ sex	Model	BMR (mg/m³)	BMC (mg/m³)	BMCL (mg/m³)	POD_{ADJ} (mg/m³)
Ozen et al. (2002) Decreased relative testis weight (13 week) *Medium* confidence	Rat/M	LOAEL (24.4 mg/m³)[a]	N/A	N/A	N/A	5.81
Ozen et al. (2005) Decreased serum testosterone (13 week) *Medium* confidence	Rat/M	Power	1 SD	1.935	1.465	0.349

[a] BMD modeling at both 10%RD and 1SD were unsuccessful (see Appendix D.1.5). As decreased weights (i.e., a statistically significant decrease of 7.7%) were observed at the lower dose of 12.2 mg/m³, the lower dose could not be reasonably supported as a NOAEL.

For female reproductive or developmental toxicity, a POD was identified based on the findings of Taskinen et al. (1999). The study was well-conducted, a robust exposure assessment was used, and the data analysis was adjusted for other risk factors and workplace exposures that could be associated with developmental toxicity. However, because the study evaluated an occupational cohort, generalization to the entire general population is more uncertain. Stratification by use of gloves (yes/no) indicated that women who did not use gloves had a lower FDR. The stronger association among this group implies that dermal absorption might have

resulted in a greater response. Therefore, the level of certainty concerning the value of the NOAEL associated solely with inhalation exposure is lessened.

For male reproductive toxicity, the lowest formaldehyde concentration tested in Ozen et al. (2002) was 12.2 mg/m^3, and in Ozen et al. (2005) was 6.2 mg/m^3 and both studies had small sample size (N = 6–7 male rats/group). Otherwise, however, both (Ozen et al., 2002; Ozen et al., 2005) studies were well conducted and interpreted with *medium* confidence, and the observed responses in each study were statistically significant, dose-dependent, and supported by the larger body of animal study data for formaldehyde. Nevertheless, while some rodent studies in the formaldehyde database demonstrated testis (and epididymal) weight deficits coherent with the observed histopathological changes in these organs, there were inconsistencies in organ weight changes across studies that complicate interpretation. Further, the reporting of only relative testes weight rather than the preferred metric of absolute weight is an added uncertainty, although this does mitigate concerns regarding the influence of systemic toxicity on this endpoint. In addition to the high formaldehyde exposure levels and lack of absolute organ weights noted above for Ozen et al. (2002), an inability to successfully model the data represents another uncertainty. For the other POD from Ozen et al. (2005), while two studies observed treatment-related decreases in serum testosterone, evidence of testosterone decreases in the absence of systemic toxicity (observed or inferred) is not available. As significant systemic toxicity is likely to have an impact, potentially a large impact, on serum testosterone levels, the uncertainty in this POD is considered to be greater than the uncertainty associated with the POD based on the organ weight changes in Ozen et al. (2002).

5.1.3. Derivation of Candidate Reference Concentrations

In this section, the PODs (either POD_{ADJ} or POD_{HEC}) calculated in Section 5.1.2 were used to derive candidate reference concentrations (cRfCs). These derivations are presented according to the specific uncertainty factors (UFs) applied (to reduce redundancy for similar decisions across health effects); the resultant cRfCs are then organized in a table and figure according to health effect. The text below explains the rationale for the UFs that are applied for each candidate RfC; the implementation of those decisions is most easily seen by looking at Table 5-16 that immediately follows the explanatory text.

Methods of Analysis

A series of five UFs were applied to each of the PODs developed for each endpoint/study, specifically addressing the following areas of uncertainty: interspecies uncertainty (UF_A) to account for animal-to-human extrapolation, and consisting of equal parts representing toxicokinetic and toxicodynamic differences; intraspecies uncertainty (UF_H) to account for variation in susceptibility across the human population (see Section 4.1), and the possibility that the available data may not be representative of individuals who are most susceptible to the effect; LOAEL-to-NOAEL uncertainty (UF_L) to estimate an exposure level where effects are not expected when a POD is based

on a LOAEL; subchronic-to-chronic uncertainty (UF_S) to account for the uncertainty in using subchronic studies to make inferences about lifetime exposure, and to consider whether lifetime exposure would have effects at lower levels (e.g., for studies other than subchronic studies); and database uncertainty (UF_D) to account for database deficiencies if an incomplete database raises concern that further studies might identify a more sensitive effect, organ system, or lifestage. The application of these UFs (i.e., assigning a value) was based on EPA's Review of the Reference Dose and Reference Concentration Processes (U.S. EPA, 2002).

UF_A interspecies uncertainty: animal-to-human variation

- For the 10 candidate RfCs derived from human epidemiology studies, an interspecies uncertainty factor (UF_A) was not applied (i.e., $UF_A = 1$).

- For the candidate RfCs for respiratory tract pathology (squamous metaplasia) and male reproductive toxicity from rat data, an HEC was estimated using either dosimetry modeling (Kerns et al., 1983), (metaplasia) or an assumption of ppm equivalence derived from pharmacokinetic principles (Woutersen et al., 1989), (respiratory pathology); (Ozen et al., 2002; Ozen et al., 2005), (male reproductive toxicity).

    - A factor of 3 was then applied to account for residual uncertainties in interspecies extrapolation from the two candidate RfCs for respiratory pathology and the two cRfCs for reproductive toxicity in males derived from rat studies.

UF_H intraspecies uncertainty: Human variation

- As summarized in Section 4.1, populations or lifestages demonstrated to have potentially increased susceptibility to the health effects of inhaled formaldehyde exposure include children, pregnant women, persons with pre-existing health conditions (particularly respiratory conditions such as asthma), and smokers. The UF_H selections below explicitly considered the ability of the selected studies to quantitatively address these potential susceptibilities. This resulted in reduced UF_Hs for several endpoints with quantitative analyses for several potentially susceptible groups, namely children, pregnant women, and asthmatics. In addition, co-exposure to tobacco smoke was considered during the evaluation of the individual studies. Section 4.1 discusses several other possible scenarios that might result in increased susceptibility to inhaled formaldehyde but for which the currently available information is inconclusive. While they may have an impact, these potential susceptibility factors without specific experimental support were not considered quantitatively.

- For five candidate RfCs derived from human epidemiology studies, an intraspecies uncertainty factor (UF_H) of 3 (i.e., $10^{1/2}$) was used.

    - For the cRfC for sensory irritation in populations with residential formaldehyde exposures using the combined data from Hanrahan et al. (1984) and Liu et al. (1991), a UF_H of 3 was used. The identified POD was not based on evaluation of differential susceptibility among subgroups with conditions or characteristic that might contribute to variation in response. However, the combined studies were judged to encompass a sufficiently large number (N = 897 households, combined) of

individuals representing a broad range of age, sex, health behavior, occupational status, and health status to partially address increased susceptibility. Notably, quantitative estimates of the individual studies and the combined studies are in close agreement, varying by < 20% (as demonstrated in Appendix D.1.1 and by independent estimation of the BMC_{10} values (NASEM, 2023)), despite the combined studies including more than 10-fold more participants than Hanrahan et al. (1984) alone, and a correspondingly greater representation of potentially susceptible individuals[53]. In addition, although quantitative susceptibility information specific to formaldehyde inhalation-induced sensory irritation is unavailable, the combined studies included large numbers of individuals potentially most susceptible based on understanding of dry eye disease (e.g., women and individuals over 50 have a higher prevalence, with those aged 65+ being < 2-fold more likely to develop disease than 50–64-year-olds) (Farrand et al., 2017). Note that for dry eye disease, younger individuals (under age 18 years) have a lower background incidence due to physiological differences; however, it remains unclear whether this decreased susceptibility applies to formaldehyde-induced stimulation of trigeminal nerve endings in the respiratory epithelium. Taken together, the size and composition of the combined dataset, as well as the stability of the selected POD, supports this value as representative of the response in the general population. However, some residual concern for increased sensitivity in specific groups of individuals remains. Considering the specific examples above as well as the broader evidence synthesis (Section 3.2.1), the evidence supports that the potentially increased sensitivity within any given group is likely to be < 3-fold (and typically less than 2-fold). Thus, a 3-fold factor for the UF_H was considered to be reasonably protective of potentially susceptible populations or lifestages.

- For Venn et al. (2003), a UF_H of 3 was used because the POD was based on the degree of asthma control in children with asthma, a highly sensitive group. (A UF_H of 1 was considered but not used because the number of individuals in the two higher exposure groups was relatively low (n = 31–35), and likely did not characterize all possible human variability.)

- For the POD for decreased peak expiratory flow rates (PEFRs) among children from Krzyzanowski et al. (1990), a UF_H of 3 was used with support from the model results reported by the authors. The authors of this study evaluated a model of the association of formaldehyde with PEFR that assessed differences between asthmatic and nonasthmatic children. Multiple observations in the study indicate that a UF_H of 3 applied to the endpoint can be expected to be protective of asthmatic children and other susceptible individuals. EPA used the published regression coefficients from the random effects model to calculate the predicted decrease in PEFR from the baseline level (i.e., formaldehyde concentration equal to zero) for each group (for details of the analysis see Appendix D.1.2). At the BMC (i.e., PEFR change of 10% in

[53] The large population (over 1000 individuals) in Liu et al. (1991) included approximately ⅓ smokers, ½ women, ⅓ individuals with chronic respiratory/allergic conditions, and ⅓ aged 65 and older. The first three groups had a higher symptom prevalence, with women and smokers having a < 1.4-fold increased prevalence of sensory irritation symptoms and those with chronic respiratory/allergy conditions having an approximately 2.5-fold increased prevalence. The authors reported that symptoms did not always increase with age using groupings of 5–19, 20–64, and 65+ years; for nearly half the symptoms, those 20–64 years old had the highest prevalence rates (although it is unclear if this included the sensory irritation symptoms).

the entire group), the asthmatic children experienced a decrement in PEFR that was 1.5-fold greater than that of the nonasthmatic children. Further, at the BMCL (0.021 mg/m^3), which was selected as the POD, the decrease in PEFR among asthmatic children was 10.5% while that in nonasthmatic children was 7.2%. The authors also stated that other characteristics that could affect variability such as acute respiratory illness episodes during the observation period, environmental tobacco smoke in the home, or socioeconomic status (education level of head of household) did not increase sensitivity. All of these observations indicate that a UF_H of 3 can be expected to be protective of asthmatic children and other susceptible individuals.

- For rhinoconjunctivitis and current asthma prevalence among children (school exposure) from Annesi-Maesano et al. (2012), a UF_H of 3 was used for the POD. Although Annesi-Maesano et al. (2012) did not select the study population based on characteristics that increased susceptibility to formaldehyde's respiratory effects, childhood is a susceptible lifestage for asthma and allergy, and the sample size of 6,600 children was large enough to have characterized an adequate spectrum of human variability. However, a UF_H of 1 was not used because susceptibility among subsets of the study population was not specifically assessed.

- Matsunaga et al. (2008) was a study of pregnant women, a sensitive population for eczema prevalence and an UF_H of 3 was used for the POD. An UF_H of 1 was not applied because the study participants were adult women and no information was available for other sensitive lifestages, including children, a subgroup with a higher prevalence of eczema compared to adults.

- A UF_H of 10 was used for the POD for current asthma prevalence in children (Krzyzanowski et al., 1990), the two PODs for sensory irritation in controlled human exposure studies (Kulle et al., 1987; Andersen and Molhave, 1983), the POD for reduced fecundity in reproductive-age women (Taskinen et al., 1999), and four PODs derived from animal studies (Woutersen et al., 1989; Ozen et al., 2002; Ozen et al., 2005; Kerns et al., 1983).

  - For current asthma prevalence among children with residential exposure (Krzyzanowski et al., 1990), a UF_H of 10 was used because susceptibility among subsets of the population was not specifically assessed, and the precision of the NOAEL was lower compared to Annesi-Maesano et al. (2012).

  - For the two sensory irritation PODs derived from short-term controlled human exposure studies (Kulle et al., 1987; Andersen and Molhave, 1983), as well as the developmental toxicity POD based on reduced fecundity in reproductive-age women in an occupational cohort studied by Taskinen et al. (1999), a factor of 10 was applied to account for variation in the broader human population not represented by occupationally exposed groups or participants in controlled human exposure studies who met the eligibility criteria. Physiological differences that affect sensitivity may become less of a concern for exposure to acute, high concentrations of direct-acting irritants (such as formaldehyde) for the derivation of an acute RfC, which could justify application of a lessor UF_H as noted by the NRC (2001); however, this consideration does not apply within the context of chronic exposure.

- For the four cRfCs based on studies in animals, a factor of 10 was applied to account for the limited variability in susceptibility factors encompassed by these typical studies of inbred laboratory animal populations.

UF_L LOAEL uncertainty: LOAEL-to-NOAEL extrapolation

- A LOAEL-to-NOAEL UF was not applied to the five PODs based on a NOAEL (i.e., UFL = 1).

- For the eight PODs derived from BMD modeling, a factor was not applied in keeping with EPA guidelines (U.S. EPA, 2012). EPA selected a BMR of 10% to identify a POD based on specific studies for several effects: sensory irritation, pulmonary function, and respiratory pathology. A BMR of 5% was selected for the POD identified using the Venn et al. (2003) study for effects on degree of asthma control. A BMR of 1 standard deviation from the control mean was selected for male reproductive toxicity manifest as decreased serum testosterone.

- For the POD based on a LOAEL for decreased relative testis weight as a marker of male reproductive toxicity, a UF = 3 rather than a UF = 10 was selected. Although neither a BMDL or NOAEL could be reliably identified, the selected LOAEL was associated with an 11% decrease in weight, likely only slightly higher than the concentration causing a 10% decrease (the target BMR). Thus, a 3-fold downward extrapolation from the LOAEL was interpreted to reasonably approximate a NOAEL.

UF_S subchronic uncertainty: extrapolation to chronic exposure

- Three experimental studies in animals evaluated exposures of durations less than a lifetime (Ozen et al., 2002; Ozen et al., 2005; Kerns et al., 1983).

    - A factor of 10 was applied to the two PODs for male reproductive toxicity to approximate the potential effect of lifetime exposure, as these effects are not necessarily dependent on a specific exposure window and they are expected to worsen with continued exposure (Ozen et al., 2002; Ozen et al., 2005).

    - A factor of 3 was applied to the respiratory tract pathology POD from Kerns et al. (1983) because it was based on 18-month exposure data from that rodent study in lieu of the 24-month exposure data available in the same study. As discussed in Section 3.2.4, there are data to suggest that exposure concentration would be more important to the development of this lesion than duration, although the specifics of this relationship have not been defined. However, the lesion incidences for this particular study were substantially higher with the longer duration data (i.e., 24-month versus 18-month), and thus a lower POD would be expected if the 24-month data could have been modeled. Thus, while use of the 18-month exposure duration is expected to reduce the uncertainty associated with extrapolating to lifetime exposure compared with a shorter duration such as 90 days, this reduction in extrapolation to lifetime was considered incomplete and a factor of 3 was applied, consistent with EPA guidelines [a factor other than 10 may be used, depending on the duration of the studies and the nature of the response (U.S. EPA, 1994, 1998, 2002)].

- For one study in a human population, a UF_S of 3 was applied to the POD. Matsunaga et al. (2008) evaluated the occurrence of atopic eczema during the past 12 months in a group of pregnant women and analyzed this outcome in relation to formaldehyde concentrations measured in their homes, which is a less-than-lifetime window of vulnerability. However, this outcome may have been pre-existing in a portion of the study sample and the window of susceptibility may not have been sufficiently represented by the shorter exposure period (Cho et al., 2010). Therefore, a UF_S of 1 was not applied.

- For the remaining seven PODs derived from human studies, a UF_S of 1 was applied. Three studies were of sensory irritation, which is considered to be predominantly an acute response (Kulle et al., 1987; Hanrahan et al., 1984; Andersen and Molhave, 1983). Notably, the controlled exposure studies by Kulle et al. (1987) and Andersen and Molhave (1983) demonstrate formaldehyde-induced sensory irritation after only brief periods of exposure; thus, these studies would be relevant for estimating the sensory irritant effects resulting from acute formaldehyde exposure. Three studies that were used for PODs for pulmonary function, allergic conditions, current asthma, and asthma control evaluated these outcomes in children and considered an appropriate window of exposure (Venn et al., 2003; Krzyzanowski et al., 1990; Annesi-Maesano et al., 2012). The study of Taskinen et al. (1999) evaluated TTP, which in this review is categorized as a female reproductive or developmental endpoint and the exposure window was considered to be appropriate. Matsunaga et al. (2008) evaluated the occurrence of atopic eczema during the past 12 months in a group of pregnant women and analyzed this outcome in relation to formaldehyde concentrations measured in their homes, which is a less-than-lifetime window of vulnerability.

UF_D database uncertainty

- A factor to account for database deficiencies was not applied to any of the PODs (i.e., UF_D = 1). The formaldehyde database is not considered complete, as important questions remain regarding the potential for formaldehyde inhalation exposure to cause reproductive and developmental toxicity and nervous system effects (both of which demonstrate an incomplete evidence base with methodological limitations). An incomplete database can raise concern that further studies might identify a more sensitive effect, organ system, or lifestage (U.S. EPA, 1991, 1994, 1996, 1998, 2002). However, given the breadth of the literature on formaldehyde toxicity, and given the poor distribution of inhaled formaldehyde to distal sites, an expectation that additional data are likely to reveal systemic effects (i.e., by indirect MOAs) at lower exposure levels than those eliciting adverse respiratory system changes seems unlikely; thus, this assessment uses a database uncertainty factor (UF_D) of 1.

Summary of Candidate Reference Concentrations

Table 5-16 summarizes the application of UFs to each POD from the *medium* or *high* confidence studies advanced based on the evaluations described in Section 5.1.1 to derive one or more cRfC(s) in each health effect system. Figure 5-2 presents graphically these cRfCs, composite UFs, and PODs, along with the confidence classification for each cRfC described in the next section (Section 5.1.4).

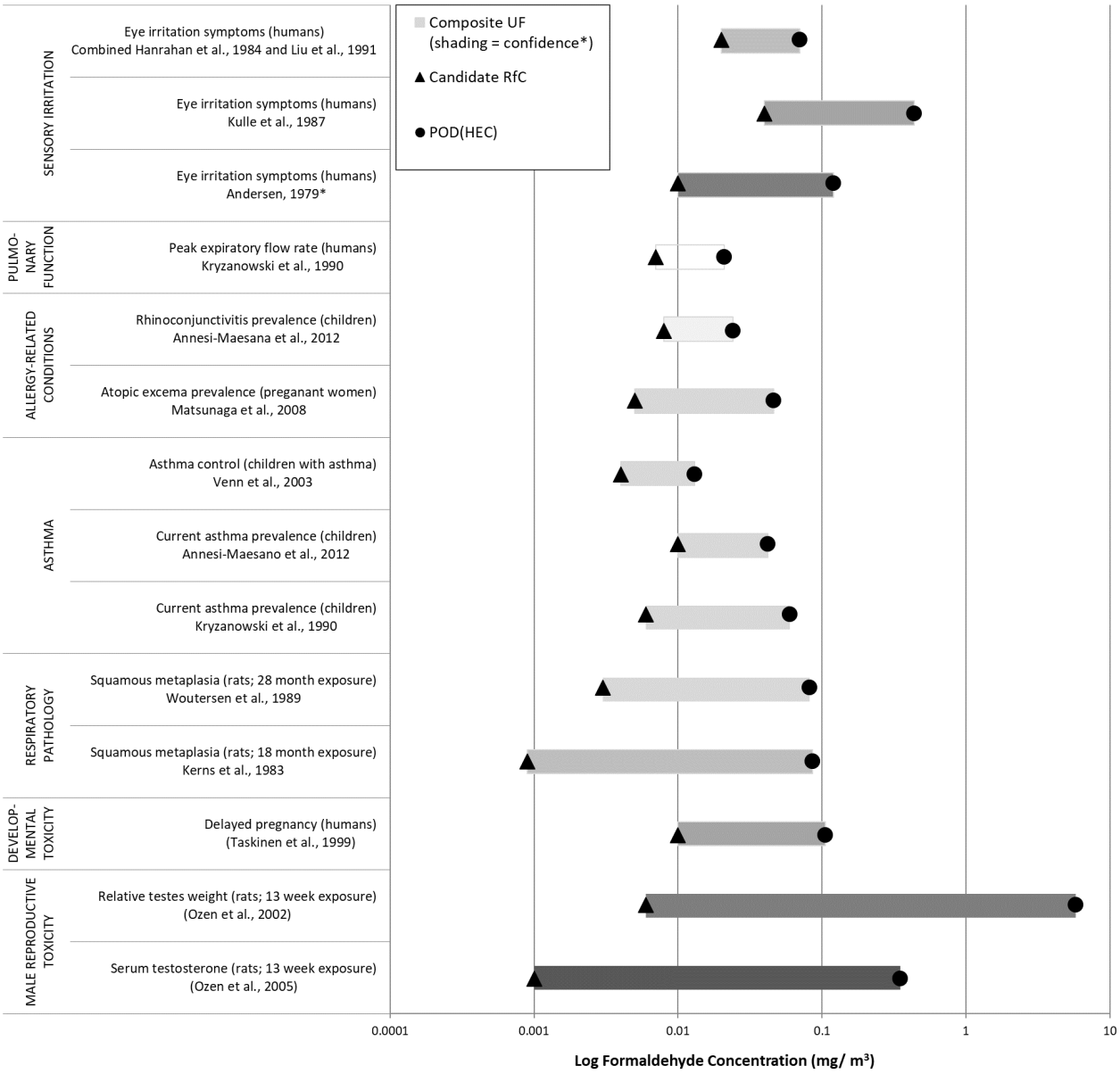
Table 5-16. Health effects and corresponding derivation of candidate RfCs

Endpoint (reference; population)	POD[a] (mg/m^3)	POD basis	UF_A	UF_H	UF_L	UF_S	UF_D	$UF_{COMPOSITE}$	cRfC (mg/m^3)
Sensory Irritation									
Eye irritation symptoms (Hanrahan et al., 1984) combined with (Liu et al., 1991); teenage and adult M + F, n = (61+836)=897 households, residential; 3% background prevalence	0.070	$BMCL_{10}$	1	3	1	1	1	3	**0.02**
Eye irritation symptoms (Kulle et al., 1987); adult M + F, *n* = 10, controlled exposure; 3% background prevalence	0.44	$BMCL_{10}$ (99^{th} %-tile)	1	10	1	1	1	10	**0.04**
Eye irritation symptoms (Andersen and Molhave, 1983); adult M + F, *n* = 16, controlled exposure; 3% background prevalence	0.12	$BMCL_{10}$ (99^{th} %-tile)	1	10	1	1	1	10	**0.01**
Pulmonary Function									
Peak expiratory flow rate (Krzyzanowski et al., 1990); Children M + F, *n* = 298, residential	0.021	$BMCL_{10}$	1	3	1	1	1	3	**0.007**
Allergy-related Conditions									
Rhinoconjunctivitis prevalence (Annesi-Maesano et al., 2012); children M + F, *n* = 2,200 at POD, school-based exposure	0.024	NOAEL	1	3	1	1	1	3	**0.008**
Atopic eczema prevalence (Matsunaga et al., 2008); adult F (pregnant), *n* = 301 at POD, residential (personal monitor)	0.046	NOAEL	1	3	1	3	1	10	**0.005**
Asthma									
Current asthma prevalence (Annesi-Maesano et al., 2012); children M + F, *n* = 2,200 at POD, school-based	0.042	NOAEL	1	3	1	1	1	3	**0.01**
Current asthma prevalence (Krzyzanowski et al., 1990); children M + F, *n* = 24 at POD, residential	0.060	NOAEL	1	10	1	1	1	10	**0.006**
Asthma control (Venn et al., 2003); children with asthma M + F, *n* = 35 at POD, residential	0.013	$BMCL_5$	1	3	1	1	1	3	**0.004**
Respiratory Tract Pathology									
Squamous metaplasia: (Kerns et al., 1983; Battelle, 1982); adult F344 rat M + F, 18-month exposure	0.086	$BMCL_{10}$	3	10	1	3	1	100	**0.0009**
Squamous metaplasia: (Woutersen et al., 1989); adult Wistar rat, M + F, 28-month exposure	0.082	$BMCL_{10}$	3	10	1	1	1	30	**0.003**
Female Reproductive and/or Developmental Toxicity									

Endpoint (reference; population)	POD[a] (mg/m^3)	POD basis	UF_A	UF_H	UF_L	UF_S	UF_D	$UF_{COMPOSITE}$	cRfC (mg/m^3)
Delayed pregnancy (Taskinen et al., 1999); pregnant F, *n* = 77 at POD, occupational	0.106	NOAEL	1	10	1	1	1	10	**0.01**
Male Reproductive Toxicity									
Relative testis weight (Ozen et al., 2002); adult Wistar rat, M, 13-week exposure	5.81	LOAEL	3	10	3	10	1	1,000	**0.006**
Serum testosterone (Ozen et al., 2005); adult Wistar rat, M, 13-week exposure	0.349	$BMCL_{1SD}$	3	10	1	10	1	300	**0.001**

Abbreviations: cRfC = candidate reference concentration; UF = uncertainty factor; POD = point of departure; BMC = benchmark concentration; BMCL = benchmark concentration, lower confidence bound; NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level.

[a]POD may be adjusted (e.g., to continuous exposure; to a human equivalent concentration) (see Section 5.1.2).



As the PODs reflect exact values, and the cRfCs are rounded to one significant figure, the $UF_{COMPOSITE}$ extrapolation between the two is not always exact. *Shading reflects confidence (i.e., "high" confidence = lightest shading; "low" confidence = darkest shading), as described in Section 5.1.4 below.

Figure 5-2. Candidate RfCs with corresponding PODs and composite UFs.

5.1.4. Selection of Organ- or System-specific Reference Concentrations

This section distills the cRfCs from Table 5-16 for each identified health hazard into a single value representing a level without an appreciable risk of deleterious effects on each particular organ or system during a lifetime. These organ- or system-specific RfCs (osRfCs) may be useful for subsequent cumulative risk assessments that consider the combined effect of multiple agents acting at a common site. For each cRfC, a set of three confidence descriptors (reflecting confidence in the

study, the accuracy of the quantitative estimate, and the evidence base available for each hazard) and an overall level of confidence are presented, with a corresponding level of confidence presented for each selected osRfC.

Methods of Analysis

EPA selected the osRfC for each specific organ or system using rationales specific to the data and studies for that health area, as described below. In general, studies of human populations with exposures that best represent that of the general population, and human or animal studies that evaluated long-term exposure were preferred, when available, unless a shorter window of susceptibility was appropriate. In addition, cRfCs with lower composite UFs were generally preferred. An osRfC was typically selected from cRfCs from higher confidence studies and higher confidence in the POD estimate used to derive the cRfC. osRfCs were sometimes derived using a method that combined two or more cRfCs.

As described in Section 2.7, an overall confidence level of **high**, **medium**, or **low** (or a combination of two of these terms) was assigned to each cRfC and osRfC. Largely, these classifications were based on the accuracy and reliability of the associated POD and study. The POD confidence classifications are supported by the summary descriptions in Section 5.1.2. Confidence in the POD included considerations of the quality and variability of the exposure assessment in an epidemiology study or the exposure protocols in an animal study. Moreover, higher confidence in the osRfC POD was drawn when the POD was identified close to the range of the observed data and the magnitude of exposure was relevant to those experienced in the general U.S. population. In addition, although less influential to the selected overall confidence classification, a confidence judgment is included to describe the coverage and quality of studies that informed the hazard conclusion for that specific organ/system. The evidence base for different health effects varies in size, coverage of critical endpoints, and quality of the studies; this confidence level generally reflects database completeness for each of the organ systems.

Because the studies that are the basis of each of the osRfCs are interpreted to be representative of the sets of studies available for each of the health outcomes evaluated, the overall hazard determination for each database is presented for each osRfC, noting that these judgments reflect the overall confidence in the findings from the sets of available studies, as compared to the confidence in the individual *medium* or *high* confidence studies most amenable to estimating a cRfC (and, by association, an osRfC).

Sensory Irritation

The osRfC for sensory irritation of 0.02 mg/m^3 is based on the cRfC for eye irritation derived using the combined results of Hanrahan et al. (1984) and Liu et a. (1991). The overall confidence in this cRfC (**medium-low** confidence) was higher than the confidence in the cRfCs based on the controlled exposure studies. The cRfC from Kulle et al. (1987) is interpreted with **low-medium** confidence and Andersen et al. (1983) with **low** confidence). As described previously, the

population in the combined residential studies was more representative of the general population in terms of demographic characteristics and exposure levels, resulting in higher confidence in the combined studies. There was also less uncertainty in calculating a POD for derivation of a chronic RfC, although uncertainties in the POD estimate from the combined studies did warrant a lower confidence in the POD (**medium-low**) that drove the overall confidence lower. Specifically, while the POD is based on formaldehyde measurements in the participants' homes and within the range of the data, there were concerns regarding the timing of outcome evaluation in relation to exposure for one of the two studies and important details (e.g., exposure levels and sample sizes for each prevalence data point) were either unavailable or had to be estimated from published graphs. There is an extensive literature on this response to formaldehyde and the completeness of the database is considered to be **high** for all cRfCs. Because sensory irritation is an immediate response to exposure, the osRfC is applicable to short-term as well as long-term exposure scenarios.

Table 5-17. Confidence determinations for candidate noncancer toxicity values for sensory irritation

Endpoint, reference, population, exposure type	POD, basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence[a] in cRfC
Prevalence of eye irritation symptoms (Hanrahan et al., 1984) combined with (Liu et al., 1991); teenage and adult (M + F), n = 897 households, residential	0.07 $BMCL_{10}$	3	0.02	**Medium-low** • Uncertainty related to the precise correspondence of the window of exposure with the period symptoms were experienced in Hanrahan et al. (1984), partly mitigated by the inclusion of Liu et al. (1991) • Uncertainty in estimating data presented graphically. • Inability to include any weighting of the data points in the modeling (e.g., based on sample size). • Uncertainty regarding background prevalence.	**Medium** • *Medium* confidence classification • Diverse population representative of general population. • Endpoint directly supports hazard.	**High** Extensive evidence base considered to be generally comprehensive and stable. [Judgment of **evidence demonstrates**]	**Medium-low** Concern regarding uncertainty in precisely estimating the POD is the primary driver of the confidence classification.

Endpoint, reference, population, exposure type	POD, basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence[a] in cRfC
Prevalence of eye irritation symptoms (Kulle et al., 1987) adult (M + F), n = 10 controlled exposure	0.44 $BMCL_{10}$ [99%]	10	0.04	**Low-medium** • Large uncertainty related to ability to accurately address repeated measures in the same small numbers of individuals, partly mitigated by use of 99th%. • Uncertainty regarding background prevalence.	**Low-medium** • *Medium* confidence classification • Healthy, adult population unlikely to reasonably represent the general population. • Endpoint directly supports hazard.		**Low-medium** Concerns regarding generalizability are primary drivers of the confidence classification in the context of chronic RfC derivation.
Prevalence of eye irritation symptoms (Andersen and Molhave, 1983) adult (M + F), n = 16 controlled exposure	0.12 $BMCL_{10}$ [99%]	10	0.01	**Low** As above, but with additional concern regarding precision of exposure levels due to high variability.	**Low** As above, but with additional concern regarding confounding by smoking status.		**Low** Concerns regarding generalizability and confounding are primary drivers of the confidence classification in the context of chronic RfC derivation.

[a]As described in Section 2.7, for hyphenated confidence classifications, the order of the terms is used to provide greater transparency in the confidence judgment for the purposes of this assessment, which also aids selection of osRfCs. Specifically, when hyphenated, the first term reflects the confidence category and the second term indicates whether the judgment is closer to a higher or lower confidence category, based on the term used (e.g., **Medium-high** would reflect a **medium** confidence judgment that is almost a judgment of **high** confidence).

Pulmonary Function

Data from a study in a residential population exposed over multiple years was used to calculate a cRfC for pulmonary function of 0.007 mg/m^3 (Krzyzanowski et al., 1990). Overall confidence in this value is **high** and it was chosen to represent the osRfC. Confidence in the use of the study for RfC derivation is **high**. The results are generalizable to the general population, and a robust exposure assessment was used based on two one-week average measurements in multiple rooms and the stability of the concentrations between sampling periods was established. The average formaldehyde concentrations are concluded to reasonably represents exposures in the homes during the previous weeks and months (i.e., the etiologically relevant exposure window for pulmonary function status), the etiologically relevant exposure window for average pulmonary function. A strong exposure-response relationship with formaldehyde concentration was observed by this study, which reduces concern that residual confounding by unmeasured coexposures (smoking status, environmental tobacco smoke, and NO_2 were controlled for) strongly influenced

the association. Hence, confidence in the POD value is also **high**. There is evidence for the association of pulmonary function with formaldehyde exposure from multiple studies at higher exposure levels from occupational studies (both cross-sectional and longitudinal designs) and studies of anatomy students with episodic exposure, as well as a few studies among residential and school populations; however, some uncertainties remain and thus confidence in the evidence base is considered to be **medium-high**.

Table 5-18. Confidence determinations for candidate noncancer toxicity values for pulmonary function

Endpoint, reference, population, exposure	POD (mg/m^3) Basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence in cRfC[a]
Peak expiratory flow rate (Krzyzanowski et al., 1990) Children (M + F), *n* = 298 residential	0.021 $BMCL_{10}$	3	0.007	**High** • Reliable exposure assessment representing etiologically relevant time window. • Well-characterized dose-response relationship addressing potential confounding. • POD within the range of the data.	**High** • *High* confidence classification • In potentially susceptible individuals (children) • Population representative of the general population. • Endpoint directly supports hazard.	**Medium-high** Evidence base provides clear support for effects on pulmonary function. However, some unexplained inconsistency across studies remains for some markers and fewer studies were available among residential populations. [Judgment of **evidence indicates**]	**High** Confidence in the POD and study are primary drivers of the confidence classification.

[a]As described in Section 2.7, for hyphenated confidence classifications, the order of the terms is used to provide greater transparency in the confidence judgment for the purposes of this assessment, which also aids selection of osRfCs. Specifically, when hyphenated, the first term reflects the confidence category and the second term indicates whether the judgment is closer to a higher or lower confidence category, based on the term used (e.g., **Medium-high** would reflect a **medium** confidence judgment that is almost a judgment of **high** confidence).

Allergic Conditions

Candidate RfCs (cRfCs) for allergy-related conditions were derived based on one study in children (Annesi-Maesano et al., 2012) and one study in adults (Matsunaga et al., 2008). Overall confidence was higher (**high-medium**) for the study in children than in the study in adults (**medium-high**) because of the higher specificity of the outcome assessment used in the former

study[54], and thus the cRfC of 0.008 mg/m^3 from Annesi-Maesano et al. (2012) was selected to represent the osRfC. Both PODs were based on NOAELs and are interpreted with **high-medium** confidence, primarily due to the inability to derive a BMCL. Although both studies adequately addressed potential confounding, as compared to the study by Matsunaga et al. (2008), the large study of children (n = 6,683) by Annesi-Maesano et al. (2012) was better able to address the variability in susceptibility that would be anticipated within a population. The greater strength of the outcome assessment, length of the exposure assessment protocol (5 days) and generalizability of the study by Annesi-Maesano et al. (2012) were the main reason for the confidence in the study, and the cRfC overall, was interpreted with higher confidence. The completeness of the database relating formaldehyde exposure to allergic sensitization is considered to be **medium-high.** While the evidence integration judgments were based on consistent findings across a variety of endpoints, populations, and exposure scenarios, important uncertainties remain (Section 3.2.3).

Table 5-19. Confidence determinations for candidate noncancer toxicity values for allergy-related conditions

Endpoint, reference, population, exposure	POD, basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence in cRfC[a]
Rhinoconjunctivitis prevalence (Annesi-Maesano et al., 2012); children M + F, n = 2,200 at POD, school-based exposure	0.024 NOAEL	3	0.008	**High-medium** • No BMCL derived	**High** • *High* confidence classification • Confounding unlikely • Generalizable • Endpoint directly supports hazard.	**Medium-high** Allergy-related symptoms were consistently increased across a variety of endpoints, populations, and exposure scenarios; however, the effect sizes were small and other uncertainties remain [Judgment of **evidence indicates]**	**High-medium** Confidence in the POD and study are primary drivers of the confidence classification
Atopic eczema prevalence (Matsunaga et al., 2008); adult F (pregnant), n = 301, residential	0.046 NOAEL	10	0.005	**High-medium** • No LOAEL or BMCL derived	**Medium** • *Medium* confidence classification • Confounding unlikely • Precise exposure measurement		**Medium-high** Confidence in the POD and concerns regarding ability of the study to address the variability in susceptibility that would be anticipated within a population are

[54] The Annesi-Maesano study (Annesi-Maesano et al., 2012) used ISAAC-based questions regarding rhinitis and rhinoconjunctivitis symptoms, which was recommended based by the expert panel consulted by EPA regarding study designs used for studies of allergies. For eczema, the Matsunaga study (Matsunaga et al., 2008) used a question relating to medication use for atopic eczema. The panel also noted that retrospective assessment of the prevalence of allergic symptoms using self- or parent-reported questionnaires was an appropriate approach based on the validation work that had been done regarding the accuracy of these measures.

Endpoint, reference, population, exposure	POD, basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence in cRfC[a]
					(personal monitor) • Low participation rate • Less generalizable to susceptible individuals • Less database support for this specific endpoint as compared to other allergy measures		primary drivers of the confidence classification

[a]As described in Section 2.7, for hyphenated confidence classifications, the order of the terms is used to provide greater transparency in the confidence judgment for the purposes of this assessment, which also aids selection of osRfCs. Specifically, when hyphenated, the first term reflects the confidence category and the second term indicates whether the judgment is closer to a higher or lower confidence category, based on the term used (e.g., **Medium-high** would reflect a **medium** confidence judgment that is almost a judgment of **high** confidence).

Prevalence of Current Asthma or Degree of Asthma Control

There were three cRfCs developed for asthma, with two based on the prevalence of current asthma (Krzyzanowski et al., 1990; Annesi-Maesano et al., 2012), and one based on the degree of asthma control (Venn et al., 2003). Although the same evidence integration judgments were drawn, confidence in the evidence base for these outcomes (**medium** confidence) was lower than confidence in the evidence base for allergic conditions for two reasons. Although the database of studies examining prevalence of current asthma in relation to exposures below 0.05 mg/m^3 is large and relatively robust, there is a smaller number of studies with exposures between 0.05 and 0.1 mg/m^3, and there were limitations in these studies (e.g., low statistical power, incomplete reporting of study results and exposure measures). The second factor is the scarcity of data pertaining to asthma control among people with asthma. Although the data available indicates this may be a more sensitive outcome than prevalence of current asthma, there is uncertainty regarding that conclusion because of the limited number of studies examining this endpoint. This affected the overall confidence determinations for these three cRfCs.

The POD based on Annesi-Maesano et al. (2012) was derived from a NOAEL using a large study with a relatively long exposure measurement period and using a method for the outcome assessment recommended by an expert panel consulted by EPA regarding study designs used for

studies of asthma,[55] supported by a collection of several other smaller studies; however, a LOAEL or BMCL were unavailable (i.e., **high-medium** confidence in the POD) and there were no specific evaluations of the most susceptible individuals (i.e., **medium-high** confidence in the study), resulting in an overall confidence of **medium-high**. Overall **medium-high** confidence was also determined for the study by Krzyzanowski et al. (1990). The NOAEL identified from Krzyzanowski et al. (1990) is considered to be more uncertain (i.e., **medium-high** confidence in the POD) because it was based on only one case and a small number of participants in the higher exposure group. Confidence in this large study was also **medium-high**. Although Venn et al. (2003) used a strong study design to assess the degree of symptom control (based on one-month daily symptom diaries) among children with asthma, adjusted the statistical analyses to address key confounders, and observed an exposure-related trend among a susceptible population, asthmatic children (i.e., **high-medium** confidence in the study), the effect estimates derived by Venn et al. (2003) were less precise because of relatively small group sizes, resulting in **medium** confidence in the POD and overall **medium-high** confidence.

Thus, all three cRfCs had the same overall confidence, but each determination was driven by a different type of uncertainty. To account for the different uncertainties in the PODs from the three studies, the median of the three cRfCs, 0.006 mg/m^3, was selected for the osRfC. Quantitatively, this corresponds to the cRfC value from Krzyzanowski et al. (1990). The overall confidence in the osRfC matches the confidence for each composite cRfC, **medium-high**.

Table 5-20. Confidence determinations for candidate noncancer toxicity values for current asthma or degree of asthma control

Endpoint, reference, population, exposure	POD, basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence in cRfC[a]
Current asthma prevalence (Annesi-Maesano et al., 2012); children M + F, *n* = 2,200 at POD, school-based	0.042 NOAEL	3	0.01	**High-medium** • No LOAEL or BMCL derived	**Medium-high** • *High* confidence study • No evaluation of most susceptible • Endpoint directly supports hazard.	**Medium** The evidence on current asthma is reasonably clear at high and low exposure levels, but few studies	**Medium-high** Confidence reflects an equal contribution from confidence in the POD, Study, and evidence base.
Current asthma prevalence	0.06 NOAEL	10	0.006	**Medium-high**	**Medium-high**		**Medium-high**

[55] The Annesi-Maesano study (Annesi-Maesano et al., 2012) used ISAAC-based questions and the Krzyzanowski study (Krzyzanowski et al., 1990) used ATS-based questions regarding prevalence of current asthma, both of which were recommended based by the expert panel consulted by EPA regarding study designs used for studies of asthma. The panel also noted that retrospective assessment of the prevalence of asthma using self- or parent-reported questionnaires was an appropriate approach based on the validation work that had been done regarding the accuracy of these measures.

Endpoint, reference, population, exposure	POD, basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence in cRfC[a]
(Krzyzanowski et al., 1990); children M + F, *n* = 24 at POD, residential				• Small number of cases • Wide exposure range and multiple exposure groups	• *Medium* confidence study • Large study • Endpoint directly supports hazard.	were available to inform the important exposure range of 0.5-1.0 mg/m^3 and the sensitive endpoint of control of asthma symptoms was only sparsely studied [Judgment of **evidence indicates**]	Confidence in the POD (due to few cases) and study are primary drivers of the confidence classification
Asthma control (Venn et al., 2003); children with asthma M + F, *n* = 35 at POD, residential	0.013 $BMCL_5$	3	0.004	**Medium** • Imprecise due to small group sizes	**High-medium** • *High* confidence study • Asthmatic children likely amongst most susceptible • Concerning severity. • Less support for this specific endpoint as compared to asthma prevalence		**Medium-high** Confidence in the POD (due to imprecise results) and evidence base on this outcome are primary drivers of the confidence classification

[a]As described in Section 2.7, for hyphenated confidence classifications, the order of the terms is used to provide greater transparency in the confidence judgment for the purposes of this assessment, which also aids selection of osRfCs. Specifically, when hyphenated, the first term reflects the confidence category and the second term indicates whether the judgment is closer to a higher or lower confidence category, based on the term used (e.g., **Medium-high** would reflect a **medium** confidence judgment that is almost a judgment of **high** confidence).

Respiratory Tract Pathology

Two cRfCs for respiratory tract pathology were derived based on squamous metaplasia observed in anterior rat nasal passages in two studies of long-term exposure. There was no clear basis for selecting either the Woutersen et al. (1989) study or Kerns et al. (1983; Battelle, 1982) study over the other on grounds of confidence in the study methods (both **high** confidence) or known differences in sensitivity between Wistar and F344 rats. In addition, the PODs were nearly identical and the cRfCs are similar for the two data sets [i.e., cRfCs of 0.0009 for Kerns et al. (1983) and 0.003 for Woutersen et al. (1989), which are comparable given the exposure levels tested in the studies and the limited precision of the calculations]. However, there was lower confidence (**low** confidence as compared to **medium** confidence for Woutersen et al. (1989)) in the derivation of the POD from Kerns et al. (1983), which involved an extrapolation well below the tested formaldehyde concentrations. In addition, the cRfC for Kerns et al. (1983) involved the application of a UF for exposure duration. While exposure duration is important to the development of this lesion, such effects appear to be more dependent on exposure concentration (see MOA discussion in Section 3.2.4). Thus, although completeness of the database for respiratory tract pathology is considered **high**, based primarily on the numerous well-conducted, long-term studies in

experimental animals, if a factor describing the concentration-duration relationship[56] were available for formaldehyde (and interpretable in the context of metaplasia), a data-defined UF could have been applied. These uncertainties contributed to a lower confidence of **medium** overall for the cRfC based on Kerns et al. (1983; Battelle, 1982) as compared to overall **medium-high** confidence in the cRfC based on the study by Woutersen et al. (1989). Thus, the **medium-high** confidence cRfC of 0.003 mg/m^3 from Woutersen et al. (1989) was selected to represent osRfC for respiratory tract pathology.

Table 5-21. Confidence determinations for candidate noncancer toxicity values for respiratory tract pathology

Endpoint, reference, population, exposure	POD, basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence in cRfC[a]
Squamous metaplasia: (Kerns et al., 1983; Battelle, 1982); adult F344 rat (M + F), *n* = 121/sex/group; 18-month exposure	0.086 $BMCL_{10}$	100	0.0009	**Low** • POD for longer, more relevant exposure duration, not possible • Extrapolation outside of range of data • Dosimetric evaluation of formaldehyde flux possible • No exposure levels below 2.5 mg/m^3	**High** • *High* confidence study • Large GLP study • Endpoint directly supports hazard.	**High** Thoroughly studied effect with abundant support from animal studies and confirmatory findings from studies in humans [Judgment of **evidence demonstrates**]	**Medium** Confidence in the POD and study are primary drivers of the confidence classification
Squamous metaplasia: (Woutersen et al., 1989); adult Wistar rat (M + F), *n* = 30/group 28-month exposure	0.082 $BMCL_{10}$	30	0.003	**Medium** • Smaller study increases variability • No exposure levels between 1.2 and 11.2 mg/m^3 • Default dosimetric extrapolation	**High** • *High* confidence study • No notable limitations (note: while an apparent insensitivity of this strain to nasal tumors was observed, this was not as clear for		**Medium-high** Confidence in the POD and study are primary drivers of the confidence classification

[56]Studies of other irritants have, on average, identified a factor of ~1.8–1.9 for relationships between acute exposure and mortality (i.e., the observed mortality is more attributable to concentration, by 1.8- to 1.9-fold, than duration; see Section 3.2.4). A value for formaldehyde was not identified, nor were values for long-term exposure.

Endpoint, reference, population, exposure	POD, basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence in cRfC[a]
					metaplasia and thus did not reduce confidence) • Endpoint directly supports hazard.		

[a]As described in Section 2.7, for hyphenated confidence classifications, the order of the terms is used to provide greater transparency in the confidence judgment for the purposes of this assessment, which also aids selection of osRfCs. Specifically, when hyphenated, the first term reflects the confidence category and the second term indicates whether the judgment is closer to a higher or lower confidence category, based on the term used (e.g., **Medium-high** would reflect a **medium** confidence judgment that is almost a judgment of **high** confidence).

Female Reproductive or Developmental Toxicity

Data from one study of women exposed to formaldehyde in the Finnish woodworking industry are available to derive a cRfC for effects on delayed pregnancy (Taskinen et al., 1999). This cRfC of 0.1 mg/m^3, interpreted with **low-medium** confidence overall, was chosen as the osRfC. Confidence in the study for cRfC derivation was **medium-low**, primarily due to use of a healthy worker population unlikely to address variability in response. Although TTP is a sensitive measure of effects on the reproductive system, confidence in the POD is judged to be **low** because the high exposure levels required substantial extrapolation and dermal exposure may have augmented the response to inhaled formaldehyde. More complete assessments of developmental endpoints by epidemiology or toxicology studies were not available. Thus, the completeness of the database is considered **medium-low**. The relevant period for exposure effects on TTP through unrecognized fetal losses or factors controlling the ability to conceive could range from the weeks just prior and after conception, to the entire period of prior exposure during the life of the individual because the mechanisms and events through which formaldehyde may cause this outcome are not known.

Table 5-22. Confidence determinations for candidate noncancer toxicity values for female reproductive or developmental toxicity

Endpoint, reference, population, exposure	POD, basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence in cRfC[a]
Delayed pregnancy (Taskinen et al., 1999); pregnant F, *n* = 77 at POD, occupational	0.106 NOAEL	10	0.01	**Low** • High exposure requiring large extrapolation	**Medium-low** • *Medium* confidence classification • Healthy worker	**Medium-low** Although the evidence was sufficient to identify a potential	**Low-medium** Confidence in the POD and study are primary drivers of the confidence classification

Endpoint, reference, population, exposure	POD, basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence in cRfC[a]
				• Likely dermal co-exposure contribution to dose-response	population unlikely to reflect variability in the general population or susceptible groups.	health hazard, few human studies were available on each endpoint and there were no medium or high confidence animal studies. [Judgment of **evidence indicates**]	

[a]As described in Section 2.7, for hyphenated confidence classifications, the order of the terms is used to provide greater transparency in the confidence judgment for the purposes of this assessment, which also aids selection of osRfCs. Specifically, when hyphenated, the first term reflects the confidence category and the second term indicates whether the judgment is closer to a higher or lower confidence category, based on the term used (e.g., **Medium-high** would reflect a **medium** confidence judgment that is almost a judgment of **high** confidence).

Male Reproductive Toxicity

Two cRfCs were derived for male reproductive toxicity, based on two studies in rats from the same research group, (Ozen et al., 2002; Ozen et al., 2005). Both cRfCs were interpreted with **low** confidence. However, the cRfC derived from Ozen et al. (2002) was considered the stronger of the two candidates for male reproductive toxicity, and thus was chosen to represent the osRfC. Specifically, although the magnitude of the testes weight response in Ozen et al. (2002) was less than that of the testosterone decreases observed in Ozen et al. (2005), there is lower confidence in the POD for decreased testosterone as this endpoint is considered more likely to be affected by the expected overt toxicity (and reflex bradypnea) resulting from the high exposure levels in these studies. The confidence in the PODs for both cRfCs is **low**, primarily because the lowest formaldehyde concentrations tested in these studies were 6 or 12 mg/m^3. Confidence in the database is considered **low-medium** because while there are a number of published studies that evaluated reproductive toxicity in males, the interpretation of study results is complicated by their methodological limitations, the exclusive use of formaldehyde concentrations above 6 mg/m^3, and lack of data regarding functional endpoints.

Table 5-23. Confidence determinations for candidate noncancer toxicity values for male reproductive toxicity

Endpoint, reference, population, exposure	POD, basis	UF_C	cRfC (mg/m^3)	Confidence in POD	Confidence in Study	Confidence in Evidence Base	Overall Confidence
Relative testis weight (Ozen et al., 2002); adult Wistar rat (M), *n* = *7*; 13-week exposure	5.81 LOAEL	1,000	0.006	**Low** • No NOAEL or BMCL • Small magnitude of change at LOAEL	**Low** • Absolute testes weight preferred but not reported • Lowest tested exposure 12 mg/m^3	**Low-medium** No testing of lower exposure levels or chronic exposure scenarios, most other studies had serious methodological concerns, and available human studies do not provide clear support. [Judgment of **evidence indicates**]	**Low** Confidence in the POD and study are primary drivers of the confidence classification
Serum testosterone (Ozen et al., 2005); adult Wistar rat (M), *n* = 6; 13-week exposure	0.349 $BMCL_{1SD}$	300	0.001	**Low** • BMCL extrapolation orders of magnitude lower than tested exposure levels	**Low**[b] • Overt toxicity expected to affect endpoint • Lowest tested exposure 6 mg/m^3		**Low**[b] Confidence in the POD and study are primary drivers of the confidence classification

[a]As described in Section 2.7, for hyphenated confidence classifications, the order of the terms is used to provide greater transparency in the confidence judgment for the purposes of this assessment, which also aids selection of osRfCs. Specifically, when hyphenated, the first term reflects the confidence category and the second term indicates whether the judgment is closer to a higher or lower confidence category, based on the term used (e.g., **Medium-high** would reflect a **medium** confidence judgment that is almost a judgment of **high** confidence).

[b]This confidence classification is interpreted as at the lower end of the **low** confidence category.

Summary of Organ- or System-specific RfCs

Table 5-24. Organ- or system-specific RfCs for formaldehyde inhalation

Health effect	Basis reference(s) [species]	UF_C	osRfC (mg/m^3)	Hazard Evidence Integration judgment	Confidence[a] in osRfC
Sensory irritation	Hanrahan et al. (1984) and Liu et al. (1991) combined [human (M + F, adult, and children)]	3	0.02	**Evidence demonstrates**	**Medium-low**
Pulmonary function	Krzyzanowski et al. (1990) [human (M + F, children)]	3	0.007	**Evidence indicates (likely)**	**High**
Allergy-related conditions	Annesi-Maesano et al. (2012) [human (M + F, children)]	3	0.008	**Evidence indicates (likely)**	**High-medium**
Asthma (prevalence of current asthma/degree of asthma control)	Krzyzanowski et al. (1990) (with co-critical cRfCs[b]) [human (M + F, children)]	10	0.006	**Evidence indicates (likely)**	**Medium-high**

Health effect	Basis reference(s) [species]	UF_C	osRfC (mg/m^3)	Hazard Evidence Integration judgment	Confidence[a] in osRfC
Respiratory pathology	Woutersen et al. (1989) [rat (M + F, adult)]	30	0.003	**Evidence demonstrates**	**Medium-high**
Female or developmental toxicity	Taskinen et al. (1999) [human (F, pregnant adult)]	10	0.01	**Evidence indicates (likely)**	**Low-medium**
Male reproductive toxicity	Ozen et al. (2002) [rat (M, adult)]	1,000	0.006	**Evidence indicates (likely)**	**Low**

Abbreviations: osRfC = organ- or system-specific reference concentration; cRfC = candidate RfC; UF = uncertainty factor; POD = point of departure; M = male; F = female.

[a]As described in Section 2.7, for hyphenated confidence classifications, the order of the terms is used to provide greater transparency in the confidence judgment for the purposes of this assessment, which also aids selection of osRfCs. Specifically, when hyphenated, the first term reflects the confidence category and the second term indicates whether the judgment is closer to a higher or lower confidence category, based on the term used (e.g., **Medium-high** would reflect a **medium** confidence judgment that is almost a judgment of **high** confidence).

[b]Co-critical cRfCs were used quantitatively in the osRfC derivation and support the selected osRfC. Specifically, for asthma, the osRfC represents the median cRfC of the three co-critical cRfCs of comparable confidence and uncertainty [Annesi-Maesano et al. (2012); Krzyzanowski et al. (1990); and Venn et al. (2003)]. Because this median corresponds to the cRfC based on Krzyzanowski et al. (Krzyzanowski et al., 1990), quantitatively this study reflects the osRfC based on the three studies.

5.1.5. Selection and Characterization of the Overall Reference Concentration

The following discussion outlines the selection of an overall RfC from among the osRfCs presented in Table 5-24. The overall RfC was chosen to reflect an estimate of continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The amount of risk between the RfC and the PODs (see Figure 5-3 below for context) from which the RfC is derived is not known.

Methods of Analysis

Choice of the overall RfC involves consideration of both the level of certainty in the estimated organ- or system-specific values, as well as the level of confidence in the observed effect(s) (see Figure 5-3). An overall confidence level is assigned to the RfC to reflect an interpretation regarding confidence in the collection of study/studies used to determine the hazard(s) and derive the RfC, the RfC calculation itself, as well as the overall completeness of the database on the potential health effects of formaldehyde exposure.

Comparison

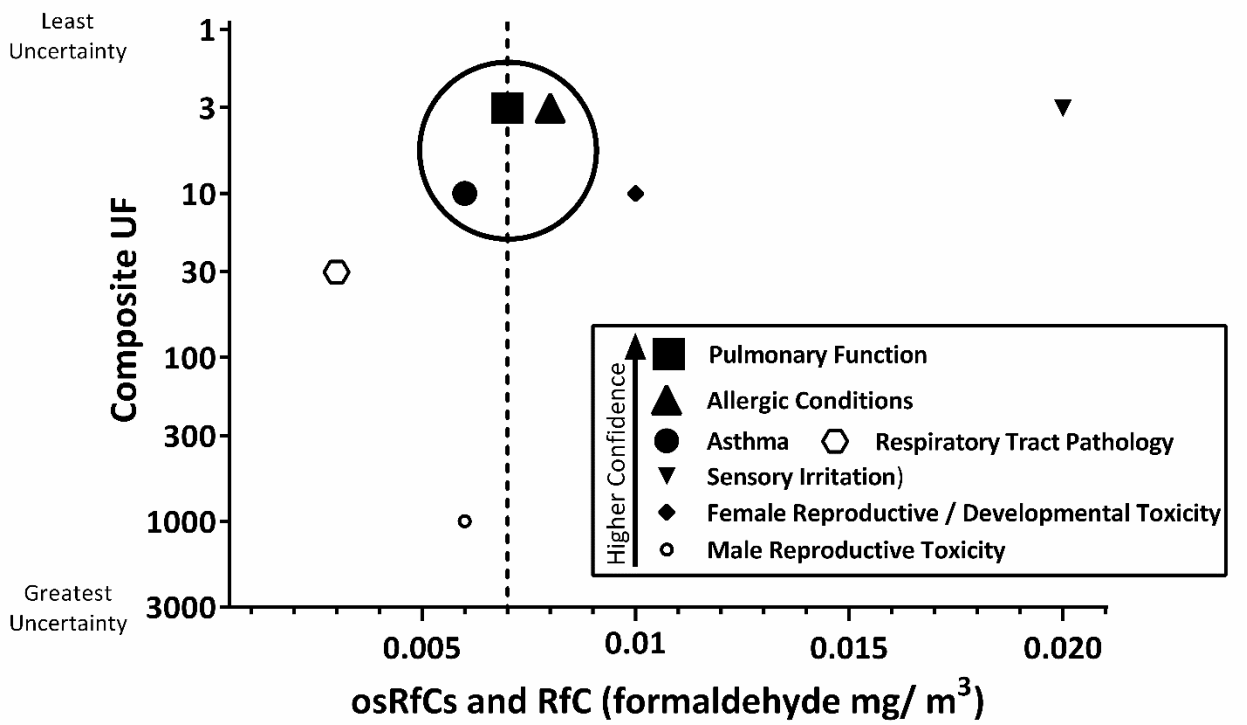


Figure 5-3. Organ- or system-specific RfC scatterplot.

Organ/system RfCs (osRfCs) represented by larger shapes and that are closer to the top of the graph are interpreted with higher confidence regarding the basis from which the value was derived (see Table 5-24), and with less uncertainty (i.e., lower UFs were applied). Larger shapes indicate higher confidence; solid shapes indicate studies in humans; hollow shapes indicate animal studies. For asthma (i.e., prevalence of current asthma or control of asthma symptoms), the composite UF of 10 reflects the UF_C for the cRfC from Krzyzanowski et al. (1990), which quantitatively matches the value selected for the osRfC (see Table 5-24). The dashed line represents the RfC of 0.007 mg/m^3; the circled osRfCs indicate the cluster of effects selected as the basis for this value.

Choice of the Overall RfC

An overall RfC for formaldehyde of 0.007 mg/m^3 was selected. This value is the median of three osRfCs (0.006, 0.007, and 0.008 mg/m^3) representing a group of respiratory system-related effects (pulmonary function, allergic conditions, and current asthma prevalence or degree of control) in children,[57] which together are interpreted with **high confidence** (see Figure 5-3). These osRfCs are based on cRfCs interpreted with the highest confidence and with the lowest composite uncertainty (see Figure 5-3), although they are not the lowest cRfCs that were derived. The osRfCs for female reproductive or developmental toxicity and sensory irritation, only slightly higher and approximately 3-fold higher than the selected RfC, respectively, were associated with less confidence and therefore not used for the RfC. The osRfCs for respiratory pathology and male reproductive effects, while lower than the RfC, were associated with a larger degree of uncertainty, as reflected by their position along the y-axis, and thus similarly not used for the RfC.

The exposure paradigm used by controlled human exposure studies evaluates an immediate response (i.e., on the order of minutes to hours) to acute formaldehyde exposure and it may be appropriate to use the results from these studies to derive an acute RfC. The evidence base for formaldehyde included results from controlled human exposure studies of formaldehyde inhalation and sensory irritation endpoints, pulmonary function response among healthy or asthmatic individuals, and hyperbronchoreactivity among allergic asthmatics in response to an allergen challenge. Two cRfCs for sensory irritation were derived from short-term controlled human exposure studies (Kulle et al., 1987; Andersen and Molhave, 1983), Generally, pulmonary function measures were not changed by acute exposure in several controlled human exposure studies of healthy or asthmatic volunteers, although small decrements were observed after longer exercise components (15 minutes). Two additional studies did not observe pulmonary function changes in response to acute formaldehyde inhalation but did observe an early phase increase in airway reactivity in response to an allergen challenge indicating a potential exacerbation effect by formaldehyde inhalation on asthma symptoms (Ezratty et al., 2007; Casset et al., 2006). Casset et al. (2006) observed a statistically significant response at lower dust mite amounts with formaldehyde levels of 0.092 mg/m^3 and mouth breathing only, while Ezratty et al. (2007) observed an increase in

[57] It is important to note that while the RfC is based on findings in children, who appear to be susceptible to the respiratory effects of inhaling formaldehyde (Section 4.1), the assessment does not conclude that these respiratory effects do not occur in exposed adults. Section 3.2.2 describes the consistent and strong evidence for declines in pulmonary function in workers with long-term exposure to formaldehyde; however, these long-term occupational studies generally only tested higher (≥ 0.2 mg/m^3) levels of formaldehyde as compared to the residential studies examining effects in adults or in both adults and children. Section 3.2.3 highlights that there are few studies on the potential effects of formaldehyde on allergic conditions in adults, with concerns noted regarding the methods and imprecise results in those studies that prevent drawing a reliable judgment. However, Section 3.2.3 also shows that studies of workers with long-term exposure to formaldehyde collectively provide strong support for increases in asthma prevalence, but as with pulmonary function these findings are generally at higher formaldehyde levels (> 0.1 mg/m^3) than the more sensitive residential- and school-based studies in children advanced for the purposes of developing the RfC.

a reactivity index in response to a grass allergen challenge (p = 0.06) using a higher formaldehyde concentration (0.5 mg/m^3).

The RfC is an estimate of exposure that is likely to be without an appreciable risk of adverse health effects over a lifetime (U.S. EPA, 2000). For context, the RfC is higher than most estimates of the formaldehyde concentration in outdoor air and lower than most estimates of the formaldehyde concentrations in indoor air[58]. However, it is important to reiterate that this level is interpreted to be without appreciable risk, even in susceptible individuals. It is also important to note that the RfC does not provide information about the magnitude of the risk of respiratory-related effects that might occur at different concentrations above the RfC (e.g., at 0.02 or 0.03 mg/m^3). As illustrated in Figure 5-4, nearly all the study-specific findings of effects (e.g., LOAELs, BMCs) were not observed until formaldehyde levels well above the estimated median indoor air concentrations in the U.S., with effects generally being observed at or above 33 µg/m^3 (0.033 mg/m^3). One study that contributed to the RfC derivation involved an analysis of the degree of asthma control in children with current asthma (Venn et al., 2003), and the RfC is expected to apply to this susceptible subgroup in the population. Although current asthma symptoms and allergic conditions were not observed in studies of children with exposures less than approximately 0.05 mg/m^3, at 0.021 mg/m^3, a 10.5% decrease in PEFR among asthmatic children could be estimated using results of Krzyzanowski et al. (1990). Thus, attributes that increase susceptibility in individuals are expected to play a role in increasing the advent of adverse responses to formaldehyde levels above the RfC (e.g., somewhere between 0.007 and 0.033 mg/m^3).

[58] Exposure assessments are not conducted or included as part of IRIS toxicological reviews, and authoritative sources on exposure assessment should be consulted. Most recently (as of the time of this assessment), a draft formaldehyde exposure assessment is underway in EPA's TSCA Office (see https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-formaldehyde#re-findings).Although draft, the TSCA risk evaluation provides potentially useful context to the noncancer values in Figure 5-4. Specifically, the draft TSCA evaluation cites studies supporting that, while formaldehyde concentrations in U.S. homes vary, the median is approximately 20 µg/m^3, with most homes falling below 40 µg/m^3. Exceptions to this include newly constructed homes, which tend to have higher formaldehyde levels, and trailers and mobile homes, which can have formaldehyde levels an order of magnitude (or more) higher, particularly if they are poorly ventilated, For comparison purposes, the draft TSCA risk evaluation uses recent (2023) ambient monitoring data to estimate U.S. formaldehyde concentrations in outdoor air to have a median of 1.88 µg/m^3 (95th percentile range: 0.382 to 6.2 µg/m^3). It is important to emphasize that estimates can vary substantially, and that these estimates (provided for contextual purposes) are not final.

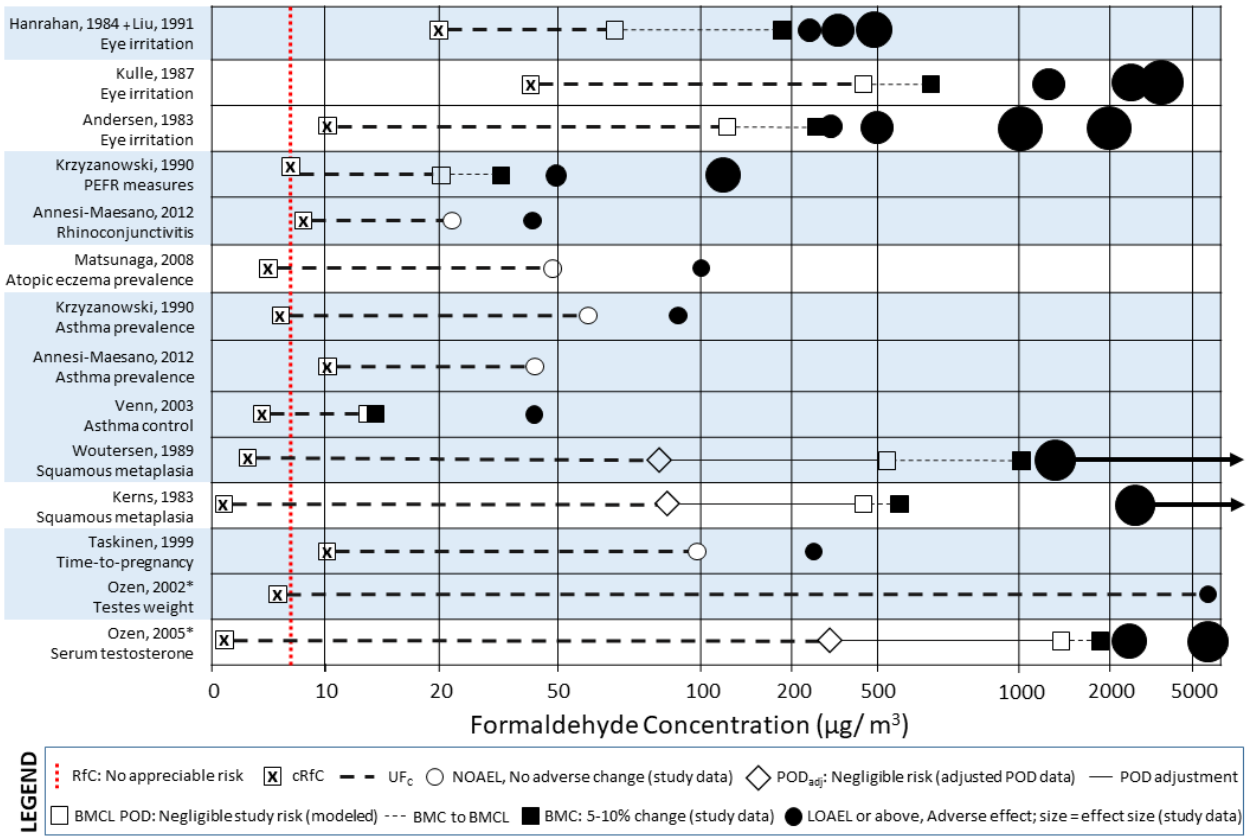


Figure 5-4. Illustration of noncancer toxicity value estimations.

This figure provides a representation of the estimates from studies supporting the cRfCs and those selected to represent the osRfCs (blue shading)**.** Horizontal lines in the figure reflect the extrapolation process for arriving at points of departure (PODs) and toxicity values (unfilled symbols) in the context of the study-specific evidence for effects (filled symbols; effect magnitude estimated based on study figures, tables, or reported regressions; see previous sections). Note: The *x*-axis is intentionally not on a linear or log scale so as not to convey a false level of precision. Abbreviations: cRfC = candidate RfC; N/LOAEL = no-/lowest-observed-adverse-effect level; UFs = uncertainty factors; BMCL = benchmark concentration, lower confidence bound. The horizontal arrows indicate that effects continue at higher exposure levels within those studies. *For the studies by Ozen et al., the shaded circles represent adjusted (for continuous exposure) values, not study-specific tested concentrations. Exposure assessments are not part of IRIS assessments (see Appendix A.3 for a background summary on exposure for general context). Draft exposure assessments are underway in EPA's TSCA Office (see https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-formaldehyde#re-findings).

Although the RfC is designed to apply to exposures over a lifetime, the relevant window of exposure for some of the effects observed in the contributing studies may be less than lifetime. For instance, the relevant window of exposure for effects on asthma outcomes is less than lifetime, although the time frame for the control of asthma symptoms (i.e., a few weeks) is expected to be different than that for the prevalence of current asthma symptoms or a decrease in pulmonary function (i.e., the last 12 months).

Table 5-25. Overall RfC for formaldehyde inhalation

Health effects and basis	RfC (mg/m^3)	Overall confidence
Pulmonary function, allergy-related conditions, and degree of asthma control/prevalence of current asthma in children based on human residential- and school-based studies[a]	0.007	**High**

[a]Based on the following studies: Venn et al. (2003); Krzyzanowski et al. (1990); Annesi-Maesano et al. (2012).

Uncertainties in the Derivation of the Overall Reference Concentration

Research in experimental animals with regard to two health effects, respiratory tract pathology and male reproductive toxicity, indicates that the overall RfC may not be protective against these hazards. Based on these effects, an alternative RfC of 0.003–0.006 mg/m^3 would be derived. However, the confidence in this alternative RfC would be lower because uncertainties regarding these osRfCs are greater and the extrapolation from concentrations at which effects were observed in these experimental animal studies was much larger.

The potential for formaldehyde to adversely affect the nervous system, female and male reproduction, as well as development are not well studied, and the systemic effects of inhaled formaldehyde are not well understood. The potential for a localized, immunosuppressive effect in the respiratory tract, with implications for infectious diseases spread through inhalation, is another understudied issue. Additional research in these areas would increase understanding of the spectrum of effects seen with formaldehyde exposure, formaldehyde concentrations that pose a hazard for specific types of effects, and MOAs for these effects.

Confidence Statement Regarding the Overall Reference Concentration

An overall confidence level of **high**, **medium**, or **low** is assigned to reflect the level of confidence in the study(ies) and hazard(s) used to derive the RfC, the overall database, and the RfC itself, as described in Section 4.3.9.2 of EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Overall confidence in the RfC is **high** based on the confidence determinations for the three osRfCs supporting the RfC (see Table 5-25) and there are minimal associated uncertainties (i.e., the UF_Cs for the values supporting the RfC were either 3 or 10). The RfC is based on a spectrum of adverse effects reported in multiple well-conducted studies involving different populations of exposed humans. The study populations were exposed to formaldehyde levels in a residential or school setting, thus requiring no high-to-low exposure extrapolation, and some of the studies focused on sensitive individuals. An extensive literature database supports the hazard conclusions.

5.1.6. Previous IRIS Assessment: Reference Value

An inhalation RfC for formaldehyde has not previously been derived. In 1990, an oral reference dose (RfD) of 0.2 mg/kg-day was developed. This value was based on reduced weight gain and histopathology (primarily of the gastrointestinal system) in Wistar rats during a 2-year

bioassay in which formaldehyde was administered in the drinking water (Til et al., 1989). A UF_C of 100 was applied to the NOAEL to account for inter- and intraspecies differences. This RfD was interpreted with **medium** confidence, based on *high* confidence in the principal study and *medium* confidence in the database.

5.2. INHALATION UNIT RISK FOR CANCER

Unit risk estimates for cancer were derived from different data sets available from both epidemiological and experimental animal studies. Quantitative estimates could be derived for two of three cancer types for which the evidence supporting a human health hazard was sufficiently strong (**evidence demonstrates**): nasal cancers (i.e., nasopharyngeal cancer in human studies; nasal SCC in experimental animal studies) and myeloid leukemia, although there was too much uncertainty in the estimate for myeloid leukemia to incorporate it into the inhalation unit risk (IUR). While the evidence supporting a human health hazard from sinonasal cancer from studies in occupational cohorts and experimental animals also was sufficiently strong to support the derivation of unit risk estimates, no adequate exposure-response data sets were available to derive unit risk estimates.

Section 5.2.1 focuses on the derivation of unit risk estimates for nasal cancers with an examination of sources of uncertainty, and Section 5.2.2 summarizes the attempts to derive unit risk estimates for myeloid leukemia and examines sources of uncertainty. Section 5.2.3 presents a summary of the quantitative estimates obtained from the different data sets and selection of the IUR. Section 5.2.4 describes adjustments to the IUR for assumed early-life susceptibility for cancers with a mutagenic MOA. Finally, Section 5.2.5 provides a summary of the final adjusted unit risk estimate and uncertainties.

The IUR for cancer was ultimately estimated based on the unit risk estimate for extra risk of NPC using the results from an occupational study and cumulative exposure. Because the MOA for formaldehyde's effect on nasal cancer risk was concluded to involve mutagenicity, the unit risk estimate was adjusted for assumed increased early-life susceptibility. While, ideally, estimates for NPC and myeloid leukemia (and sinonasal cancer, were sufficient quantitative data available) would be combined to derive the inhalation unit risk (IUR) for formaldehyde[59], there is considerable scientific uncertainty in the data used to estimate a unit risk for myeloid leukemia. Therefore, a unit risk estimate for myeloid leukemia is not included in the IUR.

[59] EPA's approach to deriving an IUR for myeloid leukemia is described in Appendix D.2.3. This provides some context regarding the potential magnitude of the total cancer risk had a more certain analysis of myeloid cancer risk been achievable, with the estimate interpreted by EPA as the best that could be currently derived suggesting the combined risk of NPC and myeloid leukemia together is 4-fold higher than the risk for NPC alone. Although the magnitude is uncertain, the IUR based on NPC alone is certainly an underestimate.

5.2.1. Unit Risk Estimates for Nasal Cancer

A judgment that the **evidence demonstrates that** formaldehyde inhalation causes NPC cancer was based on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels, and *robust* animal evidence of nasal cancers in rats and mice that exhibits steeply increasing incidence at high formaldehyde levels. Strong mechanistic support is provided across species (primarily rats, but also mice, monkeys, and humans), including genotoxicity (sometimes at low formaldehyde levels in rats), epithelial damage or remodeling, and cellular proliferation that are consistent with neoplastic development in a regional, temporal, and dose-related fashion.

EPA's standard approach for deriving an inhalation unit risk (IUR) estimate using results from epidemiology studies involves using a regression coefficient that describes the relationship between increases in cancer risk and increases in cumulative exposure, and estimating a (upper-bound) lifetime extra risk-per-unit exposure concentration through a life-table analysis. Cumulative exposure, which incorporates both average concentration and the duration of time over which exposure occurred, is generally the preferred metric for quantitative estimates of lifetime risk from environmental exposure to carcinogens, and thus cumulative exposure was chosen as the exposure metric for calculations in this assessment. The "true" exposure metric best describing the biologically relevant delivered dose of formaldehyde is unknown. Few epidemiological studies presented dose-response analyses based on cumulative measures of formaldehyde concentration that could support the derivation of unit risk estimates. A unit risk estimate was derived based on dose-response modeling of mortality and cumulative formaldehyde exposure for nasopharyngeal cancer (NPC) in a human occupational cohort. Upper respiratory tract (URT) cancer risk was also extrapolated from the incidence of nasal squamous cell carcinoma (SCC) in experimental studies on F344 rats. Results from several approaches used to model these data are evaluated and compared, including biologically based dose-response (BBDR) modeling, statistical time-to-tumor modeling, and statistical benchmark dose modeling using data on DNA-protein crosslinks (DPXs) and formaldehyde flux as dose measures. Additional analyses and comparisons were conducted based on mechanistic hypotheses, including derivation of RfCs based solely on estimates of cell proliferation (i.e., one contributing MOA to formaldehyde exposure-induced nasal cancers; see MOA discussion in Section 3.2.5), and assessing impacts of endogenous formaldehyde concentration on dosimetric estimates.

Derivation of Nasopharyngeal Cancer Unit Risk Estimates Based on Human Data

Choice of epidemiology studies

While several studies of cancer in workers exposed to formaldehyde evaluated exposure-response relationships, most reported the results of categorical analyses, only a few reported risk estimates in relation to changes in formaldehyde concentration or cumulative exposure rather than duration of exposure, TSFE, probability of exposure, or exposure intensity

score, measures which are not generally adequate for the derivation of cancer unit risk estimates. One *high* confidence result from Beane Freeman et al. (2013) presented results of the follow-up of the large National Cancer Institute (NCI) retrospective cohort mortality study [originally described by Blair et al. (1986)] of workers at 10 U.S. plants producing or using formaldehyde. Six medium confidence study reported results but did not have critical information on slope parameters that could be used to derive an IUR. The available *high* and *medium* confidence epidemiology studies of NPC cancer were evaluated for use in deriving a cancer unit risk estimate (see Table 5-26).

Table 5-26. Eligible epidemiology studies for POD derivation and rationale for decisions to not select specific studies for nasal cancer

Study, Endpoint	Dose-Response Considerations (see Section 2.7)					Decision
	Study Evaluation	Population or Subjects	Exposure	Outcome Measure(s)	Result(s) Utility	
(Beane Freeman et al., 2013**) Nasopharyngeal cancer**	[+] High confidence [+] Potential information bias unlikely [+] Selection bias and confounding unlikely	[+] Diverse population (Adult M+F) [+] Participation rate of cases (96%) and controls (94%)	[+] 2000 air samples [+] Individual-level continuous exposure [+] Wide range (0.0–107.4 ppm-years) [+] Blinded to outcome	[+] Mortality: underlying cause from death certificates ICD-8: 147	[n] N = 11 cases among 25,619 workers [+] Poisson regression with slope parameters provided by Beane Freeman (Jinot and Beane-Freeman, 2014)	POD derived, no notable limitations.
(Hauptmann et al., 2009) Nasopharyngeal cancer	[n] Medium confidence [-] Possible information bias (low sensitivity) [+] Selection bias and confounding unlikely	[+] Diverse population (Adult M+F)	[+] Individual level, based on lifetime work practices and exposures to formaldehyde using a predictive model based on exposure-assessment data [+] Low levels and wide range (0 to >9253 pp-hrs level = 0.01 ppm	[+] Mortality: underlying cause from death certificates ICD-8: 147	**Critical concern:** [--] N = 4 cases out of 6,808 embalmers and funeral directors; N=2 exposed cases [--] Analysis limited to ever/never exposed	No POD derived. Critical concern with results utility for dose-response analysis.
(Hildesheim et al., 2001) Nasopharyngeal cancer	[n] Medium confidence [+] Selection bias and confounding unlikely	N/A	*Some concern*: [-] Possible information bias (low sensitivity)	N/A	[+] N=375 cases with N = 74 exposed [+] Logistic regression analysis **Critical concern:** [--] No regression	No POD derived. Critical concern with results utility for dose-response analysis.

Study, Endpoint	Dose-Response Considerations (see Section 2.7)					Decision
	Study Evaluation	Population or Subjects	Exposure	Outcome Measure(s)	Result(s) Utility	
					analyses by continuous exposure	
(Vaughan et al., 2000) Nasopharyngeal cancer	[n] Medium confidence [+] Selection bias and confounding unlikely	N/A	*Some concern*: [-] Possible information bias (low sensitivity)	N/A	[+] N = 196 cases with n = 79 exposed [+] Logistic regression analysis **Critical concern**: [--] No regression analyses by continuous exposure	No POD derived. Critical concern with results utility for dose-response analysis.
(West et al., 1993) Nasopharyngeal cancer	[n] Medium confidence [+] Selection bias unlikely [n] Negative confounding possible by controlling for mosquito coils	N/A	*Some concern*: [-] Possible information bias (low sensitivity)	N/A	[+] N = 104 cases with n = 27 exposed [+] Logistic regression analysis **Critical concern:** [--] No regression analyses by continuous exposure	No POD derived. Critical concern with results utility for dose-response analysis.
(Roush et al., 1987b) Nasopharyngeal cancer	[n] Medium confidence [+] Selection bias and confounding unlikely	N/A	*Some concern*: [-] Possible information bias (low sensitivity)	N/A	[+] N = 173 cases with n = 21 exposed [+] Logistic regression analysis **Critical concern**: [--] No regression analyses by continuous exposure	No POD derived. Critical concern with results utility for dose-response analysis.
(Olsen et al., 1984) Nasopharyngeal cancer	[n] Medium confidence [+] Selection bias and confounding unlikely	N/A	*Some concern*: [-] Possible information bias (low sensitivity)	N/A	[+] N = 266 cases [+] Matched case-control analysis **Critical concern:** [--] No regression	No POD derived. Critical concern with results utility for dose-response analysis.

Study, Endpoint	Dose-Response Considerations (see Section 2.7)					Decision
	Study Evaluation	Population or Subjects	Exposure	Outcome Measure(s)	Result(s) Utility	
					analyses by continuous exposure	

Thus, the quantitative analyses presented in this Toxicological Review are based on the NPC (Beane Freeman et al., 2013) results from the latest follow-up of the NCI cohort of industrial workers exposed to formaldehyde. The NCI cohort study is the largest of the three independent industrial worker cohort studies [the other two being Meyers et al. (2013) and Coggon et al. (2014)] and, more importantly, it is the only one with sufficient individual exposure data for exposure-response modeling. In addition, the NCI study is the only one of the three studies that used internal comparisons rather than standardized mortality ratios (SMRs), thus minimizing the potential impact of the healthy worker effect by addressing unmeasured confounding, which can bias effect estimates.

The NCI cohort consists of 25,619 workers (88% male) employed in any of the 10 plants prior to 1966. The most recent follow-up, based on 998,239 person-years of observation (through 2004) reported a total of 13,951 deaths (Beane Freeman et al., 2013). Beane Freeman et al. (2013) analyzed 10 deaths from NPC as well as deaths from other solid tumors. Some demographic details about the cohort are summarized in Table 5-27.

Table 5-27. Demographic details about the NCI industrial workers cohort[a]

Factor	Quantity
Number of workers	25,619
Person-years of follow-up	998,239
Percentage male	87.8%
Percentage white	92.7%
Percentage hourly workers	78.5%
Median duration of follow-up	42 years
Median (range) length of employment	2.6 years (<1 day–47.7 years)
Number of deaths	13,951
Number of cancer deaths	3,703

[a]Follow-up through December 31, 2004 (Beane Freeman et al., 2013).

A detailed exposure assessment was conducted for each worker in the NCI cohort, based on exposure estimates for different jobs held and tasks performed (Stewart et al., 1986). Exposure estimates were made using several different metrics—peak exposure, average intensity, cumulative exposure, and duration of exposure. Respirator use and exposures to formaldehyde-containing

particulates and other chemicals were also considered. Some exposure details about the cohort are summarized in Table 5-28.

Table 5-28. Exposure details about the NCI industrial workers cohort[a]

Factor	Quantity
Percentage workers never exposed	10.5%
Median (range) formaldehyde TWA8 for exposed workers	0.3 (0.01–4.3) ppm
Median (range) cumulative exposure for exposed workers	0.6 (0.0–107.4) ppm × years
Number of workers who experienced peak exposures ≥4 ppm	6,255

[a]Follow-up through December 31, 2004 (Beane Freeman et al., 2013).

For NPC, RR estimates were increased in the highest exposure category for each of the exposure metrics (Beane Freeman et al., 2013), although these increases were generally not statistically significant, given the small number of deaths involved. A statistically significant trend was observed only for the peak exposure metric and only among the exposed person-years [two of the 10 deaths from this rare cancer were in the unexposed workers (Beane Freeman et al., 2013)]. The (log-linear) trend for cumulative exposure (as a continuous variable) approached statistical significance (p = 0.06 among exposed person-years only and p = 0.07 among all person-years). With respect to the other solid cancers of interest, while Beane Freeman et al. (2013) reported results for cancers of the nose and nasal sinus, there were just five deaths for that endpoint. Marsh et al. (2002) reported some exposure-response results from their case-control study of all pharyngeal cancers in one of the industrial plants studied by the NCI, but they did not observe positive trends for cumulative or average exposure.

Exposure assessment and choice of exposure metric from the National Cancer Institute cohort

A detailed exposure assessment was conducted for the NCI cohort of industrial workers exposed to formaldehyde, and quantitative exposure estimates were generated for each worker (Stewart et al., 1986). Formaldehyde exposure estimates, including TWA8 concentration and categories of peak concentrations, were derived for each job, work area, and calendar year combination. A peak was defined as a short-duration exposure (typically <15 minutes) above the TWA, which could be related to either routine or nonroutine tasks (Beane Freeman et al., 2009). The frequency of peak exposures was also estimated, but these estimates were based on assumptions made by the assessors rather than direct measures or observations, making this metric highly uncertain. Cumulative exposures (in ppm × years) were estimated by multiplying the time a worker spent in a specific job by the TWA exposure for that job and summing over all the jobs held by the worker. Duration was the total time spent in jobs with formaldehyde exposure, and average intensity was the ratio of cumulative exposure to duration. Formaldehyde exposures after

1980 were not taken into account in the follow-up study, but this was considered to have a generally minimal impact on the results (Beane Freeman et al., 2013).

Some of the strongest exposure-response relationships in the NCI cohort studies (Beane Freeman et al., 2013) (e.g., for NPC) were observed for the peak exposure metric. It is not clear how to extrapolate RR estimates based on peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from continuous exposure to low environmental levels. In addition, peak exposure level is a more subjective measure than the other metrics, it is not based on formaldehyde concentration measurements, and it is a categorical rather than continuous measure. Individual workers were assigned to peak exposure level categories based on their work histories and a matrix of job-, work area-, and calendar time-specific TWA8 formaldehyde measurements. Historical sampling records and sampling conducted by the investigators contributed to the development of this matrix. If a short-term (<15 minute) excursion above the TWA8 concentration for a job was observed, or expected based on industrial hygiene expertise, then that job was assigned to a peak exposure category: none, >0 to <0.5 ppm (>0 to 0.62 mg/m^3), 0.5 to <2.0 ppm (0.62 to <2.46 mg/m^3), 2.0 to <4.0 ppm (2.46 to 4.92 mg/m^3), or ≥4.0 ppm (≥4.92 mg/m^3). Individual workers may have experienced these peak concentrations rarely, intermittently, or routinely, and in jobs they held for a long time or only briefly. At a given time point, a worker's peak exposure estimate is the highest peak exposure category ever attained by the worker. As such, this exposure metric is not interpretable in terms of a lifetime exposure risk.

Similarly, the average exposure metric is not a measure of long-term exposure for chronic effects because it does not account for duration of exposure (e.g., exposure to a given exposure level for 1 year conveys the same amount of risk as exposure to the same level for 70 years). Likewise, duration of exposure does not account for the level of exposure and is not a useful metric for the calculation of risk estimates as a function of exposure level, such as the cancer unit risk estimate.

Cumulative exposure, which incorporates both average concentration and the duration of time over which exposure occurred, is generally the preferred metric for quantitative risk assessment of lifetime risk from environmental exposure to carcinogens, and cumulative exposure was chosen as the exposure metric for the risk estimate calculations for the cancer endpoints in this assessment. The "true" exposure metric best describing the biologically relevant delivered dose of formaldehyde is unknown.

Dose-response modeling of the National Cancer Institute cohort

The results of the internal analyses (i.e., comparing exposed workers to an internal referent group of other workers in the cohort) of Beane Freeman et al. (2013) for NPC using the cumulative exposure metric, with comparisons to the results using the peak exposure and average intensity metrics, are presented in Table 5-29. The relative risks (RRs; in this case, rate ratios) were estimated using log-linear Poisson regression models stratified by calendar year, age (in 5-year intervals), sex, and race (black/white) and adjusted for pay category (salary/wage). As shown by Callas et al. (1998), when age is well characterized and adjusted for, as it was in the Beane Freeman

et al. (2013) study, the Poisson regression and Cox proportional hazards models yield essentially the same results. Beane Freeman et al. (2013) used a 15-year lag interval in estimating exposures to account for a latency period for the development of solid cancers, including NPCs. Lag intervals of 2–20 years were evaluated, and changing the interval had little impact on the RR estimates; thus, the interval of 15 years that was used in the previous follow-up analyses (Hauptmann et al., 2004) was retained. For all cancer types, the NCI investigators used the low-exposure category as the reference category to "minimize the impact of any unmeasured confounding variables since nonexposed workers may differ from exposed workers with respect to socioeconomic characteristics" (Hauptmann et al., 2004). Table 5-29 also presents the *p*-value for the (log-linear) trend of risk changing with exposure level for all workers and for only those workers exposed to formaldehyde. The strongest exposure-response relationship for NPC is observed for the peak exposure metric among exposed workers.

The log-linear trend analyses for the cumulative exposure metric approach statistical significance (*p*-trend = 0.07 for all person-years; *p*-trend = 0.06 for exposed person-years only). The fact that the two-sided *p*-values are not strictly <0.05 is not critical here, given that the hazard for NPC was established a priori in Chapter 1. The nonexposed person-years were included in the primary cancer risk analyses to use all the available exposure-response data. Furthermore, the data were stratified by pay category, which provided at least partial adjustment for socioeconomic characteristics. Final results for the exposed person-years only are also presented for comparison.

The log-linear trend tests conducted by Beane Freeman et al. (2013) used exposure as a continuous variable (except for peak exposure, for which categorical ranks were used) (general model form: $RR = e^{\beta X}$, where β represents the regression coefficient and X is exposure). Dr. Beane Freeman provided EPA with the β estimates (and their standard errors) from the trend tests for NPC and the cumulative exposure metric for all person-years and for exposed person-years only (personal communication to EPA from Laura Beane Freeman, NCI, to Jennifer Jinot, EPA, February 22, 2013). These estimates are presented in Table 5-29.

Table-5-29. Relative risk estimates for mortality from nasopharyngeal malignancies (ICD-8 code 147) by level of formaldehyde exposure for different exposure metrics

Rate ratio (number of deaths)				*p*-Trend	
				All person-years[a]	Exposed person-years[b]
Peak exposure (ppm)					
0	**>0 to <2.0[c]**	**2.0 to <4.0**	**≥4.0**		
4.39 (2)	1.0 (1)	– (0)	7.66 (7)	0.10	0.005
Average intensity (ppm)					
0	**>0 to <0.5[c]**	**0.5 to <1.0**	**≥1.0**		
6.79 (2)	1.0 (1)	2.44 (1)	11.54 (6)	0.16	0.09

Rate ratio (number of deaths)				*p*-Trend	
				*A*ll person-years[a]	*E*xposed person-years[b]
Cumulative exposure (ppm × years)					
0	>0 to <1.5[c]	1.5 to <5.5	≥5.5		
1.87 (2)	1.0 (4)	0.86 (1)	2.94 (3)	0.07	0.06

[a]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (continuous variable, except for peak exposure metric) among all (nonexposed and exposed) person-years.
[b]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (continuous variable, except for peak exposure metric) among exposed person-years only.
[c]Reference category for all categories with the same exposure metric.
Source: Beane Freeman et al. (2013).

Table 5-30. Regression coefficients from NCI log-linear trend test models for NPC mortality from cumulative exposure to formaldehyde[a]

Person-years	β (per ppm × year)	Standard error (per ppm × year)
All	0.04311	0.01865
Exposed only	0.0439	0.01852

[a]Models stratified by calendar year, age, sex, and race and adjusted for pay category; cumulative exposures calculated using a 15-year lag interval.
Source: Personal communication to EPA from Laura Beane Freeman to Jennifer Jinot (February 22, 2013).

Prediction of lifetime extra risk of nasopharyngeal cancer mortality

The regression coefficients presented in Table 5-30 were used to predict the extra risk of NPC mortality from environmental exposure to formaldehyde.

$$\text{Extra risk} = (R_x - R_o) \div (1 - R_o), \qquad \text{(Eq. 5-3)}$$

where R_x is the lifetime risk in the exposed population and R_o is the lifetime risk in an unexposed population (i.e., the background risk). Extra risk estimates were calculated using the β regression coefficients and a life-table program that accounts for competing causes of death.[60] U.S. age-specific 2010 all-cause mortality rates and 2000–2010[61] NPC (ICD-10 C11.0-C11.9) mortality rates for all race and sex groups combined[62] were used to specify the all-cause and cause-specific background mortality rates in the life-table program. Risks were computed up to age 85 because cause-specific

[60]This program is an adaptation of the approach that was previously used in BEIR IV, "Health Risks of Radon and Other Internally Deposited Alpha Emitters." National Academy Press, Washington, DC, 1988, pp. 131–134. A spreadsheet illustrating the life table used for the extra risk calculation for the derivation of the LEC_{0005} for NPC incidence is presented in Appendix D.2.1.
[61]Typically, 5-year ranges are used as the basis for population cause-specific disease and mortality rates; a larger range is used here to get better stability in the rates because NPC is a rare cancer.
[62]Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death on CDC WONDER Online Database. Accessed at http://wonder.cdc.gov/ucd-icd10.html on September 19, 2013.

mortality (and incidence) rates for ages above 85 years are less reliable. Conversions between occupational formaldehyde exposures and continuous environmental exposures were made to account for differences in the number of days exposed per year (240 versus 365) and in the amount of air inhaled per day (10 versus 20 m^3). An adjustment was also made for the 15-year lag period. The reported standard errors for the regression coefficients were used to compute the one-sided 95% upper confidence limits (UCLs) for the extra risks based on a normal approximation.

Point estimates and one-sided 95% UCLs for the extra risk of NPC mortality associated with varying levels of continuous exposure to formaldehyde are presented in Table 5-31. The model predicts extra risk estimates that are fairly linear for exposures below about 0.001 to 0.01 ppm but not for exposures above 0.01 ppm.

Table 5-31. Extra risk estimates for nasopharyngeal cancer mortality from various levels of continuous exposure to formaldehyde

Exposure concentration (ppm)	Extra risk	95% UCL on extra risk
0.0001	1.24×10^{-7}	2.12×10^{-7}
0.001	1.24×10^{-6}	2.13×10^{-6}
0.01	1.28×10^{-5}	2.25×10^{-5}
0.1	1.79×10^{-4}	4.12×10^{-4}
1	2.67×10^{-1}	8.74×10^{-1}
10	9.83×10^{-1}	9.87×10^{-1}

Consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the same data and methodology were also used to estimate the exposure level (effective concentration [ECx]) and the associated (one-sided) 95% lower confidence limit (LECx) corresponding to an extra risk of 0.05% (x = 0.0005). Although EPA guidelines emphasize the use of exposure levels associated with a 10% extra risk level for the POD for low-dose extrapolation, that would not be appropriate in this instance. A 10% extra risk level is very high for responses generally observed in epidemiology studies; thus, a 1% extra risk level is typically used for epidemiological data to avoid upward extrapolation. However, NPC has a very low background mortality rate (e.g., lifetime background risk is about 0.00019); therefore, even a 1% extra risk (i.e., 0.01) would be a large increase relative to the background risk. This is consistent with the fact that, even with a large cohort followed for a long time, only 10 NPC deaths were observed in the NCI follow-up through 2004.[63] The 1% level of risk is associated with RR estimates that are substantially higher than those observed in the epidemiology study. Based on the life-table program, the RR estimate for an extra risk of 1% for NPC mortality is 53, an upward extrapolation. Even 0.1% yields an RR estimate on the high end of

[63]Eleven NPCs were reported on death certificates and included in NCI's SMR analyses, but one of these cases was apparently misclassified on the death certificate, so only 10 cases were used to estimate the RRs in the internal comparison analyses (Beane Freeman et al., 2013).

the observable range of the epidemiology study (RR = 6.2). A 0.05% extra risk level yields an RR estimate of 3.6, which better corresponds to the RRs in the range of the data. Thus, 0.05% extra risk was selected for determination of the POD, and, consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the LEC value corresponding to that risk level was used as the POD.

Based on a detailed analysis conducted according to EPA's cancer MOA framework (U.S. EPA, 2005a), it was concluded that two primary MOAs contribute to nasal cancers caused by formaldehyde inhalation exposure, namely mutagenicity and cytotoxicity-induced regenerative proliferation. Overall, there is strong and consistent evidence for both MOAs (see Section 3.2.5 for details). The data are insufficient to conclude that mutagenicity does not contribute at low exposure levels. In fact, multiple well-conducted studies demonstrate effects associated with mutagenicity (e.g., chromosomal changes) at exposure levels well below those causing cellular cytotoxicity, which is incompatible with a theory of carcinogenesis based solely upon exceedance of a cytotoxicity-based threshold. In accordance with the EPA cancer guidelines (U.S. EPA, 2005a, b), given the strong evidence for mutagenicity as a contributing MOA and the evidence-based understanding that mutagens can give rise to cancers with an apparently low-dose linear response, a linear low-dose extrapolation was performed. The EC_{0005}, LEC_{0005}, and IUR estimates for NPC mortality are presented in Table 5-32.

Table 5-32. EC_{0005}, LEC_{0005}, and unit risk estimates for nasopharyngeal cancer mortality from formaldehyde exposure based on the Beane Freeman et al. (2013) log-linear trend analyses for cumulative exposure

Person-years	EC_{0005} (ppm)	LEC_{0005} (ppm)	Unit risk[a] (per ppm)	Unit risk (per mg/m^3)
All	0.191	0.112	4.5×10^{-3}	3.7×10^{-3}
Exposed only	0.187	0.111	4.5×10^{-3}	3.7×10^{-3}

[a]Unit risk = $0.0005/LEC_{0005}$.

Prediction of lifetime extra risk of nasopharyngeal cancer incidence

EPA cancer risk estimates are typically derived to represent a plausible upper bound on increased risk of cancer incidence, as from experimental animal incidence data. Cancer data from epidemiology studies are more often mortality data, as is the case in the NCI study. For cancers with low survival rates, mortality-based estimates are reasonable approximations of cancer incidence risk. However, for NPC, the survival rate is substantial (51% at 5 years in the 1990s in the United States, according to Lee and Ko (2005) and incidence-based risks are preferred because EPA is concerned with cancer occurrence, not just cancer mortality.

Therefore, an additional calculation was done using the same regression coefficients provided by Dr. Beane Freeman (see Table 5-30) but with age-specific NPC incidence rates from NCI's Surveillance, Epidemiology, and End Results (SEER) Program in place of the NPC mortality rates in the life-table program. SEER collects cancer incidence data from a variety of geographical

areas in the United States. The incidence data used here are from SEER-18, a registry covering about 27.8% of the U.S. population, which was the most current SEER registry at the time this analysis was done. SEER-18 age-specific background incidence rates for NPC (ICD-10 C11.0-C11.9) for 2000–2010 were obtained from the SEER public-use database (www.seer.cancer.gov) using NCI's SEER*Stat software (www.seer.cancer.gov/seerstat). The incidence-based calculation relies on the reasonable assumptions that NPC incidence and mortality have the same exposure-response relationship for formaldehyde exposure and that the incidence data are for first occurrences of NPC or that relapses provide a negligible contribution. The calculation, as presented in the life-table spreadsheet in Appendix D.2.1, also takes advantage of the fact that NPC incidence rates are negligible compared with the all-cause mortality rates and thus no special adjustment to the population at risk to account for live individuals who have been diagnosed with NPC is necessary.

The resulting EC_{0005}, LEC_{0005}, and IUR estimates for NPC incidence are presented in Table 5-33. The unit risk estimate for cancer incidence is two-fold higher than the corresponding mortality-based estimate, for all person-years, reflecting the high survival rates for NPC.

Table 5-33. EC_{0005}, LEC_{0005}, and unit risk estimates for nasopharyngeal cancer incidence from formaldehyde exposure based on the Beane Freeman et al. (2013) log-linear trend analyses for cumulative exposure

Person-years	EC_{0005} (ppm)	LEC_{0005} (ppm)	Unit risk[a] (per ppm)	Unit risk (per mg/m^3)
All	0.0942	0.0550	9.1×10^{-3}	7.4×10^{-3}
Exposed only	0.0925	0.0546	9.2×10^{-3}	7.5×10^{-3}

[a]Unit risk = $0.0005/LEC_{0005}$.

The selected estimate for the cancer unit risk for NPC, prior to any age adjustments is the estimate of **9.1×10^{-3} per ppm (7.4×10^{-3} per mg/m^3)** derived using incidence rates for the cause-specific background rates, for all person-years. The results from the exposed person-years are essentially identical.

Because NPC is a rare cancer in the United States, with a relatively low number of cases occurring per year, a rough calculation was done to ensure that the unit risk estimate derived for NPC incidence is not implausible in comparison to actual case numbers. For example, assuming an average constant lifetime formaldehyde exposure level of 5 ppb for the U.S. population, the IUR estimate for NPC equates to a lifetime extra risk estimate of 4.6×10^{-5}. Assuming an average lifetime of 75 years (this is not EPA's default average lifetime of 70 years but rather a value more representative of actual demographic data) and a U.S. population of 300,000,000, this lifetime extra risk estimate suggests a crude upper-bound estimate of 180 incident cases of NPC attributable to formaldehyde exposure per year. Alternatively, assuming an average constant lifetime formaldehyde exposure level of 20 ppb, the calculation suggests a crude upper-bound estimate of 730 incident cases of NPC per year. Both upper-bound estimates, using different assumed lifetime

exposure levels, are well below the estimated 2,300 total incident NPC cases per year calculated from the SEER NPC incidence rate of 0.75/100,000.[64,65]

Derivation of Nasal Cancer Unit Risk Estimates Based on Squamous Cell Carcinoma in the Respiratory Tract Using Animal Data

In this section, dose-response analyses of cancer risk based on nasal tumor data from laboratory rodent bioassays are presented. The Agency takes the position that human data, if adequate data are available, provide a more appropriate basis for estimating human cancer risk than do rodent data (U.S. EPA, 2005a), primarily because uncertainties in extrapolating quantitative risks from rodents to humans are avoided; therefore, the epidemiology-derived estimates presented in the previous section are the selected unit risk estimates for nasal cancers.

Nonetheless, it is useful to compare human health risk estimates from available epidemiology data with estimates extrapolated from animal studies. Furthermore, a large body of mechanistic data on cell replication, DPX and DNA monoadduct formation, and dosimetry modeling of formaldehyde flux to local tissue exist for formaldehyde that can potentially inform the shape of the dose-response curve. This information, as well as data on the incidence of hyperplasia, facilitates the interpretation and extrapolation of nasal squamous cell carcinoma (SCC) incidence results from rodent bioassays within the context of formaldehyde's reactivity and MOAs. The estimates derived from animal data incorporate this information into the modeling.

Choice of Animal Studies

The available *high* and *medium* confidence animal studies of nasal cancers were evaluated for use in deriving a cancer unit risk estimate (see Table 5-34). As was the case for hazard identification (see Section 3.2.5), studies of subchronic or shorter duration without long-term follow up to allow for the development of cancers were not considered.

Table 5-34. Eligible experimental animal studies for POD derivation and rationale for decisions to not select specific studies for nasal cancers

Study, species	Dose-response considerations (see Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Rat Studies						

[64]The crude NPC (ICD-10 C11.0-C11.9) incidence rate from 2000–2010 SEER-18 data was obtained from the SEER public-use database (www.seer.cancer.gov) using NCI's SEER*Stat software (www.seer.cancer.gov/seerstat). This value is similar to a published NPC incidence rate for the United States of 0.7/100,000 person-years (Lee and Ko, 2005). The age-adjusted NPC incidence rate from SEER was also 0.75/100,000.

[65]With the application of age-dependent adjustment factors (see Section 5.2.4), the lifetime unit risk estimate for NPC would increase by a factor of 1.42, and the crude upper-bound estimates of the incident cases per year attributable to formaldehyde exposure would similarly increase by a factor of 1.42. The resulting adjusted upper-bound estimates of 260 and 1,030 for 5- and 20-ppb exposure levels, respectively, are still well below the estimated total number of 2,300 incident cases per year in the United States.

Study, species	Dose-response considerations (see Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Monticello et al. (1996) *Rats*: F344 (M)	[+] *High* confidence [+] Good exposure quality	*Some concern*: [-] Males only	[+] 2-year exposure [+] Broad exposure range (0.85 to 18.4 mg/m^3)	[+] 6 nasal cross sections [n] Lack of blinding for tumor analyses not a significant limitation	[+] Large N (N = 90 - 147)	POD derived. Concern noted regarding testing of males only.
Woutersen et al. (1989) *Rats:* Wistar (M)	[+] *High* confidence [+] Good exposure quality	*Some concern*: [-] Males only [-] strain is less sensitive than other strains	[+] > 2-year exposure [+] Broad exposure range (0.1 to 12.1 mg/m^3)	[+] 6 nasal cross sections [n] Lack of blinding for tumor analyses not a significant limitation	*Some concern*: [-] Small N for detecting rare cancers (N = 32)	No POD derived. Study design more limited than others due to use of small N and males only.
Sellakumar et al. (1985) *Rats*: Sprague Dawley (M)	[+] *High* confidence [n] Adequate exposure quality	*Some concern*: [-] Males only	**Critical concern**: [--] Single, high exposure (18.2 mg/m^3)	[+] Multiple (interpreted as ≥ 5 based on study description) sections of the head (including nasal cavity), lung, trachea, and larynx [n] Lack of blinding for tumor analyses not a significant limitation	[+] N = 99-100	No POD derived. Critical exposure concern.
Kerns et al. (1983) *Rats*: F344 (M+F) Related studies: (Battelle, 1981, 1982); [interim findings presented in Swenberg et al. (1980b)]	[+] *High* confidence [+] Good exposure quality	*Some concern*: [-] viral infection at weeks 52–53 caused transiently decreased body weight not expected to affect the cancer data (see Section 3.2.5).	[+] 2-year exposure (with follow-up to 30 months)	[+] 5 sections of nasal turbinates (Levels I–V) at all interim sacrifices and at study end [n] Lack of blinding for tumor analyses not a significant limitation.	[+] Large N (N = 119 - 121) [n] Limited reporting of dysplasia findings	POD derived. Concern noted regarding transient viral infection.

Study, species	Dose-response considerations (see Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Kamata et al. (1997) *Rats*: F344 (M)	[n] *Medium* confidence [n] Adequate exposure quality	*Some concern*: [-] Males only	[+] > 2-year exposure (28-months) [+] Broad exposure range (0.40 to 18.3 mg/m^3) *Some concern*: [-] Use of formalin as test article (even with a methanol control group) introduces some quantitative uncertainty.	[+] Nasal region (sections from 5 anatomical levels) and trachea [n] Lack of blinding for tumor analyses not a significant limitation.	*Some concern*: [-] Small N for detecting rare cancers (N = 32)	No POD derived. Study design more limited than others due to use of formalin, small N, and males only.
Holmstrom et al. (1989b) *Rats*: Sprague Dawley (F)	[n] *Medium* confidence [+] Good exposure quality	*Some concern*: [-] Females only [-] Some health concerns noted	**Critical concern**: [--] Single, high exposure (15.3 mg/m^3)	[+] 5 sections of the nose, and the lungs [+] slides blinded	**Critical concern**: [-] Very small N for detecting rare cancers (N = 15-16)	No POD derived. Critical exposure and sample size concerns.
Appelman et al. (1988) *Rats*: SPF Wistar (M)	[n] *Medium* confidence [+] Good exposure quality	*Some concern*: [-] Males only [-] strain is less sensitive than other strains	[+] Broad exposure range (0.12 to 12.1 mg/m^3) **Critical concern**: [--] *Short duration for nasal cancers to develop (1 year) with no follow up*	[+] Nose (6 standard cross levels), larynx, trachea, and lungs [n] Lack of blinding for tumor analyses not a significant limitation	**Critical concern**: [--] Very small N for detecting rare cancers (N = 10)	No POD derived. Critical exposure and sample size concerns.
Woutersen et al. (1989) *Rats:* Wistar (M)	[+] *High* confidence [+] Good exposure quality	*Some concern*: [-] Males only [-] strain is less sensitive than other strains	[+] Broad exposure range (0.1 to 11.3 mg/m^3) **Critical concern**: [--] *3-month exposure (note: with long-term follow up)*	[+] 6 nasal cross sections [n] Lack of blinding for tumor analyses not a significant limitation.	*Some concern*: [-] Small N for detecting rare cancers (N = 30)	No POD derived. Critical exposure concern.
Feron et al. (1988) *Rats*: Wistar (M)	[n] *Medium* confidence	*Some concern*:	**Critical concern**: [--] 13-week exposure (note:	[+] 6 standard cross levels of the nose.	[n] N = 45	No POD derived. Critical

Study, species	Dose-response considerations (see Section 2.7)					Decision
	Study evaluation [a]	**Population or subjects**	**Exposure**	**Outcome measure(s)**	**Result(s) utility**	
	[+] Good exposure quality	[-] Males only [-] strain is less sensitive than other strains	with long-term follow up) [--] High exposure levels only (> 11 mg/m^3)	[n] Lack of blinding for tumor analyses not a significant limitation.		exposure concerns.
					Some concern: [-] Limited reporting on timing of tumor development to inform quantitative analyses.	
Mouse Studies						
Kerns et al. (1983) *Mice*: B6C3F1 (M+F) Related studies: Battelle (1981, 1982)	[+] *High* confidence [+] Good exposure quality	*Some concern*: [-] Survival to 18 mo. < 33% in exposed males [-] mice are less sensitive than rats[b]	[+] 2-year exposure (with follow-up to 30 months) [+] Broad exposure range (2.5 – 17.6 mg/m^3)	[n] Lack of blinding for tumor analyses not a significant limitation. *Some concern*: [-] only 3 nasal sections evaluated	[+] Large N (N = 119-121) [n] Limited reporting of dysplasia findings	No POD derived. Results less useful than others due to concerns regarding survival, sampling, and reporting.
Other species						
Dalbey (1982) *Hamsters*: Syrian golden (M)	[n] *Medium* confidence [+] Good exposure quality	*Some concern*: [-] Males only [-] hamsters are less sensitive than rats	**Critical concern**: [--] Single, high exposure (12.3 mg/m^3)	[n] Lack of blinding for tumor analyses not a significant limitation *Some concern*: [-] Only two nasal sections, with sections of the larynx, trachea, and lungs	[+] Large N = 132 controls and 88 exposed *Some concern*: [-] multiple concerns noted regarding reporting (see Appendix B.3.9)	No POD derived. Critical exposure concern.

[a] Select features of the study evaluations that may have the most impact on quantification may be highlighted (if not otherwise highlighted in other columns), but the bullets in this column do not represent a full synopsis (see Appendix B.3.9 for details).
[b]Mice, and possibly other species, have a greater reflex bradypnea response to irritants than rats, which can result in a lower internal exposure at the same external formaldehyde concentrations (see Appendix C.2).

Section 3.2.5 provides the details of the long-term cancer bioassays of *high* and *medium* confidence in rats. The two largest studies (Kerns et al., 1983) and (Monticello et al., 1996) involved F344 rats with at least 230 animals and 90 animals, respectively, in each dose group and a well-defined spread of multiple dose groups. The Woutersen et al. (1989) study involved Wistar rats,

and as discussed in the synthesis text, this strain is thought to be resistant to the formation of SCCs. The studies by (Holmstrom et al., 1989b) and (Sellakumar et al., 1985) were on SD rats and were single dose studies. The study by (Kamata et al., 1997) on F344 male rats had multiple doses but was limited by its small sample size and the use of formalin as the test article. While long term inhalation bioassays were conducted in mice and this species also develops nasal tumors after formaldehyde inhalation exposure, the available data indicate rats to be the most sensitive lab rodents, and the mouse dose response may not be the appropriate model because of the ability of mice to lower their inhalation rate in response to formaldehyde induced irritation. Therefore, EPA focused on the (Kerns et al., 1983) and (Monticello et al., 1996) bioassays for dose-response modeling of the animal nasal cancer data.

The following section describes the data and modeling approaches available; presents PODs from the considered models at benchmark response rates in the range of the available data; presents results from a biologically based model for extrapolation to human exposure scenarios; evaluates uncertainties in the dose-response models and discusses the use of any of the models for extrapolating below the POD, including implications for low-dose risk; and presents candidate IURs and RfCs derivable from the modeled PODs.

Animal nasal tumor incidence data

An increased incidence of nasal SCC was seen in two long-term bioassays using F344 rats (Monticello et al., 1996; Kerns et al., 1983). The dose-response data from these two studies were statistically evaluated for heterogeneity by combining the data and stratifying the analysis by study (see Appendix D.2.2). Model parameters for the two studies were found to be statistically equivalent (p-value> 0.05). Therefore, it was considered appropriate to combine these studies for greater power in dose-response analysis even though they were conducted 13 years apart. The pooled data (Table 5-35) provide a well-defined spread of concentrations and provide the most robust data among the various animal studies for analyses. The individual animal data from these studies, along with results from an additional 94 animals not previously examined in the Monticello et al. (1996) study, were provided to EPA by the Chemical Industry Institute of Toxicology (CIIT) which contracted or conducted the studies. In 2004, CIIT issued a memo to EPA that corrected errors in the original report for the (Kerns et al., 1983) study; the memo (Bermudez, 2004) is reproduced in the Appendix D.2.2. Table 5-35 shows only the grouped incidence from the two studies combined, the individual animal incidence data used in the assessment are tabulated in Appendix D.2.2.

Table 5-35. F344 rat nasal cancer data

Formaldehyde exposure levels	Incidence of SCC tumors	References
0, 0.7, 2.0, 6.01, 9.93, and 14.96 ppm (0, 0.86, 2.5, 7.4, 12.2, and 18.4 mg/m^3)	0/341, 0/107, 0/353, 3/343, 22/103, 162/386	Monticello et al. (1996); Kerns et al. (1983); Bermudez (2004) (combined bioassays)

Mechanistic information

In addition, three types of mechanistic information are incorporated in some of the dose-response modeling. These include site-specific measurements of DNA-protein crosslinks (DPX) formed by formaldehyde in the F344 rat and rhesus monkey, site-specific measurements of changes in cell labeling induced by inhalation exposure to formaldehyde in the F344 rat, and estimates of formaldehyde flux to the nasal tissue derived using computational fluid dynamics modeling. The DPX estimates used in the dose-response modeling are derived from physiologically based pharmacokinetic (PBPK) models that have been developed based on the DPX data in Table 5-36 to calculate DPX levels as a function of local formaldehyde flux, and to predict DPX levels in the human.

Computational fluid dynamic modeling

The ability to use mechanistic data in dose-response modeling is further facilitated by the availability of computational fluid dynamic (CFD) modeling of airflow in the rat, monkey, and human respiratory passages. The CFD modeling is useful on multiple accounts.

Formaldehyde-induced squamous cell carcinomas (SCCs) and other lesions that occur in the rat and monkey nasal passages and in the monkey LRT are seen to be distributed in localized patterns that differ across species. The anatomy of the respiratory tract, in particular the nasal passages, and the pattern of airflow, show large regional differences across species (see Appendix A). On this basis, several authors have argued that regional dose would be the main determinant of interspecies differences in tumor incidence for a highly reactive and water soluble chemical such as formaldehyde (Morgan et al., 1991; Monticello and Morgan, 1994; Monticello et al., 1996; Bogdanffy et al., 1999), thus motivating the use of modeling local formaldehyde flux in the nasal region of each species.

Kimbell et al. (1993), Kepler et al. (1998), and Subramaniam et al. (1998) developed anatomically realistic finite-element representations of the noses of F344 rats, rhesus monkeys, and humans, and used them in physical and computational models (Kimbell et al., 2001a; Kimbell et al., 2001b). The nasal dosimetry modeling by (Kimbell et al., 2001a; Kimbell et al., 2001b) was revised by Schroeter et al. (2014) to include air:tissue partitioning and air and tissue phase diffusivity; production of endogenous formaldehyde in the respiratory mucosa as a zero-order process; clearance of formaldehyde in the form of a saturable pathway for enzymatic metabolism, a first-

order pathway for nonenzymatic reactions, and a pseudo first-order pathway to include its binding to DNA to form DPX.

This assessment uses dosimetry derived from (Kimbell et al., 2001a; Kimbell et al., 2001b) when extrapolating risk-related dose from the rat to the human (discussed in detail in Appendix C.1.12 and D.2.2), and estimates the impact on the point of departure of using an alternate dosimetry model developed by Schroeter et al. (2014). Furthermore, DPX levels and cell labeling data are characterized as a function of regional formaldehyde flux to further inform the interpretation of cancer incidence results. These are tabulated in Table 5-36 and used in the risk estimates from different dose-response methods presented in Table 5-37 (see Appendix D.2.2 for additional details).

Table-5-36. Dosimetric and mechanistic information supporting dose-response assessment based on rat nasal tumors

Data or information	Formaldehyde exposure	Notes	Study references
FA dosimetry in anatomically realistic representations of the F344 rat and human nasal passages and in an idealized representation of the human lower respiratory tract	Inhaled concentrations of 0, 0.7, 2, 6, 10, or 15 ppm (0, 0.9, 2.5, 7.4, 12.3, or 18.5 mg/m^3) at various steady-state inhalation rates	Fluid dynamic models of local FA flux to tissue.	Subramaniam et al. (2008); Overton et al. (2001); Kimbell et al. (1993); Kimbell et al. (1997b); Kimbell et al. (2001a); Kimbell et al. (2001b). See Appendix B.2
DPX[a] in F344 rat (2 studies) and in rhesus monkey	Rat study 1 (1989): 0.3, 0.7, 2.0, 6.0, 10.0 ppm (0.4, 0.9, 2.5, 7.4, 12.3 mg/m^3) for 6 hours. Rat study 2 (1994): 0.7, 2.0, 6.0, 15.0 ppm (0.9, 2.5, 7.4, 18.5 mg/m^3) for 3 hours. DPX measured over whole nose in study 1, and over two regions ("low" and "high" tumor sites) in study 2. Monkey study: 0.7, 2.0, 6.0 ppm (0.9, 2.5, 7.4 mg/m^3) for 6 hours	DPX lesions observed at all exposure concentrations (0.3 ppm–15 ppm/0.37 mg/m^3–18.5 mg/m^3). DPX tracheal and lung lesions in monkeys at 6.0 ppm (7.4 mg/m^3). Data used in PBPK model for FA and DPX	Conolly et al. (2000); Casanova et al. (1989); Casanova et al. (1991); Casanova et al. (1994)
Cell labeling index[b]; F344 rats. Labeling study with two phases	0, 0.7, 2, 6, 10, or 15 ppm (0, 0.9, 2.5, 7.4, 12.3, or 18.5 mg/m^3). Phase 1 exposure duration: 1, 4, and 9 days and 6 weeks. Phase 2 exposure duration: 13, 26, 52, and 78 weeks	Phase 1 used injection labeling with a 2-hour pulse of tritiated thymidine; Phase 2 used osmotic mini pump tritiated thymidine labeling with a 120-hour release time	Phase 1: Monticello et al. (1991). Phase 2: Monticello et al. (1996); Data analyzed in Appendix B.

Abbreviations: FA = formaldehyde exposure; DPX = DNA-protein crosslink; PBPK = physiologically based pharmacokinetic.

[a]Note that these studies do not present DPX measurements on control animals.

[b]These data were used as input for modeling the nasal tumors observed in F344 rats and for benchmark modeling of cell proliferation as a precursor response by authors from the same laboratory as this study (Schlosser et al., 2003; Conolly et al., 2003). Many other studies (see below on "uncertainty in dose-response estimates") inform the effect of formaldehyde on cell proliferation and are brought to bear upon the discussion of uncertainties in modeling the dose-response. However, Monticello et al. (1996) is the only study that followed long-term exposure to formaldehyde.

Dose-response modeling of nasal SCC incidence in the rat

The results discussed in this section and presented in Table 5-37 include multiple dose-response models of the observed pooled tumor incidence in F344 rats from the two studies (Monticello et al., 1996; Kerns et al., 1983). These results include those developed by EPA in this assessment as well as those developed earlier by Schlosser et al. (2003). Dose metrics derived from PBPK modeling of formaldehyde-induced DPX or from CFD modeling of formaldehyde flux to the nasal tissue are included in these approaches in addition to presenting a result based on the inhaled exposure concentration. The approaches include modeling the grouped incidence data, multistage Weibull modeling of the individual time-to-tumor data, and a biologically based clonal expansion model of cancer. Use of the biologically based modeling allowed the use of various data, including mechanistic information, in an integrated manner. Formaldehyde is a direct-acting mutagen, and DPXs serve as a surrogate marker for the tissue dose associated with this mutagenic potential. The individual tumor incidence data, flux estimates and number of cells organized by flux bins, and DPX concentrations used in the dose-response modeling are tabulated in Appendix D.2.2.

Modeling of the grouped incidence data

Schlosser et al. (2003) applied a Kaplan-Meier survival adjustment of the grouped incidence data. The best fit in Schlosser et al. (2003) was obtained with the polynomial and Weibull models for the tumor incidence data with a nonzero intercept (threshold) on the dose axis. Two sets of results from their work are presented in Table 5-37, one using formaldehyde flux to the nasal tissue and the other using DPX concentration as dose metrics to calculate benchmark levels and corresponding HECs. DPX as the dose metric was expressed as pmol of formaldehyde equivalents covalently bound to DNA per unit volume of nasal tissue. These calculations used CFD and PBPK models to calculate formaldehyde flux and DPX concentrations in the rat and human. The assumption in using DPX data to calculate the HEC was that lifetime exposure to the same DPX concentration for a given duration each day leads to equivalent risk across species. These were exposures that resulted in the same steady-state DPX concentrations as the weekly time-weighted averaged DPX values in rats at the rat benchmark exposure concentrations. See Schlosser et al. (2003) for further details.

Time-to-tumor modeling without using mechanistic data

Because higher exposures were associated with both earlier tumor occurrence and increased mortality in the rats, methods that can reflect the influence of competing risks and intercurrent mortality on site-specific tumor incidence rates are preferred. For this reason, EPA used the multistage Weibull time-to-tumor model (Portier and Bailer, 1989; Krewski et al., 1983), which (a) models the replicate animal data, (b) includes the exact time of observation of the tumors and therefore gives appropriate weight to the amount of time each animal was on study without a tumor, and (c) acknowledges earlier tumor incidence with increasing dose level. The dose-response analyses, estimation of parameters, and plots of model fits are detailed in Appendix D.2.2.

Biologically based dose-response modeling

Biologically based time-to-tumor dose-response (BBDR) model for modeling the formaldehyde-induced rat nasal tumors, and for extrapolating the rat nasal cancer risk to human exposure scenarios are available (Conolly et al., 2003, 2004; CIIT, 1999). These models consist of interfacing dosimetry models for formaldehyde and formaldehyde-induced DPX in the rat nasal passages (Kimbell et al., 2001a; Kimbell et al., 2001b; Conolly et al., 2000) with a two-stage clonal expansion (TSCE) model for predicting the probability of occurrence of nasal SCC. The term "BBDR modeling" is used here to collectively refer to various toxicokinetic and toxicodynamic dose-response modeling components.

The CIIT BBDR models as well as their possible variations explored by EPA were carefully evaluated. Predictions using these models for humans are found to be not robust at any exposure concentration. Accordingly, the clonal expansion modeling of the rat data is employed to derive multiple PODs and corresponding HECs but it is not used for extrapolating to human exposure scenarios. Unit risks derived by straight line extrapolation from a POD as well as candidate RfCs (cRfCs) derived from benchmark modeling of data on cell proliferation and basal hyperplasia observed in F344 rats and Wistar rats, respectively, are also presented, with the cRfC interpreted as the concentration below which nasal cancers arising from increased cell proliferation due to formaldehyde-induced cytotoxicity are unlikely to occur. The assessment presents arguments from the literature that protection against these putative precursor events is sufficient to prevent a cancer response. However, the proven genotoxicity and mutagenicity of the chemical and the observation of human cytogenetic effects in human occupational exposures provide strong support for preferring the linear extrapolation from the POD to the origin. Candidate unit risks based on a point of departure at the 0.005 extra risk are found to be comparable to that derived from analysis of the NCI occupational epidemiology data on nasopharyngeal cancers (NPCs).

The cancer modeling in the BBDR approach is based on an approximation of the Moolgavkar, Venzon, and Knudson stochastic TSCE model of cancer (Moolgavkar and Venzon, 1979; Moolgavkar and Knudson, 1981; Moolgavkar et al., 1988), which accounts for growth of a pool of normal cells, mutation of normal cells to initiated cells, clonal expansion of initiated cells, and mutation of initiated cells to fully malignant cells. The molecular dose associated with formaldehyde's direct mutagenic action was represented in this approach by the DPX formed by formaldehyde. Exposure to inhaled formaldehyde induces dose-related changes in rates of cell division as inferred from cell labeling studies in the formaldehyde-exposed F344 rat. In turn, regenerative increases in cell proliferation increase the probability of errors in DNA replication. Formaldehyde-induced changes in cell replication and DPX concentrations, derived from the data indicated in Table 5-36, were considered a function of local formaldehyde flux (pmol/mm^2-hour) to each region of nasal tissue as predicted by CFD modeling on anatomically accurate representations of the nasal passages of a single F344 rat (see Appendix C.1). The TSCE model was calibrated with the observed tumor incidence data to estimate various unknown parameters as indicated below.

DPX tissue concentrations in Conolly et al. (2003) were calculated using a physiologically based pharmacokinetic model developed in Conolly et al. (2000).

Conolly et al. (2003) characterized the dose-response for cell replication rates as a J-shaped curve, indicating that cell division rates decreased below that determined for the unexposed case at low-exposure concentrations. In addition, these authors also used a hockey stick-shaped curve such that the dose-response for cell division rates remained unchanged from the baseline, rising only at 6 ppm (7.4 mg/m^3) and higher exposure concentrations. This resulted in more conservative estimates of risk when used in the clonal expansion model for cancer.

In addition to the data from the two tumor bioassays, Conolly et al. (2003) included historical control data on 7,684 animals obtained from the National Toxicology Program (NTP) F344 rat inhalation and oral bioassays. The resulting model predicts the probability of a nasal SCC in the F344 rat as a function of age and exposure to formaldehyde. EPA reimplemented the Conolly et al. (2003) model, and first examined whether the code reproduced their results under identical conditions, inputs, and assumptions, including the use of all NTP historical controls. The corresponding fits to the tumor incidence data are compared in Figure 5-5 against Kaplan-Meier adjusted probabilities. There were small residual differences between the two implementations as reflected by the better fit to the control (0 ppm), 10 ppm and 15 ppm data in the EPA reimplementation, whereas a better fit to the 6 ppm data in the original Conolly et al. (2003) implementation (see Subramaniam et al. (2007) for a discussion of these differences).

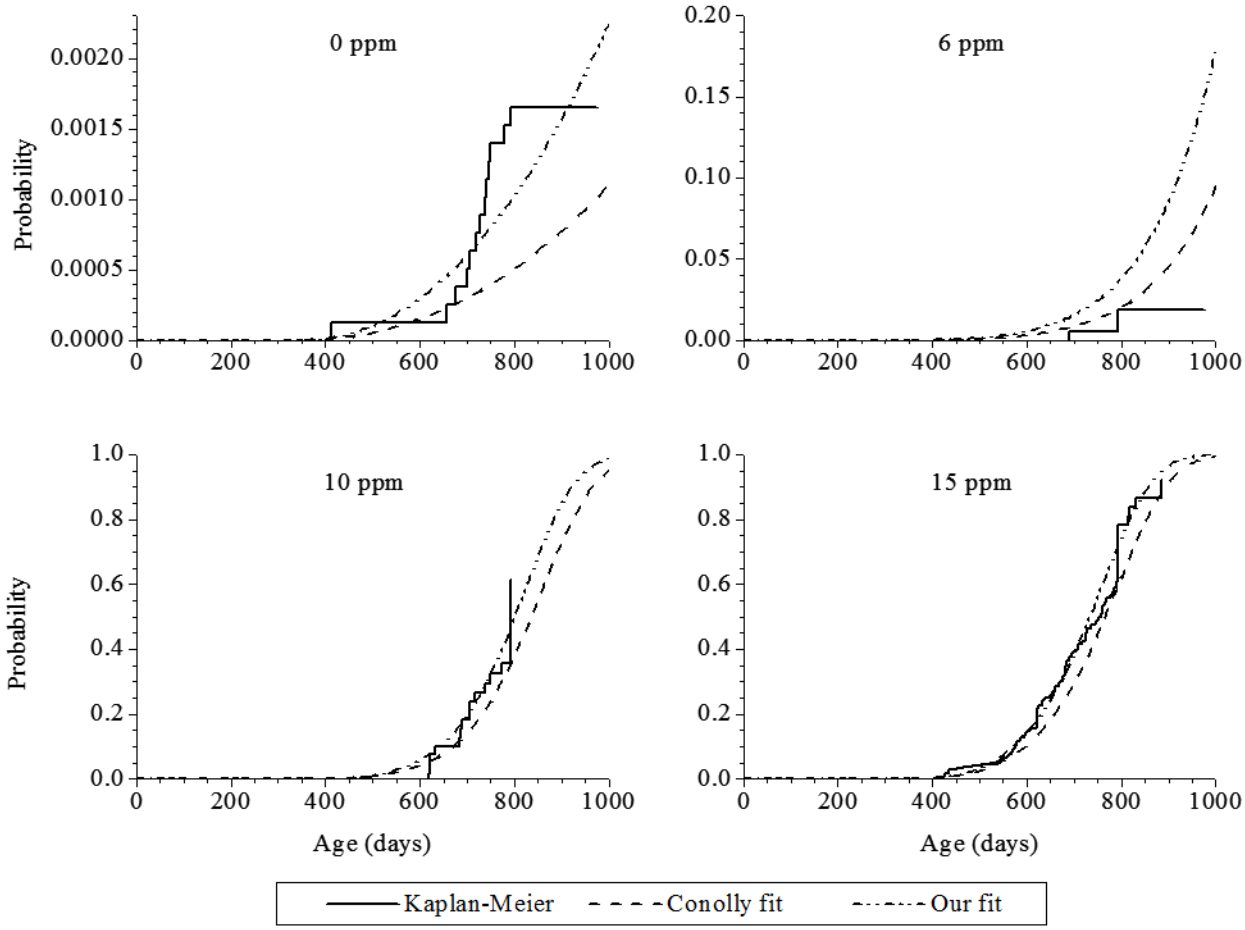


Figure 5-5. Fit to the rat tumor incidence data using the model and assumptions in Conolly et al. (2003).

Fitted curves obtained by Conolly et al. (2003) is compared with EPA reproduction of these results under identical conditions, inputs, and assumptions, including the use of all NTP historical controls; there were minor residual differences among the implementations (see (Subramaniam et al., 2007)). The tumor incidence data are shown here by the Kaplan-Meier adjusted probabilities.

The BBDR modeling approach affords a convenient way to integrate multiple types of mechanistic information in modeling the time-to-tumor data, and visually it appears to fit these data well (as shown in Figure 5-5). Further clarification pertaining to the structure and calibration of the models in (Conolly et al., 2003, 2004) that are key to understanding model assumptions is provided in Appendix C.1.12 and Appendix D.2.2.

Benchmark modeling of cancer incidence and human equivalents within the range of the data

Benchmark concentrations (BMCs) and the corresponding 95% lower confidence bounds (BMCLs) were calculated at a benchmark response level (BMR) at the lowest end of the range of the observed data (U.S. EPA, 2012). BMCs and BMCLs at the BMRs of 0.005 and 0.01 extra risk were

determined with the BBDR models. These were compared with values determined at the BMRs of 0.05 or 0.1 extra risk level to facilitate comparison with other chemicals. A BMR of 0.005 is lower than the lowest observed tumor response (0.0085), when corrected for survival, from the combined data from the Kerns et al. (1983) and Monticello et al. (1996) bioassays. Using this lower value is considered appropriate because the BBDR modeling incorporates information on regenerative cell proliferation, derived from cell labeling data, which may be considered a precursor response. The BBDR models (model 1 & model 2 below) used for this purpose provided good fits to the time-to-tumor incidence data, similar to the fit shown in Figure 5-5, and are based on the Conolly et al. (2003) model with the following modifications.

Model 1 is based on the more conservative model in Conolly et al. (2003), where the parameters governing the kinetics of normal and initiated cells were derived as hockey stick-shaped functions of flux, with a critical modification. Conolly et al. (2003) added historical control animals from *all* NTP studies to the data from the concurrent controls, whereas model 1 includes NTP historical data from only the inhalation route of exposure. This is because the incidence rate of nasal SCC is very different between these two categories of NTP historical studies, and the generally accepted practice is to not include studies from other routes of exposure when using historical controls (see (Subramaniam et al., 2007; Subramaniam et al., 2008) for an explanation of this issue). Model 1 is the same as Model E in Table III of Subramaniam et al. (2007).

Model 2 makes major modifications to Conolly et al. (2003) in regards model structure as well as values for input parameters. First, the shape of the dose-response for the division rates of normal (N) cells as a function of formaldehyde flux, α_N(flux) [an input to the TSCE model], was monotone increasing without a threshold in dose, and obtained by fitting the 13-week cell replication data in Monticello et al. (1996). (See Appendix D.2.2 for a discussion pertaining to using the 13-week data.) The raw replicate animal data from this study was provided to EPA by the Hamner Institutes for Health Research. Second, the dose-response for the division rates of initiated (I) cells, α_I(flux), was assumed to be a sigmoidal-shaped curve, increasing monotonically with flux from a background value up to an asymptotic value, and constrained by $\alpha_I(\text{flux} = 0) \geq \alpha_N(\text{flux} = 0)$. The death rate of initiated cells was given by the assumption, $\beta_I(\text{flux}) = \kappa \cdot \alpha_I(\text{flux})$, where κ is an estimated constant. This model is discussed in detail as "model 15" in Appendix D.2.2. Furthermore, as in model 1, only the historical controls from inhalation studies were added to the concurrent controls.

Weekly averaged DPX concentrations as calculated by the PBPK model described in Appendix A of Subramaniam et al. (2007), a variant of the PBPK model in Conolly et al. (2000), were used. The model fits to the observed tumor incidence data, parameter values, and respective comparisons with Conolly et al. (2003) are provided in Appendix D.2.2. The results based on these models are included in Table 5-37. The BBDR modeling fit the time-to-tumor data much better than the Multistage Weibull model (see Appendix D.2.2).

The BMCs mentioned above and their corresponding BMCLs were then converted to their equivalent concentrations in humans (HECs). This extrapolation involved multiplication by two factors: (1) a duration adjustment of (6/24) × (5/7) to the laboratory exposure regimen in order to adjust for continuous exposure; (2) a ratio of regional gas dose in the F344 rat to that of humans for the upper respiratory tract region. The regional gas dose was based on formaldehyde flux to the nasal tissue obtained using CFD modeling in the rat and human (Kimbell et al., 2001b), Subramaniam et al. (1998). In addition, two other dose metrics were also used. As mentioned earlier, Schlosser et al. (2003) presented an alternate extrapolation based on DPX as the dose metric.

For the Multistage-Weibull time-to-tumor modeling, the first result presented is based on using inhaled formaldehyde exposure concentration for the second factor. Here, the default gas dose ratio for the extrathoracic region given by equation 4-18 of U.S. EPA (1994) is used. This is equal to the ratio of the quantity (V_E/SA_{ET}) calculated for the rat and human, where V_E is the minute volume and SA_{ET} is the surface area of the extrathoracic region (in this case, the nasal passages).

The average mass flux of formaldehyde (pmol/mm^2-hour) to the entire surface of the airway lining, excluding surface lined by nonmucus-coated squamous tissue which is thought not to absorb formaldehyde, was used for the human extrapolation in all four of the models presented in the Table 5-37 (see discussion earlier in this Section, *Computational fluid dynamic modeling*). The HEC corresponding to a particular benchmark level in the rat was then calculated by assuming that continuous lifetime exposure to a given steady-state flux of formaldehyde, expressed in pmol/mm^2-hour, leads to equivalent risk of nasal cancer across species. This approach is in line with that taken in equations 4-17 and 4-18 of U.S. EPA (1994). In the CFD modeling, flux in any region is proportional to the inhaled exposure concentration; i.e., flux = f × C_{air} where f is a constant of proportionality and C_{air} is the exposure concentration. Then, the human extrapolation is achieved by multiplying the duration adjusted benchmark level in the rat by the ratio of the proportionality constants for the rat and human (f_{rat}/f_{human}). This ratio was equal to 0.71 for the calculation by Schlosser et al. (2003) and equal to 0.46 in all the other calculations in Table 5-37. This discrepancy is largely due to different values in these calculations for the minute volume for the human; 7.5 L/min by Schlosser et al. (2003) corresponding to resting breathing, but 13.8 L/min for the other three calculations as per the default value prescribed in U.S. EPA (1994) corresponding to equal durations through the day of resting, sitting and light activity levels. EPA's calculations in Table 5-37 are discussed further in the Appendix D.2.2. The minute volume used for the rat was 0.288 L/min.

The benchmark levels in the rat and the HECs obtained using the above methods and dose metrics are shown in Table 5-37. For a given benchmark response level, PODs and their corresponding HECs are remarkably similar across multiple models and internal dose metrics (formaldehyde inhaled flux to tissue and DNA-protein crosslink [DPX] concentrations).

Table 5-37. Benchmark concentrations and human equivalents using formaldehyde flux and DPX as dose metrics

Models	Rat benchmark conc (ppm)					Human equivalent conc[a] (ppm)					
		BMR= 0.005[b]	BMR= 0.01	BMR= 0.05	BMR= 0.1	Dose metric[c]		BMR= 0.005[b]	BMR= 0.01	BMR= 0.05	BMR= 0.1
Weibull[d] with threshold (Schlosser et al., 2003)	BMC BMCL		5.91 5.58	6.12 5.94	6.40 6.22	Flux	BMC BMCL		0.75 0.71	0.78 0.76	0.82 0.79
						DPX	BMC BMCL		0.76 0.71	0.79 0.76	0.84 0.81
Multistage Weibull time-to-tumor[e, g]	BMC BMCL		4.28 3.96	5.93 5.49	6.84 6.34	Exposure Conc	BMC BMCL		0.21 0.20	0.29 0.27	0.34 0.32
						Flux	BMC BMCL		0.35 0.33	0.49 0.45	0.56 0.52
Rat BBDR model 1[f]	BMC BMCL	4.99[g] 4.95	5.37[g] 5.19			Flux	BMC BMCL	0.42 0.41	0.45 0.43		
Rat BBDR model 2[f]	BMC BMCL	5.41 5.25	5.75 5.59			Flux	BMC BMCL	0.45 0.44	0.48 0.46		

Abbreviations: BMR= Benchmark response in terms of Extra Risk; BMC = benchmark concentration; BMCL = benchmark concentration; BBDR = biologically based dose-response; TWA = time=weighted average; DPX = DNA-protein crosslink; CFD = computational fluid dynamic; PBPK = physiologically based pharmacokinetic.

[a]Human benchmark levels were continuous environmental exposures that would result in steady-state flux (or DPX) levels in humans equal to the average flux (or weekly TWA DPX) levels in rats at the rat BMCs adjusted for 6 hours/day and 5 days/week. Values derived using flux as dose metric decrease by a factor of 1.4 if flux estimates based on Schroeter et al. (2014) are used instead of Kimbell et al. (2001a).

[b]The BMR of 0.005 was used only with the BBDR modeling because these models incorporate precursor response data related to cellular proliferation (see discussion in surrounding text).

[c]Flux and DPX levels were computed by CFD (Kimbell et al. (2001a), Subramaniam et al. (1998)) and PBPK modeling (Conolly et al. (2000)), respectively.

[d]*p*-value for Weibull model fit = 0.90, best fit obtained with a positive intercept on dose axis.

[e]$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k) x\, t^z]$. q_0, q_1, q_2, q_3, $q_4 = 0$, $q_5 = 2.9 \times 10^{-22}$, z = 8.1. Curve passes through origin. Fit was judged by comparing fitted curve to Kaplan-Meir survival estimates since goodness-of-fit *p*-value was not provided by software package.

[f]Fit to time-to-tumor data with the BBDR approach was superior to that obtained from the multistage Weibull model. Because benchmark concentrations at 0.005 and 0.010 extra risk levels were reported when BBDR modeling was used, they were not calculated at the 0.05 and 0.1 levels.

[g]Roughly similar result was obtained with model in Conolly et al. (2003). BMC_{005} = 4.84 ppm and BMC_{01} = 5.48 ppm for their hockey-stick model as discerned from Figure 5 of their paper. BMCL values could not be estimated for that model since confidence bounds were not reported.

As discussed in Section 3.1, Schroeter et al. (2014) revised the dosimetry model of (Kimbell et al., 2001b; Kimbell and Subramaniam, 2001), used for the flux estimates in the table above, to include endogenous formaldehyde production and to explicitly model formaldehyde pharmacokinetics in the respiratory mucosa. EPA estimated the extent to which the results in the above table change if flux estimates from Schroeter et al. (2014) are used. The average flux over nonsquamous regions of the rat nose is roughly one-third[66] of that in the human, based on the

[66]0.33 at 0.1 ppm, 0.32 at 1 ppm.

dosimetry in Schroeter et al. (2014) in which endogenous formaldehyde is taken into account compared to a ratio of roughly one-half based on the dosimetry in Kimbell et al. (2001a). Thus, wherever flux is used as the dose metric, the benchmark concentrations calculated in the above table are not altered appreciably if the revised dosimetry model by Schroeter et al. (2014) is applied, decreasing only by roughly a factor of 1.4.[67]

Benchmark modeling of precursor lesion data in the rat: cell proliferation and hyperplasia

Benchmark concentrations based on signatures of increased cell proliferation are useful in that increased regenerative cell proliferation is assumed to be a contributory MOA—a factor that can lead to a greater likelihood that DNA damage becomes heritable mutations before it is repaired. Significantly increased cell proliferation as well as hyperplasia (increased cellular proliferation that is identified to be pathologically "abnormal" in tissues) has been observed in response to exposure to formaldehyde, as described in Section 3.2.4 (additional information in Appendix C.7.1).

Cell proliferation

Schlosser et al. (2003) used cell proliferation to represent an adverse response and modeled the dose-response for unit length labeling index measurements in F344 rats. They reported benchmark concentrations and 95% lower confidence bounds corresponding to 1%, 5%, and 10% increase in this index over the mean level for controls using dose-response functions that allowed for a threshold in dose.[68] The corresponding HECs spanned a tight range of 0.44–0.47 ppm (0.54–0.58 mg/m^3) (see Table 8 of their paper.)

The data used in their modeling were constructed using a cellular labeling index over several locations on the F344 rat nose, as reported by Monticello et al. (1996). The data from Monticello et al. (1996) represent the longest duration cell proliferation study available, which included measurements across a range of study time points and nasal regions. Due to methodological constraints intrinsic to all the available cellular labeling studies, including Monticello et al. (1996), these data are based on DNA labeling of actively proliferating cells only during the last day of exposure (see Appendix C.7 for additional discussion). Schlosser et al. (2003) averaged the data collected from several nasal sites after weighting by exposure time. This introduces some uncertainty because time-weighted averaging underweights early exposures (e.g., 12–13 weeks of exposure) that may have contributed significantly to carcinogenesis (see discussion later in this section under *Uncertainty-variability in cell replication dose-response of normal cells*); for instance, the few studies that investigated latent effects in rats (i.e., Wistar) did observe an increased tumor incidence at 1 to ≥2 years following high-level formaldehyde exposure lasting only ~13 weeks (Woutersen et al., 1989; Feron et al., 1988). Similarly, additional

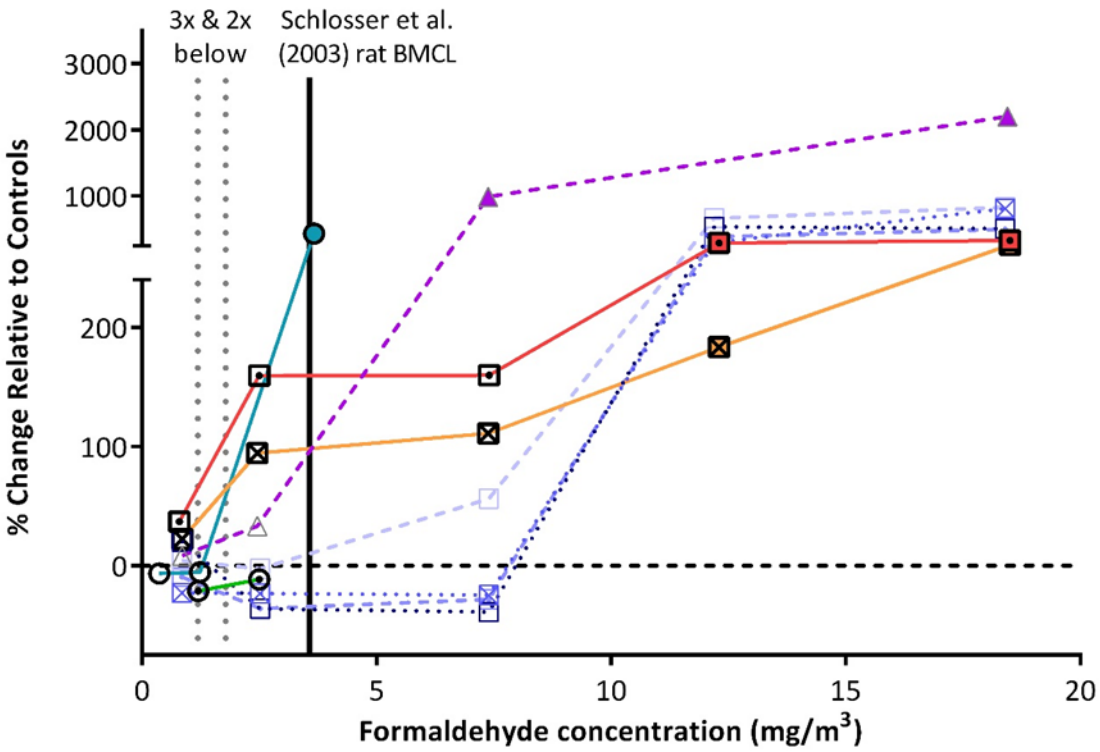
[67]This is an approximate estimate for resting inspiration. The various components of the BBDR modeling were not recalibrated or rerun in light of the revised flux estimates for both species.

[68]They also modeled the data using functions that were constrained to pass through the origin but do not report BMCL values.

methodological uncertainties that are difficult to address experimentally include large site-to-site variation in the labeling (i.e., ≥10-fold); differences in the number of cells across nasal sites; and the possibility that histologic changes and thickening of epithelium that occur at later times for the higher doses likely affect the replication rate. These issues are discussed further and several other plausible dose-response curves for cell replication from Monticello et al. (1996) are developed (see Appendix D.2.2).

Other well-conducted studies of cellular proliferation using similar labeling methods help estimate the potential impact of these uncertainties in the benchmark concentrations calculated by Schlosser et al. (2003). In general, data from other studies investigating shorter-term formaldehyde exposure durations, as well as the data for shorter duration exposures in Monticello et al. (1996), routinely indicate proliferative effects at lower formaldehyde exposure levels within similar nasal regions[69] (see Appendix C.7.1 for comparisons across various durations of exposure). As discussed in the Appendix, it appears reasonable to assume that all cell proliferation studies with formaldehyde exposures longer than 12 weeks are equally relevant to potential cancer development. The data available from *medium* and *high* confidence studies longer than 12 weeks, including multiple measures in Monticello et al. (1996), are arrayed in Figure 5-6, below, and point to a two- to-three-fold range of observed values below the benchmark concentration estimated by Schlosser et al. (2003), as represented by the dotted vertical lines in the figure. This comparison partly elucidates the uncertainty in the HEC values derived by Schlosser et al. (2003) to understand the cumulative effects of chronic formaldehyde exposure on cellular proliferation.

[69]As the regions analyzed varied across studies, comparisons in Appendix C.7 and in Figure 5-6 compare proliferation observed in locations as near to the anterior lateral meatus as possible, as this region was most commonly reported across studies and is a region at which tumors have commonly been observed (see Section 3.2.5, URT cancer in experimental animals).



	Study	High/Med	Strain	Exposure	Nasal region shown	Labeling	Metric
	Andersen et al., 2010	H	F344	13wk	ALM (L2)	3d BrdU	ULLI
	Meng et al., 2010	H	F344	13wk	ALM (note: p<0.01)	3d BrdU	LI
	Wilmer et al., 1989	H	Wistar	13wk	NT/MT	18h thym.	LI
	Zwart et al., 1988	H	Wistar	13wk	NT/MT/ALM (L2; NC in L3)	18h thym.	turnover
	Monticello et al., 1996	M	F344	12wk	ALM (note: no statistics)	18h thym.	ULLI
	Monticello et al., 1996	M	F344	6mos	ALM (note: no statistics)	18h thym.	ULLI
	Monticello et al., 1996	M	F344	1yr	ALM (note: no statistics)	18h thym.	ULLI
	Monticello et al., 1996	M	F344	18mos	ALM (note: no statistics)	18h thym.	ULLI
	Casanova et al., 1994	M	F344	12wk	LM (less in M/PM)	3h ^{14}C	^{14}C incorp.

Figure 5-6. Cellular proliferation measured by DNA labeling in studies ≥12 weeks.

Data from *high* and *medium* confidence studies (High/Med; H/M) exposing rats to formaldehyde for at least 12 weeks (wk), and up to 18 months (mos), were normalized to percentage change from controls to compare across the different metrics of proliferation reported (e.g., labeling index [LI]; unit length labeling index [ULLI]; incorporation of radiolabeled carbon). The regions compared typically included the lateral meatus (LM) in anterior regions (e.g., L1; L2; anterior LM), although one comparison was in related structures (i.e., nasoturbinates [NT] and maxilloturbinates [MT] in Wilmer et al. (1989). The DNA labeling procedures included bromodeoxyuridine (BrdU), thymidine (thym.), and radiolabel. Filled shapes represent statistical significance ($p \leq 0.05$), as reported by the study authors. The vertical lines represent the rat $BMDL_{01}$, as reported by Schlosser et al. (2003) and estimates which are two- and three-fold lower than the Schlosser et al. (2003) rat BMDL. References: Zwart et al. (1988); Wilmer et al. (1989); Monticello et al. (1996); Meng et al. (2010); Casanova et al. (1994); Andersen et al. (2010).

Hyperplasia

EPA modeled the incidence of basal hyperplasia reported by Woutersen et al. (1989) in a 28-month bioassay using Wistar rats. These animals were exposed to 0, 0.1, 1.0, and 9.8 ppm (0, 0.123, 1.23, and 12.05 mg/m^3) formaldehyde and the observed incidences of hyperplasia were 0/26, 1/26, 2/28, and 14/26. The BMC and BMCL at the benchmark response of 0.1 extra risk were 1.68 and 1.108 ppm (2.07, and 1.36 mg/m^3), respectively. The HEC corresponding to the BMCL is 0.1609 ppm (0.198 mg/m^3) when adjusted for continuous human lifetime exposure, which is roughly three times lower than the HEC derived from the time-weighted averaged labeling index by Schlosser et al. (2003). It is useful to note that this value is roughly comparable to the LEC_{0005} derived from EPA's modeling of the NPC risk from the NCI epidemiology data.

Extrapolation using a biologically based dose-response model

In the case of formaldehyde, there are multiple options available for extrapolating to human exposure scenarios which are typically at lower concentrations than the various HECs calculated above. Subsequent to their BBDR modeling (Conolly et al. (2003)) of nasal cancer in the rat, Conolly et al. (2004) developed a corresponding model for humans, which they used for the purpose of extrapolating the observed risk in the rat to human exposures. This human extrapolation model is conceptually similar to the modeling in Conolly et al. (2003) but does not incorporate any data on human responses to formaldehyde exposure. A particular contribution of this model toward extrapolation is that it uses, as input, DPX concentrations and values of local formaldehyde flux to the tissue as obtained from PBPK and fluid dynamic dosimetry models respectively (Subramaniam et al., 1998; Kimbell et al., 2001a; Conolly et al., 2000). The modeling in (Conolly et al., 2003, 2004), while still a statistical model where some key parameters are determined by model fit to the tumor data, incorporates more detailed biological hypothesis and mechanistic data than is normally employed in modeling cancer risk. Toxicodynamic models developed on the basis of an agent's MOA, if robust, are generally preferred over default approaches for extrapolation, with the extent of extrapolation determined by model uncertainty (U.S. EPA, 2005a).

EPA's evaluation of model robustness considered three criteria routinely implemented for biomathematical models (for example, PBPK models) where multiple parameters are estimated by fitting to observed data and the model(s) is/are then used in a predictive capacity for extrapolation (Barton et al., 2007).

- Model specification: Are there alternate model structures that describe the observed data and do they lead to different predictions? Are common model structures used across species?
- Model calibration: In the BBDR modeling the unknown parameters were estimated statistically using the maximum likelihood method to optimize the model fit to the available data. These data included tumor incidence data in animals as well as baseline incidence rates in humans. Does this calibration allow the model to reasonably approximate the

observed data? In robustly calibrated models, the optimal fit is highly sensitive to small variations in the estimated parameters.

- Model prediction: The purpose of the BBDR modeling was to predict outcomes to human exposure scenarios (it was also used to better describe the available data). Accordingly, the criterion for robustness is whether the predictions are unique while also maintaining tight agreement with the calibration data; i.e., predictions should not be highly sensitive to parameters for which experimental data do not provide any information (note that this consideration runs counter to how sensitivity is used in evaluating model calibration). EPA employed a common practice in sensitivity analyses where one varies parameters by a small amount from estimated values and assesses impact on predictions.

In this section, we present extrapolations of the rat nasal cancer risk to humans carried out in Conolly et al. (2004). Continuous human lifetime extra risk estimates from this model following inhalation exposure to 1.0 ppb–1.0 ppm (1.23 μg/m^3–1.23 mg/m^3) formaldehyde concentrations are provided in Table 5-38, and compared with human risk estimates derived from EPA's modeling of the NPC mortality in the NCI occupational epidemiology data (note: the comparison with mortality estimates appears appropriate since Conolly et al. (2004) had modeled the tumors as rapidly fatal). This comparison is provided only for perspective, noting in particular that NPCs are specific to tumors only in the human nasopharynx (see Section 3.2.5). Conolly et al. (2004) developed two clonal growth models based on using different representations of the low dose-response for the cell division rate as input data. The first, denoted as *optimal* in the table, was derived from using the best fit, a J-shaped curve, to the dose-response for the TWA of the cell labeling data in rats such that values at 0.7 ppm and 2.0 ppm (0.9 mg/m^3 and 2.46 mg/m^3) were below the control value; the second, presented as their *conservative* (in the sense of being more health protective) approach, was derived from using a hockey-stick shape to replace the J-shape in the low-dose portion of the *optimal* case such that values at the two lowest concentrations were the same as the control. In either case, risk estimates reported in Conolly et al. (2004) were based on using maximum likelihood estimate (MLE) values for all model parameters except the parameter *kmu* associated with formaldehyde's mutagenic potential for which they used an upper-bound value; (*kmu* is the constant of proportionality that relates DPX concentrations to the probability of formaldehyde-induced mutation occurring per-cell generation).

The *optimal* model in Conolly et al. (2004) indicates lifetime human risk estimates to be substantially below baseline risk levels (i.e., negative values of extra risk) for formaldehyde exposures less than roughly 2 ppm (2.46 mg/m^3), while their *conservative* model predicts values that do not appreciably exceed baseline levels (i.e., extra risk less than 10^{-5}) for exposures less than 0.2 ppm (0.25 mg/m^3). At the EC_{0005} benchmark concentration of 0.19 ppm (0.23 mg/m^3) derived from the NCI occupational epidemiology data, the *conservative* model in Conolly et al. (2004) predicts roughly a 100-fold lower continuous lifetime risk than the central estimate indicated by EPA's analysis of the epidemiology data. The difference is roughly the same at lower exposure

concentrations, while at 1.0 ppm (1.23 mg/m^3) the *conservative* model predicts a 1,000-fold lower value than EPA's central estimate based on the epidemiology data (see Appendix D.2.2).

The maximum likelihood value of the parameter *kmu* was estimated to be zero in the modeling, leading to the inference by the authors that formaldehyde's direct mutagenic action is not relevant to carcinogenicity in the rat or human, and that the observed tumor response in the rat can be explained on the basis of regenerative cellular proliferation in response to cell injury. These results have been interpreted by some to mean that exposures protective of the effects of cell proliferation are adequate to protect against formaldehyde-induced nasal cancers (Slikker et al., 2004; Conolly et al., 2004). The uncertainty in these estimates and conclusions are evaluated below.

Table 5-38. BBDR model (Conolly et al., 2004) estimated extra risk of SCC in human respiratory tract compared with EPA's modeling of extra risk of NPC from the human occupational epidemiology data

Formaldehyde concentrations	0.001 ppm	0.01 ppm	0.10 ppm[a]	1.0 ppm
Conolly et al. (2004) optimal estimate[b]	-1.0×10^{-5}	-1.0×10^{-4}	-9.1×10^{-4}	-5.0×10^{-3}
Conolly et al. (2004) conservative estimate[b]	$+3.1 \times 10^{-8}$	$+3.2 \times 10^{-7}$	$+3.5 \times 10^{-6}$	$+2.7 \times 10^{-4}$
EPA analysis-NCI NPC mortality MLE (UCL)[c]	$+1.2 \times 10^{-6}$ ($+2.1 \times 10^{-6}$)	$+1.3 \times 10^{-5}$ ($+2.3 \times 10^{-5}$)	$+1.8 \times 10^{-4}$ ($+4.1 \times 10^{-4}$)	$+2.7 \times 10^{-1}$ ($+8.7 \times 10^{-1}$)

[a]For reference, the mortality-based LEC_{0005} derived from the NCI occupational data is 0.11 ppm (EC_{0005} is 0.19 ppm).
[b]Conolly et al. (2004) risk estimates were based on using MLE values for all model parameters except the parameter associated with formaldehyde's mutagenic potential for which they used an upper bound.
[c]See Table 5-31; MLE = maximum likelihood estimate; UCL = 95% upper confidence limit.

Uncertainty in the dose-response estimates

The ratio of the BMCL to the BMC is a convenient way to express the statistical uncertainty in the benchmark concentration derived by a given model. Table 5-37 indicates this ratio to be tight (> 0.9) for the estimates derived from the rat nasal tumors. However, it is well-recognized (U.S. EPA, 2005a) that there is a large uncertainty inherent to using statistical models to extrapolate outside the range of observed data. The level of confidence in various components of the biologically based modeling approach and its use for extrapolation is next addressed; the relevant question is whether the BBDR modeling decreases uncertainty in extrapolating risk or, by explicitly identifying the sources of uncertainty, points to approaches and data needs that may help reduce the uncertainty.

Uncertainties and confidence in the BBDR modeling and extrapolation

EPA carefully evaluated the level of confidence and sources of uncertainties in different components of both the rat BBDR model and the corresponding human extrapolation model (Table 5-39). Seven issues that were evaluated are tabulated below and elaborated in more detail in Appendix D.2.2 and supporting references. Of these, issue numbers 3, 6 and 7—related to replication rates of normal and initiated cells and the use of historical control animals—were found

to have major impacts on qualitative and quantitative conclusions drawn from the modeling and are briefly discussed below.

Table 5-39. Evaluation of BBDR modeling issues

	Issue	Supporting references for evaluation
1	Confidence in FA airflow and flux model, and assessment of interindividual variability in FA flux; airway reconfiguration due to long-term dosing	Subramaniam et al. (1998); Kimbell et al. (1997a); Kimbell et al. (2001a); Subramaniam et al. (2008); Garcia et al. (2009); Morgan (1997); Monticello et al. (1996); Cohen Hubal et al. (1997); Kimbell et al. (1997b)
2	Uncertainties in FA-DPX PBPK model	Subramaniam et al. (2007); Subramaniam et al. (2008)
3	Uncertainties and variability in the rat cell labeling data, the derivation of cell division rates from these data, and their applicability to human cell division rates	Subramaniam et al. (2008); Conolly et al. (2004)
4	Use of an approximate method by Hoogenveen et al. to solve the two-stage clonal expansion model equations	Subramaniam et al. (2007); Crump et al. (2005)
5	Assumption that all observed SCC in rats were rapidly fatal; Model assumption of a time delay from occurrence of malignant cell to death	Subramaniam et al. (2007); Crump et al. (2005); Crump et al. (2008)
6	Sensitivity of model results to the use of historical control animals drawn from all NTP cancer bioassays	Subramaniam et al. (2007); Crump et al. (2008)
7	Uncertainties in assumed division and death rates of initiated cells	Subramaniam et al. (2008); Crump et al. (2008); Crump et al. (2009)

Uncertainty-variability in cell replication dose-response of normal cells

Use of the raw cell labeling data from (Monticello et al., 1991; Monticello et al., 1996) to calculate replication rates of normal cells for input to the TSCE models in (Conolly et al., 2003, 2004) involved several steps and assumptions. First, as previously shown, the first phase for early exposure periods Monticello et al. (1991) employed injection labeling with a 2-hour pulse labeling, whereas the second phase for longer exposure periods Monticello et al. (1996) used osmotic mini-pumps for labeling with a 120-hour labeling time. These data were pooled by using a normalization procedure for the injection labeled data. Second, the average values from the labeling (averaged over the replicate animals and after the above normalization) were weighted by the exposure times in (Monticello et al., 1991; Monticello et al., 1996) and averaged over the nasal sites. Thus, the data were combined into one TWA for each exposure concentration. Third, (Monticello et al., 1991; Monticello et al., 1996) used unit length labeling index (ULLI) to quantify cell replication within the respiratory epithelium. ULLI is a ratio between a count of labeled cells and the corresponding

length (in millimeters) of basal membrane examined. Therefore, ULLI had to be converted to the per-cell labeling index (LI), which is the ratio of labeled cells to all epithelial cells, in this case, along some length of basal membrane and its associated layer of epithelial cells. This was accomplished by using data from a different experiment (Monticello et al., 1990a) where both quantities had been measured for two sites in the nose. Fourth, cell division rates were then calculated from the TWA using an approximation developed by Moolgavkar and Luebeck (1992).

Fifth, the empirical data could be used in Conolly et al. (2003) to directly calculate cell replication rates only for approximately the lower one-fourth of the full flux range (0−39,600 pmol/mm^2-hour) needed to model the bioassay data. The unknown cell replication rates for the upper three-fourths of the flux range were determined by linear interpolation to a maximum cell replication rate that was estimated as a statistical parameter fit to model predictions of the tumor incidence data (see (Subramaniam et al., 2008) for further details and biological implications of this procedure).

Finally, because there are no equivalent labeling index data available for the human respiratory epithelium, the above dose-response for normal cell replication derived for the rat was also directly assumed to apply to the human except for different values for the fraction of rat and human nasal epithelial cells capable of dividing (Conolly et al., 2004).

The TSCE model is generally sensitive to normal cell division rates, and there are considerable uncertainties (quantitative and qualitative) and variability in the dose-response for the replication rates of normal cells (α_N) as characterized in the above steps. For example, Figure 5-7, below, shows α_N as a function of formaldehyde flux to the rat nasal epithelial tissue [using only values derived from the continuous ULLI data in (Monticello et al., 1996)]. Corresponding to any particular dose (in terms of formaldehyde flux to tissue) α_N varies by one to two orders of magnitude. As shown in Appendix D.2.2, a variety of cell replication dose-response curves can be drawn to fit these data, and the use of an exposure TWA of cell labeling data over sites was found to be problematic on multiple accounts. Furthermore, the formula relating LI to α_N was for continuous labeled data and its use for pulse labeled data, as evaluated in the appendix, was found to be extremely uncertain.

The results in Table 5-38 for the *optimal* and *conservative* models in Conolly et al. (2003) represent a sensitivity analysis of the impact on risk estimates of varying the dose-response for normal cell replication rates at the low-dose range, and the differences between the two model results point to large variations in predicted human risk estimates from incorporating some of the variability and uncertainty in normal cell division rates in inputs to the TSCE model. In the neighborhood of the POD from the observed occupational epidemiology data, these models compute extra risk estimates of -9.1×10^{-4} and $+3.5 \times 10^{-6}$ respectively compared to a value of $+4.1 \times 10^{-4}$ indicated by the epidemiology data.

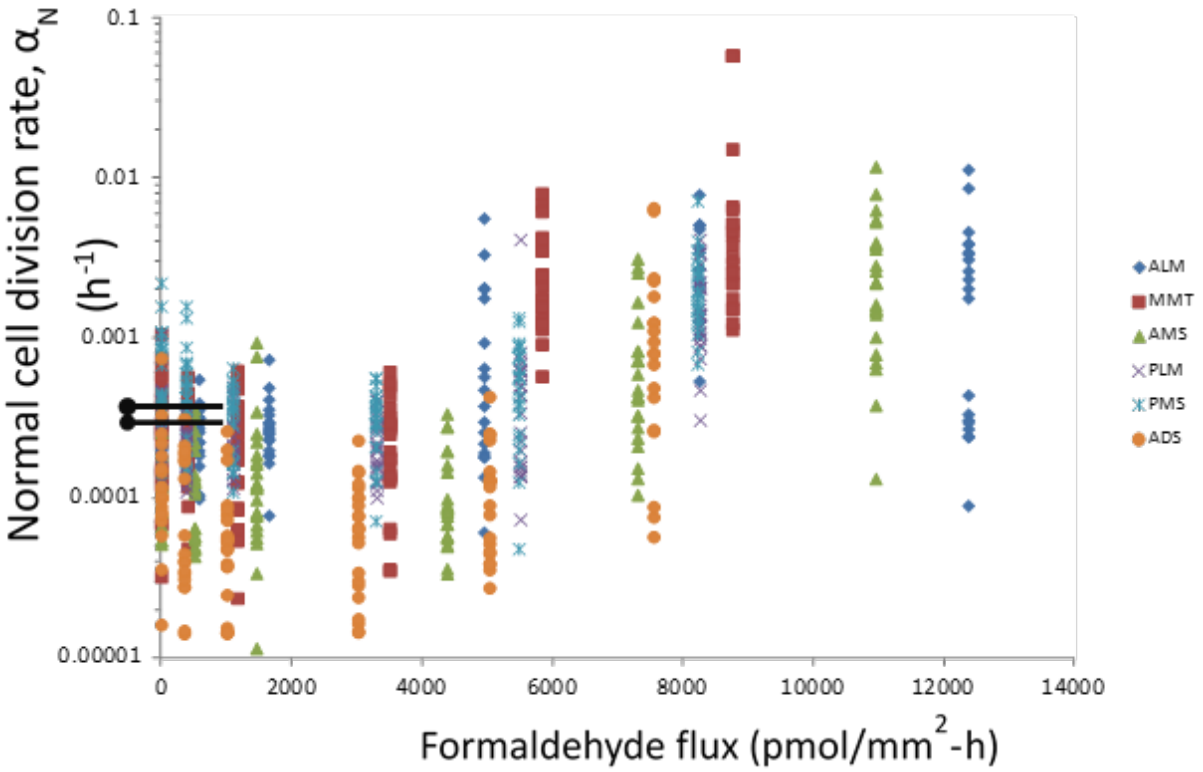


Figure 5-7. Dose-response for normal cell division rate, α_N, versus formaldehyde flux to tissue for the F344 rat nasal epithelium.

Values were derived from continuous unit length labeled data by Monticello et al. (1996). Each point represents a measurement for one rat, at one nasal site, and at a given exposure time. Data shown for six nasal sites (legend, nasal sites are as denoted in original paper) and four exposure durations (13, 26, 52, 78 weeks). For comparison purposes, the double black bars on the y-axis indicate the extent of difference between two curves, mod0 and mod5, for the dose-response for cell division rates of initiated cells.

The assumption in Conolly et al. (2004) that cell division rates exhibit a similar dose-response across rats and humans appears uncertain (Conolly et al. (2004) did consider different values for rats and humans for the fractions of cells with replicative potential) (see Appendix D.2.2). EPA was unable to find a rationale for this assumption in the literature. To the contrary, it seems possible that basal cell division rates may scale allometrically across species, considering that enzymatic metabolism is likely to play a role in mitosis. [For example, West and Brown (2005) argue that DNA nucleotide substitution rates and inverse of lifespan scale as mass to the inverse one-fourth power.]

Miller et al. (2017) found the modeling in Conolly et al. (2004) [that is, their human extrapolation model] to be sensitive to the fraction of cells considered to have replicative potential in the human respiratory tract, a parameter in the human model. For example, added risk over background increased (by 87%) from -1.0×10^{-3} to -1.3×10^{-4} at 0.4 ppm exposure concentration but decreased (by 127%) from $+7.7 \times 10^{-4}$ to -2.1×0^{-4} at 2.0 ppm, when this parameter was

changed from that experimentally observed by Mercer et al. (1994) for various cell types to a value of 1.0 (i.e., all cells to have replicative potential) for the nonsmoking population at resting breathing.

Miller et al. (2017) also reported new results obtained with the Conolly et al. (2004) model in regards the site distribution of extrapolated human risk estimates over the respiratory tract. At 0.2 ppm and 1.2 ppm (0.25 mg/m^3 and 1.48 mg/m^3) inhaled exposure concentrations of formaldehyde, the highest risk was predicted to occur in nasal tissue that received the lowest formaldehyde flux, but which comprised the largest surface areas. Based on the flux patterns displayed in Kimbell et al. (2001), this likely overlaps with the human nasopharyngeal region, and suggests an important role for dosimetry in regards the epidemiological observation of nasopharyngeal carcinomas. For the high exposure concentrations (3.6 ppm and 4.5 ppm; 4.43 mg/m^3 and 0.62 mg/m^3), the highest risk region was instead predicted to occur in regions of the nose that received intermediate levels of formaldehyde flux.

Kinetics of initiated cells

There are no data on initiated (I) cells (the available empirical cell labeling data are for normal [N] cells). Therefore, Conolly et al. (2004) assumed relationships that linked the division rate, α_I, and death rate, β_I, for initiated cells to the division rate for normal cells, α_N, as a function of local formaldehyde flux (since local flux was the most sensitive dose metric):

$$\alpha_I(flux) = \alpha_N(flux) \times \{c_1 - c_2 \cdot \max[\alpha_N(flux) - \alpha_{Nbasal}, 0]\} - \quad \text{(Eq. 5-4)}$$

$$\beta_I(\text{flux}) = \alpha_N(\text{flux}), \text{ for all values of flux. –} \quad \text{(Eq. 5-5)}$$

where c_1 and c_2 are constants estimated by fitting the clonal expansion model to the tumor incidence data. No biological rationale was provided for these assumptions; however, these assumptions allowed for a good fit to the rat tumor incidence data. The TSCE model is known to be very sensitive to the kinetics of initiated cells, and the authors did not examine whether other expressions would also fit the rat data but lead to different predictions of human risk. Therefore, to evaluate the sensitivity of model predictions to the assumed relation (Eq. 5-4) between α_I and α_N in the low flux region, EPA slightly modified this relation for α_I(flux) for flux <475 pmol/mm^2-hour, while keeping it identical to the values in Conolly et al. (2004) for 475 <flux levels <39,300 pmol/mm^2-hour, and retaining the biological constraints imposed on it in the original model (i.e. mod0 in Table 5-40). The sensitivity analysis evaluated the effect both upon the fit to the rat tumor incidence data and the predictions of human risk. The changes made for the sensitivity analysis were small enough so as not to affect the model calibration.

Six such modified implementations of α_I(flux) were considered (see mod-1, mod1, … mod5 in Figure 5-8 and in Table 5-40), in each case constrained to be small enough that they did not degrade the fit to the rat tumor incidence data when applied in the rat model or the fit to

background incidence rates in the U.S. population when applied in the human model. The maximum extent of these modifications to the assumed replication rates of initiated cells is overlaid by the double black bars in Figure 5-7, above, on the rates for normal cells, α_N(flux), that are derived from empirical data. As seen in the Figure, the extent of the modifications is extremely small in relation to the empirical variability seen in normal cells. Thus, the modifications considered in the sensitivity analysis appear biologically reasonable.

EPA's sensitivity analyses retained the same values for β_I (equation 5-5) as considered in the original analysis. However, the ratio α_I:β_I over the flux range in the modeling was closely monitored. Because this ratio represents the growth advantage of initiated cells in the model, it was kept close to the value of 1.0, similar to the range of 0.96–1.07 for the values of α_I/β_I in (Conolly et al., 2004) [mod0]. In the sensitivity analysis, α_I/β_I varied from 0.96–1.07 in mod-1; 0.96–1.08 for mod1, mod2, mod3, mod4; and 0.96–1.10 for mod5. Table 5-40 provides MLEs of continuous lifetime human extra risk estimates at 0.15 ppm (0.18 mg/m^3) exposure concentration for the original Conolly model (mod0) and compares those derived from the above modifications. For perspective, the table also compares with human risk estimates derived from EPA's modeling of the NPC mortality[70] in the NCI occupational epidemiology data (see Section 5.2.1, *Derivation of NPC unit risk estimates based on human data*).

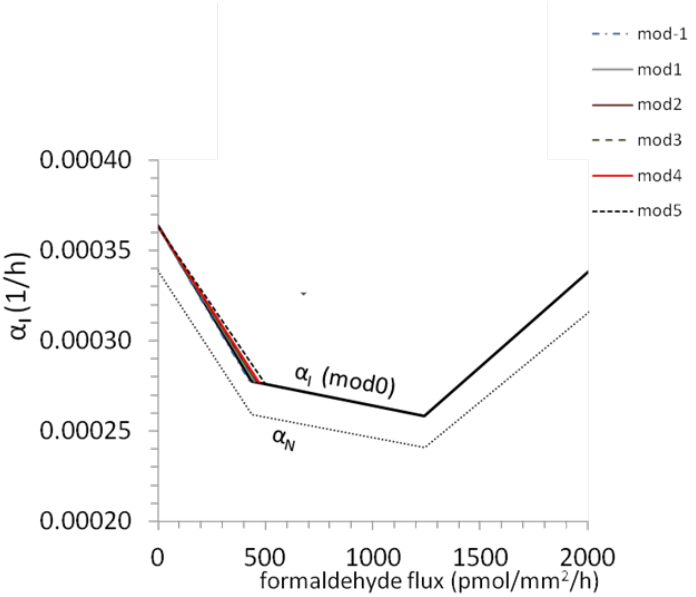


Figure 5-8. Small variations to α_I(flux) for flux <475 pmol/mm^2-hr carried out for sensitivity analysis.

Mod0 is the original model in Conolly et al. (2004); mod-1 decreases α_I and mod1-5 increase α_I in mod0 for low flux.

[70]The comparison with mortality estimates appeared appropriate since the tumors were modeled as rapidly fatal in (Conolly et al., 2003, 2004).

Table 5-40. Sensitivity of BBDR modeled human SCC risk at 0.15 ppm to small variations in normal (α_N) and initiated (α_I) cell replication rates

Model*	Extra risk
mod0: Conolly et al. (2004), J-shaped α_N, α_I	-1.0×10^{-3}
mod-1: Decrease α_I for low flux in mod0	-1.5×10^{-3}
mod1: Increase α_I for low flux in mod0	-3.0×10^{-4}
mod2: Increase α_I for low flux in mod0	$+9.0 \times 10^{-5}$
mod3: Increase α_I for low flux in mod0	$+3.0 \times 10^{-4}$
mod4 Increase α_I for low flux in mod0	$+9.0 \times 10^{-4}$
mod5: Increase α_I for low flux in mod0	$+3.0 \times 10^{-3}$
Conolly et al. (2004), hockey-stick shaped α_N, α_I	$+5.7 \times 10^{-6}$
EPA analysis of NCI NPC	$+5.5 \times 10^{-3}$

*See Figure 5-8 for depiction of mod0, mod-1, mod0-5.

The results in this table indicate that extremely small differences in assumptions for α_I appear to have extremely large effects on the human model predictions. This analysis is continued in Appendix D.2.2, where similar sensitivity of model predictions is demonstrated over a large range of exposure concentrations. Larger variations in α_I (see (Crump et al., 2008)), while still in agreement with the model constraint of reproducing the observed tumor incidence data and the background rate of lung tumors in humans, considerably broaden the range of predicted risk on either side (below and above) of the baseline risk. Such an extreme sensitivity indicates that the formaldehyde human TSCE model is unstable in response to the slight perturbations carried out to the assumed values of α_I and is therefore not robust. It is well known that models are generally uncertain outside of the range of the data over which they were calibrated (Crump et al., 2010) and this is indeed the case with the rat BBDR model. As discussed by (Crump et al., 2008; Crump et al., 2009), the human extrapolation BBDR model, on the other hand, is noteworthy for its extreme uncertainty at ***all*** exposure concentrations, above as well as below the HECs that were calculated in the benchmark modeling section.

There are currently no data of any kind, even in rats, to inform the effect of formaldehyde on the kinetics of initiated cells. However, assuming that initiated cells related to tumors in the respiratory tract can be identified and their division rates measured, it is reasonable to suppose that these rates would be at least as variable as division rates of normal cells. Based on the normal variation in such rates observed in normal cells in Figure 5-8, and the extreme sensitivity of the formaldehyde model to small differences in assumed division rates of initiated cells, EPA concluded that it would be impossible to measure these accurately enough to lead to any substantive reduction in the large uncertainty in risk estimated by this model.

Use of historical control animals

Because SCC in the nose is a rare tumor, (Conolly et al., 2003, 2004) included in their model 7,684 control rats from all NTP cancer bioassays in addition to the 347 control animals in the Kerns et al. (1983) and Monticello et al. (1996) inhalation bioassays used in the dose-response modeling. In general, the inclusion of all NTP historical control animals regardless of exposure route, time of study, etc. is problematic because there are legitimate questions regarding comparability of results in rats from different stocks, studied at different times, in different laboratories, and by different routes of exposure and evaluated by using somewhat different pathological procedures (Rao et al., 1987; Haseman and Hailey, 1997). In particular, the incidence rate in the inhalation historical controls was found to be an order of magnitude lower than the rate in all historical controls combined (see (Subramaniam et al., 2007)). Therefore, EPA examined the sensitivity of the BBDR model predictions to the use of historical NTP control animals by restricting the historical controls to only inhalation studies or by using only the concurrent controls.

When the NTP control data were restricted to those animals from NTP inhalation studies, the upper-bound human risk estimate obtained by Conolly et al. (2004) (i.e., with everything else in their modeling retained unchanged) was increased by 50-fold (Crump et al., 2008). If only concurrent controls are used, as is normally the practice in dose-response analysis of animal bioassays, the Conolly et al. (2004) model for extrapolation of risk to humans becomes numerically unstable, i.e., the MLE and upper-bound estimates of risk become infinite (Subramaniam et al. (2007), Crump et al. (2008)).

Overall confidence in the formaldehyde BBDR models

The other issues listed in Table 5-39 are evaluated at length in Appendix D.2.2. Although CFD model predictions of formaldehyde flux to the respiratory lining have not been verified experimentally (due to formidable experimental challenges), predictions from other models that use the calculated formaldehyde flux as input have been shown to agree with various kinds of available data, and thus project a reasonable, albeit indirect, level of confidence in the formaldehyde dosimetry modeling in both the rat and human nasal passages (see Appendix D.2.2). The CFD models of formaldehyde flux are based on data collected from a single individual of each species. Therefore, interindividual differences in regional dosimetry, particularly in the human, are not accounted for (Subramaniam et al., 2008; Garcia et al., 2009).

Repair of DPX was assumed to be rapid and complete in 18 hours in the PBPK model for DPX (Conolly et al., 2000); this assumption was found to be highly uncertain (Subramaniam et al., 2008). While it has no impact on the rat BBDR model predictions (see Appendix D.2.2), the impact of this assumption on the human extrapolation model, on the other hand, was significant (Crump et al., 2008). Furthermore, more recent results by Lai et al. (2016) indicate that in vivo DPX repair may be slow and that DPX readily accumulates long-term in the nasal respiratory tissue in contrast to its rapid hydrolysis in vitro.

In summary, the human extrapolation modeling in Conolly et al. (2004) is extremely uncertain on two accounts, and does not provide robust measures of human nasal SCC risk at *any* exposure concentration. Therefore, the human extrapolation model is not used in this assessment to directly calculate risk at human exposure scenarios. On the other hand, the rat BBDR modeling improves the dose-response modeling of the observed nasal cancers in the F344 rat, and multiple BBDR model implementations provide similar estimates of risk and confidence bounds in the general range of the observed rat tumor incidence data. Therefore, the rat BBDR models are used to calculate benchmark concentrations for PODs, and the benchmark response was extended slightly below the observed. There is reasonable confidence in flux estimates derived from the rat and human CFD models, which were accordingly used in deriving HECs corresponding to these PODs. A candidate RfC and candidate unit risk estimates using these values are included in the following section.

RfC approach for precursor lesion data in the rat: cell proliferation and hyperplasia

The highly curvilinear and steeply increasing dose-responses for DPX formation and cell proliferation, concomitant with the highly nonlinear observed tumor incidence in the F344 rat, have led to mechanistic arguments that formaldehyde's nasal carcinogenicity arises only in response to significant cytotoxicity-induced regenerative cell proliferation (Swenberg et al., 2011; Morgan, 1997; Conolly et al., 2002). In particular, Conolly et al. (2003) and Slikker et al. (2004) inferred from BBDR modeling results that the direct mutagenicity of formaldehyde is less relevant compared to the importance of cytotoxicity-induced cell proliferation in explaining the rat tumor response. Thus, candidate RfCs (cRfCs) derived from available experimental data relevant to this mechanism are presented and discussed. These cRfCs are interpreted as formaldehyde concentrations below which it is unlikely that hyperplastic lesions develop or that cancers arising from cytotoxicity-induced regenerative cell proliferation occur. In this interpretation, cytotoxicity-induced regenerative cell proliferation, which increases the probability of errors in DNA replication, and the subsequent development of hyperplastic lesions, are considered to be precursor events that, if protected against, would prevent these mechanisms from contributing to the cancer response. Below these cRfCs, formaldehyde may still increase the risk of nasal or upper respiratory cancer through *direct* mutagenicity or other mechanisms, but the magnitude of cancer risk may be significantly lower due to the absence of increased cellular proliferation or hyperplasia.

The following benchmark PODs and corresponding HECs were developed based on increased cell proliferation as well as hyperplasia: (a) 0.44 ppm (0.54 mg/m^3) corresponding to the $BMCL_{01}$ in Schlosser et al. (2003), and roughly two- to three-fold lower estimates based on examining data from other cell labeling studies (as discussed above in the section on modeling precursor lesion data), resulting in an overall range from 0.18 to 0.54 mg/m^3; and (b) 0.16 ppm (0.20 mg/m^3) based on EPA's modeling of the incidence of basal hyperplasia reported by Woutersen et al. (1989) in Wistar rats. To these values, it is necessary to apply a UF = 3 to reflect other uncertainties in extrapolating from animals to humans and a UF = 10 to account for human

variability (total UF = 30). This results in cRfCs that range from **0.006 mg/m³ to 0.018 mg/m³** when based on cell proliferation data and a cRfC of **0.007 mg/m³** from the hyperplasia data.

As noted earlier, it has been argued that the rat nasal tumors can be quantitatively explained based solely on formaldehyde's cytotoxic potential. In accordance with this point of view, a cRfC estimated from benchmark concentrations derived using the two rat BBDR models may be a reasonable approximation for the dose at which there is no regenerative cell proliferative contribution to the nasal or upper respiratory cancer response. A cRfC of **0.017 mg/m³** may be obtained in this manner corresponding to the average HEC estimated using the two models at a benchmark response of 0.005 extra risk reduced by a UF of 30. This value is encompassed by the overall range of **0.006–0.018 mg/m³** obtained as explained above for the cRfCs based on cell proliferation and hyperplasia.

However, Chapter 1 of this assessment also provides multiple lines of evidence that the direct mutagenicity of formaldehyde plays a key role in its carcinogenicity. Cytogenetic effects in occupational studies and the formation of DPXs in experimental animals have been reported at exposures well below those considered to be cytotoxic (e.g., approximately 0.7–2 ppm or 0.9–2.5 mg/m³ in rats), and as noted earlier, DPX formation was detected in rats at exposures ranging from 0.3 ppm (0.37 mg/m³) to 15 ppm (18.5 mg/m³). The DPX dose-response shows a trend consistent with an increase over baseline levels at 0.7 ppm (0.86 mg/m³), which becomes statistically significant at 2 ppm (2.46 mg/m³) and above.

Furthermore, the previously mentioned inference that formaldehyde's direct mutagenic action is relatively irrelevant to describing the observed rat tumor response was found to be extremely uncertain in EPA's uncertainty analysis. A reanalysis presented in Subramaniam et al. (2007) indicated that, depending on the choice of control animals and alternate model assumptions, a large contribution from formaldehyde's mutagenic potential may be needed to explain formaldehyde carcinogenicity at low dose as well as in describing the observed tumor incidence. Finally, as discussed in Section 3.2.5, *Evidence on mode of action for URT cancers*, genotoxicity is itself interpreted to be one of the mechanisms by which formaldehyde exerts its cytotoxic action. Thus, it is difficult to argue for a demarcation along the concentration axis of one MOA relative to the other. Therefore, because formaldehyde-induced tumors are not explained *only* by the cell proliferative MOA at *any* exposure, and since EPA does not develop an RfC specifically for one MOA when other MOAs also contribute to the tumor response, an RfC approach is not used.

Low-dose risk without extrapolating models below the observed data

The various arguments presented in the last two paragraphs of the previous section on an RfC-like approach for cancer, particularly regarding formaldehyde's direct mutagenic potential, provide greater support for a low-dose linear approach in extrapolating low-dose formaldehyde cancer risk from the rat data. And, as previously discussed and based on a detailed analysis conducted according to EPA's cancer MOA framework (U.S. EPA, 2005a), it was concluded that there is strong and consistent evidence to support that both MOAs (i.e., mutagenicity and

cytotoxicity-induced regenerative proliferation) contribute to nasal cancers caused by formaldehyde inhalation exposure (see Section 3.2.5 for details). In accordance with the EPA cancer guidelines (U.S. EPA, 2005a, b), given the strong evidence for mutagenicity as a contributing MOA and the evidence-based understanding that mutagens can give rise to cancers with an apparently low-dose linear response, this extrapolation was carried out as a straight line drawn to the origin from the HEC corresponding to the BMDL. Unit risks so calculated are shown in Table 5-41 below. The unit risks corresponding to BMRs at the 0.005 or 0.01 extra risk levels, span a remarkably tight range, 0.01–0.03 per ppm**,** across the different methods when internal dose metrics, formaldehyde flux to the tissue or formaldehyde induced DPX, are used.

Table 5-41. Unit risks based on rat nasal tumors[a]

Models	Dose metric	Unit risk extrapolations from PODs at various BMCL's (per ppm)			
		$BMCL_{005}$	$BMCL_{01}$	$BMCL_{05}$	$BMCL_{10}$
Weibull with threshold (Schlosser et al., 2003)	Flux		0.014	0.066	0.127
	DPX		0.014	0.066	0.127
Multistage Weibull time-to-tumor	Exposure Conc		0.051	0.183	0.317
	Flux		0.031	0.111	0.192
Rat BBDR model 1	Flux	0.012	0.023		
Rat BBDR model 2	Flux	0.011	0.022		

[a]Unit risks derived using flux as dose metric increase by a factor of 1.4 if flux estimates based on Schroeter et al. (2014) are used instead of Kimbell et al. (2001a). Also, see other footnotes from Table 5-37.

In conclusion, use of biologically based modeling allowed the use of various data, including mechanistic information, in an integrated manner for modeling the incidence of nasal SCC in F344 rats and for deriving benchmark levels for extrapolation. A conventional multistage Weibull time-to-tumor modeling was also used to model these data; however, the biologically based models provide better fits to the tumor incidence data. For a given benchmark response level, PODs and their corresponding HECs are remarkably similar across multiple models and internal dose metrics (formaldehyde inhaled flux to tissue, DPX concentrations) and are comparable (within a factor of 2–4) to values obtained using inhaled exposure concentration. Biologically based clonal expansion models were carefully evaluated for directly extrapolating the rat nasal cancer risk to human exposure scenarios. Predictions using these models for humans were found to be not robust at any exposure concentration. Accordingly, the clonal expansion modeling of the rat data was employed to derive multiple PODs and corresponding HECs but not used for directly extrapolating to human exposure scenarios.

Selection of a Unit risk Estimate for Nasal Cancers

The unit risk estimates derived using the available human and animal data on nasal cancers are similar (see Table 5-42), with the human estimate being only slightly lower than those values estimated using rat bioassay and mechanistic data.

Table 5-42. Comparison and basis of unit risk estimates derived from nasopharyngeal cancer in humans and nasal squamous cell carcinomas in rats[a]

	Based on human NPC	Based on nasal SCC in the rat
Study/endpoint	Beane Freeman et al. (2013) (NCI industrial cohort): NPC mortality	Monticello et al. (1996); Kerns et al. (1983): Incidence of nasal SCC in rats
Model features	Estimation of IUR using Poisson regression model and life-table analysis: • U.S. national incidence data for NPC • U.S. national all-cause mortality data to account for competing causes of death. • Regression coefficients from log-linear models of nasopharyngeal cancer (NPC) mortality (exposed and unexposed workers) • Linear low-dose extrapolation from LEC	Modeling of tumor incidence used results from multiple mechanistic and statistical models, including BBDR modeling. Mechanistic information included: • Dosimetric (CFD) modeling of formaldehyde flux to rat, monkey, and human airway lining[b] • PBPK model for rats incorporating dose-response data on DPXs[c] • site-specific cell labeling measurements in nose[d] A linear low-dose extrapolation from human equivalent dose at BMCL was employed
POD	95% lower bound on concentration at 0.05% incidence (approx. 0.05 ppm)	95% lower bound on concentration at 0.5% and 1.0% extra risk levels (0.33 to 0.46 ppm)
Unit risk estimate	7.4×10^{-3} per mg/m^3 (9.1×10^{-3} per ppm)	8.9×10^{-3} to 1.8×10^{-2} per mg/m^3 (1.1×10^{-2} to 2.2×10^{-2} per ppm)

[a]Note that these estimates are provided for comparison purposes and do not represent ADAF-adjusted values. ADAF = age-dependent adjustment factor; only results based on internal dose metrics are shown in this Table for the estimates extrapolated from the rat nasal SCC data.
[b]Kimbell et al. (2001a).
[c]Subramaniam et al. (2007).
[d]Monticello et al. (1996).

A comparison of the unit risk estimates based on human and rodent data summarized above reveals that the different databases yield similar estimates, particularly when estimates based on internal dose metrics (flux and DPX) are used. When data from epidemiological studies of sufficient quality are available, these data are generally preferred for estimating risks (U.S. EPA, 2005a). In the case of formaldehyde, the NCI epidemiological study (Beane Freeman et al., 2013) is a high-quality study for the purposes of deriving quantitative risk estimates. Although there are

uncertainties inherent in estimates from both the human and rodent databases, the estimates based on the human data are considered better estimates of the risk to humans.

Next, given that it was concluded in Section 3.2.5 that a mutagenic MOA was operative for URT cancers, the unit risk estimate for NPC is adjusted for potential increased early-life susceptibility, in accordance with EPA guidelines (U.S. EPA, 2005b) (see Section 5.2.4).

Uncertainties and Confidence in the Unit Risk Estimate for Nasal Cancers

The strengths and uncertainties in the unit risk estimate for NPC incidence are summarized in Table 5-43. One of the largest sources of uncertainty in the NPC estimate has to do with the rarity of the cancer and, thus, the small number of exposed cases (n = 8) that informed the dose-response analysis.

Table 5-43. Strengths and uncertainties in the cancer type-specific unit risk estimate for nasopharyngeal cancer

Strengths	Uncertainties
• Estimated from data that is directly relevant to humans. • Based on the results of a large, *high* confidence epidemiology study involving multiple industries with detailed, individual cumulative exposure estimates and allowance for cancer latency. • Low-dose linear extrapolation is supported by a mutagenic mode of action (i.e., not a default). • Similar unit risk estimates derived using rat bioassay and mechanistic data on nasal cancers.	• NPC is a very rare cancer. This study followed more than 25,000 workers for over 40 years and observed a statistically significant increase in RR associated with the highest category of average exposure intensity, however, only 10 cases occurred. The small number of deaths creates uncertainties for the dose-response modeling (borderline significant trend test for cumulative exposure including exposed and unexposed person-years, $p = 0.07$). • Uncertainty about optimal exposure metric(s). Cumulative exposure is the standard metric used for unit risk estimates. Use of cumulative exposure assumes equal importance of concentration and duration on cancer incidence; yet associations with peak exposure in epidemiological studies and the nonlinear shape of the dose-response from animal bioassays suggests greater influence of concentration. • Although statistically significant increases in risk for NPC were reported by multiple studies for several metrics of exposure (duration, cumulative, time since first exposure, peak), the relationship with cumulative exposure in the study used for IUR derivation was less precise (p-trend = 0.07 based on the regression coefficient for the continuous model). • Low-dose extrapolation below the POD is inherently uncertain. The presence of endogenous formaldehyde may have an effect on the delivered formaldehyde. Schroeter et al. (2014) and Campbell Jr et al. (2020) provide perspectives on this issue. Furthermore, the contribution of endogenous formaldehyde and its variability on background disease processes and dose-response remains uncertain.

Based on the attendant strengths and uncertainties outlined above, there is **medium** confidence in the unit risk estimate for NPC incidence.

5.2.2. Unit Risk Estimate for Myeloid Leukemia

A judgment that the **evidence demonstrates that** formaldehyde inhalation also causes myeloid leukemia was based on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels. Supporting mechanistic evidence consistent with leukemia development is provided across numerous studies of peripheral blood isolated from exposed workers, including evidence of mutagenicity and other genotoxic damage in lymphocytes and myeloid progenitors, and perturbations to immune cell populations.

The animal evidence is *indeterminate* and, although notable uncertainties remain (see Section 3.3.3), the findings to date suggest either a lack of concordance across species or a lack of long-term studies in animal models that characterize the disease process in humans for leukemia. Leukemia was not increased in two well-conducted chronic bioassays of rats or mice, and the available animal data provide weak mechanistic support for LHP cancers. No MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia without systemic distribution (inhaled formaldehyde does not appear to be distributed to an appreciable extent beyond the URT to distal tissues). Differences in physiology between humans and rodents, as well as the apparent relative insensitivity of rodent models to reflect the human pathogenesis of AML (Eastmond, 1997), may together contribute to the potential lack of concordance between the abundant human epidemiological data and the more limited results (e.g., most bioassays did not examine tissues relevant to LHP cancers in detail) from rodent bioassay data. Accordingly, no animal studies were sufficient for use in deriving a unit risk estimate.

Results from the follow-up of mortality from LHP cancer in the same occupational cohort were used to derive a unit risk estimate for myeloid leukemia. In this study, however, there is no apparent association between myeloid leukemia mortality and cumulative exposure. A clearer association is observed with peak exposure, though it is not statistically significant in the latest follow-up (in an earlier 1994 follow-up of that study, myeloid leukemia mortality was statistically significantly associated with peak exposure; see Section 3.3.3). Although multiple approaches for deriving a unit risk estimate for myeloid leukemia were explored, EPA did not develop an approach based on the peak exposure metric because EPA deemed the uncertainty associated with the peak exposure metric and the difficulties in translating risk from peak exposure to risk from chronic low-level exposure to be prohibitive.

Instead, EPA explored alternative approaches for deriving a unit risk estimate for myeloid leukemia based on cumulative exposure (details in Appendix D.2.3). Specifically, although an association between myeloid leukemia and cumulative formaldehyde exposure was not apparent in the key exposure-response study, there are indications that this may, at least in part, reflect a misclassification of myeloid leukemia deaths on death certificates. (Percy et al., 1981; Percy et al., 1990) have reported that myeloid leukemia is often recorded as "leukemia" (not otherwise specified) on death certificates and hence underreported]. The best available approach (see Appendix D.2.3) was to estimate a unit risk for myeloid leukemia using the regression coefficient

for myeloid and other/unspecified leukemias combined; this cancer grouping had a stronger association with cumulative exposure in the key exposure-response study than did myeloid leukemia alone and it captures the unclassified myeloid leukemias with the least inclusion of nonmyeloid leukemias. However, this estimate was concluded to be too uncertain and ultimately was not incorporated into the IUR.

Derivation of Myeloid Leukemia Unit Risk Estimates Based on Human Data

Choice of Epidemiology Studies

As noted previously, it was determined that the **evidence demonstrates** that formaldehyde inhalation exposure can cause myeloid leukemia (ML). While several studies of cancer in workers exposed to formaldehyde evaluated exposure-response relationships, most reported the results of categorical analyses, only a few reported risk estimates in relation to changes in formaldehyde concentration or cumulative exposure rather than duration of exposure, TSFE, probability of exposure, or exposure intensity score, measures which are not generally adequate for the derivation of cancer unit risk estimates.

One *high* confidence result from Beane Freeman et al. (2009) provided dose-response information on the follow-up of the large National Cancer Institute (NCI) retrospective cohort mortality study [originally described by Blair et al. (1986)] of workers at 10 U.S. plants producing or using formaldehyde. A second *high* confidence result from (Hauptmann et al., 2009) presented dose-response information from a large case-control study of embalmers and funeral directors [originally described by (Walrath and Fraumeni, 1983, 1984; Hayes et al., 1990) and not considered individually for IUR derivation]. Because of limitations in the exposure assessment, this study, while useful for hazard assessment, was not used by EPA to derive quantitative risk estimates. Of primary concern, the worker histories were obtained from surrogate responders (next of kin who had worked in the funeral home with the study subject and coworkers). There is substantial uncertainty in the application of this approach to variables such as number and duration of embalmings per calendar period and frequency of spills per calendar period, variables that are needed in the study's exposure model to estimate cumulative exposure. Furthermore, considerable amounts of data were missing. Thus, although the results of the Hauptmann et al. (2009) study were supportive of the hazard assessment, the larger uncertainty in the quantitative estimates than other available studies resulted in no POD being derived. A third *high* confidence result from (Meyers et al., 2013) and one *medium* confidence study (Coggon et al., 2014) reported some information on dose-response but did not report quantitative metrics of cumulative exposure that could be used to derive an IUR for ML.

The available *high* and *medium* confidence epidemiology studies of myeloid leukemia were evaluated for use in deriving a cancer unit risk estimate (see Table 5-44). Ultimately, only the *high* confidence study by Beane Freeman et al. (2009) was advanced for POD derivation.

Table 5-44. Eligible epidemiology studies for POD derivation and rationale for decisions to not select specific studies for myeloid leukemia

Study,endpoint	Dose-response considerations (see Section 2.7)					Decision
	Study evaluation[a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Residential Studies						
Beane Freeman et al. (2009) Myeloid leukemia	[+] *High* confidence [+] Potential information bias unlikely [+] Selection bias and confounding unlikely	[+] Diverse population (Adult M+F) [+] Participation rate of cases (96%) and controls (94%)	[+] 2000 air samples [+] Individual-level continuous exposure [+] Wide range (0.0–107.4 ppm-years) [+] Blinded to outcome	[+] Mortality: underlying cause from death certificates ICD-8: 205 [n] Incidence data not available	[n] N = 48 cases among 25,619 workers [+] Poisson regression with slope parameters provided by Beane Freeman (Jinot and Beane-Freeman, 2014) *Some concern:* [-] No apparent association between myeloid leukemia mortality and cumulative exposure	POD derived, limitation regarding results utility for dose-response analysis noted.
(Hauptmann et al., 2009) Myeloid leukemia [Nested case-control study within extension of three embalmers cohorts described in Walrath and Fraumeni (1983, 1984); Hayes et al. (1990).	[+] High confidence [+] Potential information bias unlikely [+] Selection bias and confounding unlikely	[+] Diverse population (Adult M+F)	[+] Individual level, based on lifetime work practices and exposures to formaldehyde using a predictive model based on exposure-assessment data [+] Low levels and wide range (0 to >9253 pp-hrs level = 0.01 ppm	[+] Mortality: underlying cause from death certificates ICD-8: 205	[n] N = 34 cases out of 6,808 embalmers and funeral directors **Critical concern**: Significant trends of continuous metrics for duration and peak and significant categorical metric for cumulative exposure were not suitable for IUR.	No POD derived. Critical concern regarding results utility for dose-response analysis in light of other available studies.
Meyers et al. (2013) Myeloid leukemia	[+] High confidence [+] Potential information bias unlikely	[+] Diverse population (Adult M+F)	[+] Individual level, based on lifetime work practices and exposures to formaldehyde using a predictive model based on	[+] Mortality: underlying cause from death certificates ICD-8: 205	[n] N = 21 cases out of 11,043 garment workers **Critical concern**: Multiple indications of increased risk with increased	No POD derived. Critical concern regarding results utility for dose-

	[+] Selection bias and confounding unlikely		exposure-assessment data [+] Low levels and wide range (0 to >9253 pp-hrs; level = 0.01 ppm)		duration of exposure, but no cumulative exposure metric was reported.	response analysis.
Coggon et al. (2014) Myeloid leukemia	[+] High confidence [n] Potential information bias (latency not evaluated) [+] Selection bias and confounding unlikely	N/A	N/A	N/A	[n] N = 36 cases out of 14,008 garment workers **Critical concern**: No quantitative metrics of cumulative exposure.	No POD derived. Critical concern regarding results utility for dose-response analysis.

N/A = not applicable = consideration was not influential to the decision (e.g., because a critical concern was identified).
[a] Select features of the study evaluations that may have the most impact on quantification may be highlighted (if not otherwise highlighted in other columns), but the bullets in this column do not represent a full synopsis (see Appendix B.3.9 for details).

Thus, similar to the unit risk estimate for NPC, the estimate for myeloid leukemia is based on results from the latest follow-up of the NCI cohort of industrial workers exposed to formaldehyde (Beane Freeman et al., 2009), the largest (25,619 workers) of the three independent industrial worker cohort studies and the only one with sufficient individual exposure data for dose-response modeling. Beane Freeman et al. (2009) conducted dose-response analyses of 123 deaths attributed to leukemia and leukemia subtypes, as well as deaths from other LHP malignancies. As previously described, this well-conducted study is the only one that used internal comparisons rather than standardized mortality ratios (reducing the impact of potential unmeasured confounding), and it included a detailed exposure assessment conducted for each worker based on exposure estimates for different jobs held and tasks performed (Stewart et al., 1986), and exposure estimates were made using several different metrics—peak exposure, average intensity, cumulative exposure, and duration of exposure.

For the LHP cancers, the strongest trends for the subtypes of interest were generally observed with the peak exposure metric (Beane Freeman et al., 2009). For myeloid leukemia, Beane Freeman et al. (2009) reported an increasing trend in mortality risk (p = 0.07 for all person-years) for peak exposure, but no trend was observed for cumulative exposure. For myeloid leukemia and other/unspecified leukemias combined, recognizing that a substantial proportion of the unspecified leukemias are probably myeloid leukemias, there was a nearly significant (log-linear) trend with cumulative exposure (p = 0.10 for all person-years) (personal communication from Laura Beane Freeman, NCI, to Jennifer Jinot, (Jinot and Beane-Freeman, 2014)). No exposure-response relationships were indicated for multiple myeloma for any of the exposure metrics.

Summary of Results from Exposure-response Modeling of the National Cancer Institute Cohort

The NCI cohort study (Beane Freeman et al., 2009), was the only study with adequate data for exposure-response modeling; however, the derivation of a unit risk estimate for myeloid leukemia from these data is not straightforward, and several quantitative risk assessment approaches were considered (see Appendix D.2.3).

In summary, EPA explored several approaches for deriving a unit risk estimate for myeloid leukemia based on cumulative exposure. The first approach involved using the grouping of leukemias classified as myeloid leukemia on the death certificate. The regression coefficient for this grouping had a *p*-value (0.44) indicative of a poor model fit. It was reasoned that the poor model fit could be due, at least in part, to the underreporting of myeloid leukemia deaths discussed above. As shown in Table 5-45, the regression coefficient for myeloid leukemia was only slightly lower than that for all leukemia, which had a lower *p*-value of 0.08 and should include all the myeloid leukemia deaths, both specified and unspecified. Thus, a second approach involved using the all leukemia grouping, which includes other subtypes likely not associated with formaldehyde exposure. Ultimately, the best available approach involved using the combined grouping of the myeloid leukemia and other/unspecified leukemias subcategories. The myeloid and other/unspecified leukemias grouping had a stronger association with cumulative exposure ($p = 0.10$) in the Beane Freeman et al. (2009) study than did myeloid leukemia alone and it captures the unclassified myeloid leukemias with the least inclusion of nonmyeloid leukemias. The benefits of focusing on the myeloid plus other/unspecified leukemias rather than the broader "all leukemia" grouping in attempting to be more inclusive of all the myeloid leukemias were deemed to outweigh any additional uncertainty associated with the background rates for the other/unspecified leukemias (discussed further below). The best available unit risk estimate for myeloid leukemia is the estimate of **4.2×10^{-2} per ppm (3.4×10^{-2} per mg/m^3).** Table 5-45 summarizes some of the key information comparing the different approaches attempted for different cancer groupings for the derivation of the unit risk estimate for myeloid leukemia, noting that the available estimates are all similar.

Table 5-45. Exposure-response modeling (all person-years) and (incidence) unit risk estimate derivation results for different leukemia groupings

Cancer grouping	Number of deaths in NCI cohort	Regression coefficient (per ppm × year)	SE (per ppm × year)	*p*-Value	Unit risk estimate (per ppm)	Unit risk estimate (per mg/m^3)
Myeloid leukemia	48	0.009908	0.01191	0.44	3.9×10^{-2}	3.2×10^{-2}
All leukemia	123	0.01246	0.006421	0.08	5.9×10^{-2}	4.8×10^{-2}
Myeloid + Other/Unspecified leukemias	**84[a]**	**0.01408**	**0.007706**	**0.10**	**4.2×10^{-2}**	**3.4×10^{-2}**

Note: Shaded estimate is considered the best available estimate.

[a]This is the sum of the leukemias classified as myeloid and those classified as "other/unspecified". At least 70–80% of this number is expected to be myeloid leukemias, assuming that a third to a half of leukemias not otherwise specified on death certificates are myeloid leukemias, as discussed above.

Uncertainties and Confidence in the Best Available Unit Risk Estimate for Myeloid Leukemia

The strengths and uncertainties in the unit risk estimate for myeloid leukemia incidence are summarized in Table 5-46, with additional discussion in Appendix D.2.3. The primary uncertainty in this estimate relates to the complexities in the study-specific data for cumulative formaldehyde exposure and mortality from myeloid leukemia.

Table 5-46. Strengths and uncertainties in the cancer type-specific unit risk estimate for myeloid leukemia

Strengths	Uncertainties
• IUR estimated from data that is directly relevant to humans. • Based on the results of a large, *high* confidence epidemiological study involving multiple industries with detailed, individual cumulative exposure estimates and allowance for cancer latency. • Moderate number of deaths to model (*N* = 84).	**Uncertainties with a potentially large impact**: ○ Although the dose-response relationship with peak exposure was marginally significant (p = 0.07), and statistically significant associations were reported for several metrics of exposure in other studies, the reported relationship with cumulative exposure showed a nonsignificant, small increase in risk for myeloid leukemia (based on the regression coefficient for the continuous model), potentially due in part to misclassification of myeloid leukemia cases. ○ The association with cumulative exposure was stronger for the other/unspecified grouping of leukemia diagnoses (*N* = 36) than for myeloid leukemia alone (*N* = 48). Although a sizable proportion of this category is assumed to include myeloid leukemia cases, the stronger association is surprising given the more heterogeneous set of leukemia cases in this category, some presumably not associated with formaldehyde exposure. Hence, the association would be expected to be attenuated. ○ Uncertainty about optimal exposure metric(s). Use of cumulative exposure assumes equal importance of concentration and duration on cancer incidence. The specific metrics analyzed differed across studies, and the results of the NCI study were not completely consistent with those of other studies (associated only with peak exposure). **Uncertainties likely to have a minor impact**: ○ Grouping of myeloid leukemias used for exposure-response modeling includes nonmyeloid leukemias. ○ Borderline model fit for myeloid plus other/unspecified leukemias (*p* = 0.1) and uncertain shape of exposure-response function.

Based on the attendant strengths and uncertainties outlined above, there is **low** confidence in the unit risk estimate for myeloid leukemia incidence. However, given the strength of the evidence integration judgment (i.e., **evidence demonstrates** formaldehyde inhalation causes myeloid leukemia in humans), and the associated public health burden that it poses (e.g., myeloid leukemia is far more prevalent than NPC), EPA thoroughly considered the complexity in the data and attempted an innovative approach to derive a potential unit risk estimate for myeloid leukemia.

However, the uncertainty in this value was ultimately considered too great and the best available unit risk estimate for myeloid leukemia was not used to inform the quantification of risk for cancer. The uncertainty associated with being unable to address myeloid leukemia in the IUR is discussed further below.

Derivation of LHP Cancer Unit Risk Estimates Using Animal Data

Choice of Animal Studies

The available *high* and *medium* confidence experimental animal studies of LHP cancers were evaluated for use in deriving a cancer unit risk estimate (see Table 5-47). As described for hazard identification (Section 3.3.3), the evaluation focused on advancing long-term studies with detailed evaluations of tissues relevant to LHP cancers. Subchronic and shorter duration studies were not considered. Thus, the two *low* confidence studies included in the synthesis evaluation of LHP cancers that evaluated chronic formaldehyde exposure in rats (Sellakumar et al., 1985) and 8-week formaldehyde exposure in genetically modified (p53 +/-) mice (Morgan et al., 2017) were not considered for use in dose-response analyses. Based on the evaluation presented in Table 5-47, a unit risk estimate for myeloid leukemia based on evaluations of LHP cancers was not derived from the available animal data.

Table 5-47. Eligible experimental animal studies for POD derivation and rationale for decisions to not select specific studies for LHP cancers

Study, species	Dose-response considerations (see Section 2.7)					Decision
	Study evaluation [a]	Population or subjects	Exposure	Outcome measure(s)	Result(s) utility	
Rat Studies						
(Kerns et al., 1983); (Battelle, 1982); F344 rats (M+F)	[n] *Medium* confidence [+] Good exposure quality	[n] Despite different LHP physiology, rats are considered reasonably appropriate models	[+] 2-year exposure [+] Broad exposure range	**Critical concern**: [--] Slide evaluation only for highest exposure group unless gross lesions present	[+] Large N (N = 119-121) [n] Lack of blinding for tumor analyses not a significant limitation.	No POD derived. Critical outcome measure and results utility (for dose-response) concerns.
		Some concern: [-] High mortality at highest formaldehyde levels			**Critical concern:** [--] Lesion incidence not available for all exposure levels [--] No clear LHP cancer increases (note: bone marrow hyperplasia significantly increased)	

Study, species	Dose-response considerations (see Section 2.7)					Decision
	Study evaluation [a]	**Population or subjects**	**Exposure**	**Outcome measure(s)**	**Result(s) utility**	
Kamata et al. (1997); F344 rats (M)	[n] *Medium* confidence [n] Adequate exposure quality	[n] Despite different LHP physiology, rats are considered reasonably appropriate models	[+] > 2-year exposure [+] Broad exposure range	**Critical concern**: [--] Slides evaluation only for nasal tissues unless gross lesions present	[n] Adequate N (N = 32) [n] Lack of blinding for tumor analyses not a significant limitation	No POD derived. Critical outcome measure and results utility (for dose-response) concerns.
		Some concern: [-] Males only	*Some concern*: [-] Use of formalin as test article (even with a methanol control group) introduces some quantitative uncertainty		**Critical concern:** [--] LHP lesion incidence not reported [--] Author-reported no increased LHP cancer incidence	
Mouse Studies						
Kerns et al. (1983), Battelle (1982) B6C3F1 Mice (M+F)	[n] *Medium* confidence [+] Good exposure quality	[n] Despite different LHP physiology, mice are considered reasonably appropriate models	[+] 2-year exposure [+] Broad exposure range	**Critical concern**: [--] Slide evaluation only for highest exposure group unless gross lesions present.	[+] Large N (N = 119-121) [n] Lack of blinding for tumor analyses not a significant limitation	No POD derived. Critical outcome measure and results utility (for dose-response) concerns.
		Some concern: [-] Survival to 18 mo. < 33% in exposed males			**Critical concern**: [--] Lesion incidence not available for all exposures [--] No clear LHP cancer increases (note: lymphomas were elevated in female mice at 15 ppm [27/121] as compared to controls [19/121], but not statistically significantly)	

[a] Select features of the study evaluations that may have the most impact on quantification may be highlighted (if not otherwise highlighted in other columns), but the bullets in this column do not represent a full synopsis (see Appendix B.3.9 for details).

Summary of Unit risk Estimation for Myeloid Leukemia

No unit risk estimates with adequate certainty were derived.

5.2.3. Selection of Unit Risk Estimate(s) for Derivation of the Inhalation Unit Risk

Table 5-48. Summary of unit risk estimates

Basis	Unit risk estimate (per ppm)		Unit risk estimate (per mg/m^3)	
Nasopharyngeal cancer in humans[a]	4.5×10^{-3} (mortality-based)	9.1×10^{-3} (incidence-based)	3.7×10^{-3} (mortality-based)	7.4×10^{-3} (incidence-based)
Animal nasal cancer estimate[b]	1.1×10^{-2} to 2.2×10^{-2}		8.9×10^{-3} to 1.8×10^{-2}	

[a]Based on entire cohort (exposed and unexposed) from Beane Freeman et al. (2013).

[b]Based on modeling of tumor incidence in rats incorporating results from multiple mechanistic and statistical models, including BBDR modeling (Monticello et al., 1996; Kerns et al., 1983). Range covers only the human extrapolations based on internal doses and BMR's ≤ 0.01 extra risk levels.

The unit risk estimate for NPC derived using data from the NCI occupational cohort and the nasal cancer unit risk estimate based on squamous cell carcinomas in animals are summarized in Table 5-48. As discussed previously, the NPC unit risk estimate based on data from the human occupational epidemiology study of the NCI updated by Beane Freeman et al. (2013) was selected over-estimates based on rodent cancer bioassay data, although these estimates were very similar (see more detailed comparison in Table 5-42). As described in prior sections, data were not available to quantify the potential risk for development of sinonasal cancers and the best available unit risk estimate for myeloid leukemia was considered too uncertain. Thus, **the unadjusted unit risk estimate used for the IUR is 7.4×10^{-6} per µg/m^3 (7.4×10^{-3} per mg/m^3)** based on human NPC incidence.

5.2.4. Adjustment for Potential Increased Early-life Susceptibility

When there is sufficient weight of evidence to conclude that a mutagenic MOA is operative in a chemical's carcinogenicity and there are inadequate chemical-specific data to assess age-specific susceptibility, as is the case for formaldehyde inhalation exposure-induced NPCs (see Section 3.2.5), EPA guidelines (U.S. EPA, 2005b) recommend the application of default age-dependent adjustment factors (ADAFs) to adjust for potential increased susceptibility from early-life exposure. In brief, the supplemental guidelines established ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005b). For risk assessments based on specific exposure assessments, the 10-fold and three-fold adjustments to the unit risk estimates are to be combined with age-specific exposure estimates when estimating cancer risks from early-life (<16 years of age) exposure.

These ADAFs were formulated based on comparisons of the ratios of cancer potency estimates from juvenile-only exposures to cancer potency estimates from adult-only exposures

from rodent bioassay data sets with appropriate exposure scenarios, and they are designed to be applied to cancer potency estimates derived from adult-only exposures. Thus, alternate life-table analyses were conducted for NPC to derive comparable adult-based unit risk estimates to which ADAFs would be applied to account for early-life exposure. In the NCI Poisson regression model, the RR estimates are adjusted for age, for the ages represented in the cohort. In deriving lifetime unit risk estimates, EPA generally extrapolates that relationship and assumes that RR is independent of age for all ages, for application of the RR exposure-response model across the full age range (0–85 years) considered in the life-table analysis. For the alternate life-table analyses, it was assumed that RR is independent of age for adults, which represent the lifestage for which the exposure-response data and the Poisson regression modeling results from the NCI cohort study specifically pertain, but that there is increased early-life susceptibility, based on the weight of evidence-based conclusion that formaldehyde carcinogenicity for NPC has a mutagenic MOA (see Section 3.2.5), which supersedes the more general assumption that RR is independent of age for all ages including children.

In the alternate analyses, exposure in the lifetable was taken to start at age 16 years, the age cut-point that was established in EPA's supplemental guidelines (U.S. EPA, 2005b), to derive an adult-exposure-only unit risk estimate. The adult-exposure-only unit risk estimate, when rescaled as described below, yields an adult-based unit risk estimate that is comparable to the unit risk estimate calculated from a typical (i.e., with adult exposures only) rodent bioassay and to which ADAFs can be applied in the standard way to account for early-life exposure.[71] Other than the age at which exposure was initiated, the life-table analysis is identical to that conducted for the results presented in Section 5.2.1. Using this approach yields adult-exposure-only unit risk estimates of 3.15×10^{-3} per ppm (2.56×10^{-6} per µg/m^3) for NPC mortality and 6.09×10^{-3} per ppm (4.95×10^{-6} per µg/m^3) for NPC incidence; these results are about 70 and 67%, respectively, of the unit risk estimates derived for lifetime exposure under the assumption of age independence across all ages.

When EPA derives unit risk estimates from standard rodent bioassay data, there is a blurring of the distinction between lifetime and adult-only exposures because the relative amount of time that a rodent spends as a juvenile is negligible (e.g., 9 of 104 weeks <9%) compared to its lifespan. [According to the supplemental guidelines, puberty begins around 5–7 weeks of age in rats and around 4–6 weeks in mice (U.S. EPA, 2005b), and Sengupta (2013) suggests that adulthood in

[71]In this assessment, ***adult-exposure-only unit risk estimates*** refer to estimates derived from the life-table analysis assuming exposure only for ages ≥16 years. The adult-exposure-only unit risk estimates are merely intermediate values in the calculation of adult-based unit risk estimates and should not be used in any risk calculations. ***Adult-based unit risk estimates*** refer to estimates derived after rescaling the adult-exposure-only unit risk estimates to a (70-year) lifetime, as described later. The adult-based unit risk estimates are intended to be used in ADAF calculations (U.S. EPA, 2005b) for the computation of extra risk estimates for specific exposure scenarios. Note that the unit risk estimates in this section, which are derived under an assumption of increased early-life susceptibility, supersede those that were derived in Section 5.2.1 under the assumption that RR is independent of age.

rats typically begins around postnatal day 63.] Thus, when exposure in a rodent is initiated at 5–8 weeks (most of the way through the juvenile period), as in the standard rodent bioassay, and the bioassay is terminated after 104 weeks of exposure, the unit risk estimate derived from the resulting cancer incidence data is considered a unit risk estimate from lifetime exposure, except when the ADAFs were formulated and are applied, in which case the same estimate is considered to reflect adult-only exposure. Yet, when adult exposures are considered in the application of ADAFs, the adult-exposure-only unit risk estimate is pro-rated over the full default human lifespan of 70 years, presumably because that is how adult exposures are treated when a unit risk estimate calculated in the same manner from the same bioassay exposure paradigm is taken as a lifetime unit risk estimate.

However, in humans, a greater proportion of time is spent in childhood (e.g., 16 of 70 years = 23%) (and for the purposes of unit risk estimates, exposure is considered to commence at birth), and the distinction between lifetime exposure and adult-only exposure cannot be ignored when human data are used as the basis for the unit risk estimates. Thus, adult-exposure-only unit risk estimates were calculated distinct from the lifetime estimates that were derived in Section 5.2.1 under the assumption of age independence for all ages. In calculating the adult-exposure-only unit risk estimates, RR is assumed to be independent of age for adulthood. Next, the adult-exposure-only unit risk estimates need to be rescaled to a 70-year lifespan to be used in the ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios in the standard manner, which includes pro-rating even adult-based unit risk estimates over 70 years. Thus, the adult-exposure-only unit risk estimates are multiplied by 70/54 to rescale the 54-year adult period of the 70-year default lifespan to 70 years. Then, for example, if a risk estimate were calculated for a less-than-lifetime exposure scenario involving exposure only for the full adult period of 54 years, the rescaled unit risk estimate would be multiplied by 54/70 in the standard calculation and the adult-exposure-only unit risk estimate would be appropriately reproduced. Without rescaling the adult-exposure-only unit risk estimates, the example calculation just described for exposure only for the full adult period of 54 years would result in a risk estimate 77% (i.e., 54/70) of that obtained directly from the adult-exposure-only unit risk estimates, which would be illogical. The rescaled adult-based unit risk estimates for NPC mortality and incidence for use in ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios are presented in Table 5-49.

Table 5-49. Adult-based unit risk estimates for nasopharyngeal cancer for use in ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios

NPC response	Adult-based unit risk estimate	
	(per ppm)	(per μg/m^3)
Mortality	4.08×10^{-3}	3.31×10^{-6}
Incidence	7.90×10^{-3}	6.42×10^{-6}

An example calculation illustrating the application of the ADAFs to the human-data-derived adult-based (rescaled as discussed above) NPC (incidence) unit risk estimate for formaldehyde for a lifetime exposure scenario is presented below. For inhalation exposures, assuming ppm equivalence across age groups, i.e., equivalent risk from equivalent exposure levels, independent of body size, the ADAF calculation is fairly straightforward. Thus, the ADAF-adjusted lifetime NPC unit risk estimate is calculated as illustrated in Table 5-50.

Table 5-50. NPC incidence risk from exposure to constant formaldehyde exposure level of 1 μg/m^3 from ages 0 to 70 years

Age group	ADAF	Adult-Based Unit risk (per μg/m^3)	Concentration (μg/m^3)	Duration adjustment	Partial risk[a]
0 to <2 years	10	6.42×10^{-6}	1	2 year/70 year	1.83×10^{-6}
2 to <16 years	3	6.42×10^{-6}	1	14 year/70 year	3.85×10^{-6}
≥16 years	1	6.42×10^{-6}	1	54 year/70 year	4.95×10^{-6}
				Total Lifetime (70 year) Risk:	**1.06×10^{-5}**

[a]The partial risk for each age group is the product of the values in columns 2–5 [e.g., $10 \times (6.42 \times 10^{-6}) \times 1 \times 2/70 = 1.83 \times 10^{-6}$], and the total risk is the sum of the partial risks.

This 70-year risk estimate for a constant exposure of 1 μg/m^3 is equivalent to a **lifetime inhalation unit risk (IUR) of 1.1×10^{-5} per μg/m^3 (1.3×10^{-2} per ppm)** based on NPC incidence, adjusted for potential increased early-life susceptibility, assuming a 70-year lifetime and constant exposure across age groups. Note that because of the use of the rescaled adult-based unit risk estimate, the partial risk for the ≥16 years' age group is the same as would be obtained for a 1 μg/m^3 constant exposure directly from the adult-exposure-only unit risk estimate of 4.95×10^{-6} per μg/m^3 that was presented above, as it should be. Recall that the adult exposure-only based unit risk estimate for NPC incidence for use in ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios is 6.42×10^{-6} per μg/m^3 (7.90×10^{-3} per ppm).

In addition to the uncertainties discussed in Section 5.2.1 for the IUR estimates based on human data, there are uncertainties in the application of ADAFs to adjust for potential increased early-life susceptibility. The ADAFs reflect an expectation of increased risk from early-life exposure to carcinogens with a mutagenic MOA (U.S. EPA, 2005b), but they are general adjustment factors and are not specific to formaldehyde. Overall, the application of ADAFs to the NPC unit risk estimate could be overestimating or underestimating the true extent of any increased early-life susceptibility in the total cancer unit risk estimate, although the quantitative impact of this source of uncertainty is likely to be small.

5.2.5. Final Inhalation Unit Risk Estimate and Uncertainties

The IUR, summarized in Table 5-51, reflects the estimate for NPC incidence alone. The NPC unit risk estimates are based on the modeling results of the association of cumulative formaldehyde exposure with NPC mortality in an occupational cohort followed by the NCI (Beane Freeman et al., 2013). The regression coefficient from the exposure-response model (log-linear Poisson regression model) was applied to age-specific cancer incidence rates from the SEER database using life-table methods to estimate the POD from which to derive the (upper-bound) unit risk estimate. The IUR estimate is typically expressed as the (upper-bound) increase in cancer risk expected as a function of a change of 1 μg/m^3.

EPA has concluded that early-life exposure to chemicals that are carcinogenic through a mutagenic MOA might present a higher risk of cancer than exposure during adulthood (U.S. EPA, 2005b). In this document, it was determined that formaldehyde-induced carcinogenicity of the URT is attributable, at least in part, to a mutagenic MOA (see Section 3.2.5). Therefore, the cancer unit risk estimate was adjusted by applying age-dependent adjustment factors (ADAFs). Table 5-51 can be used as a template for incorporating the ADAFs when addressing less-than-lifetime exposure scenarios. For exposure scenarios comprising primarily adult exposures, it may not be worth the additional complexity of calculating the ADAF-adjusted risk estimates, and one may choose to use the unadjusted cancer unit risk estimate presented in Table 5-51 with a "c" superscript, to calculate risk estimates in the standard way (i.e., without application of ADAFs).

Table 5-51. Inhalation unit risk[a, b]

Cancer type	Unit risk estimate (ppm^{-1})	ADAF-adjusted unit risk estimate (ppm^{-1})	Unit risk estimate $((\mu g/m^3)^{-1})$	ADAF-adjusted unit risk estimate $((\mu g/m^3)^{-1})$
Nasopharyngeal	0.0079[c]	0.013	6.4×10^{-6} [c]	1.1×10^{-5}

[a]The inhalation unit risk estimate is typically expressed as the (upper-bound) increase in cancer risk estimated for an exposure increase of 1 μg/m^3.
[b]The unit risk estimate is for cancer incidence.
[c]Adult-based (rescaled) unit risk estimate for NPC intended for the application of ADAFs.

Benchmark Response /Effective Concentration Estimates

For benefits analyses and certain other situations, "central" estimates of risk-per-unit dose may be preferred over (upper-bound) unit risk estimates. For nonlinear models, the POD-approach used by EPA for low-dose extrapolation, which is designed to distinguish between dose-response modeling in the observable range and inferences made about lower doses (U.S. EPA, 2005a) is not amenable to providing central estimates of risk at lower doses. Instead, the standard practice for IRIS assessments is to provide linear extrapolations of risk from the central estimate (here, the effective concentration [EC] estimate, which is the MLE of the exposure concentration associated with the benchmark response level of risk) corresponding to the POD, which is the lower bound on

the EC (i.e., the LEC estimate). Table 5-52 presents estimates of risk-per-unit dose linearly extrapolated from the EC (i.e., BMR/EC estimates).

Table 5-52. Summary of BMR/EC estimates[a]

Cancer type	BMR/EC estimate (ppm^{-1})	ADAF-adjusted BMR/EC estimate[b] (ppm^{-1})	BMR/EC estimate ($(\mu g/m^3)^{-1}$)	ADAF-adjusted BMR/EC estimate[b] ($(\mu g/m^3)^{-1}$)
Nasopharyngeal	0.0046[c]	0.0076	3.7×10^{-6}[c]	6.2×10^{-6}

[a]The BMR/EC estimates based on a longitudinal occupational mortality study (Beane Freeman et al., 2013) are all for cancer incidence. The BMR is 0.0005 extra risk for NPC. The EC value is the exposure concentration associated with the BMR based on the Poisson regression model and life-table analysis (see Section 5.2.1). The EC_{0005} for NPC was calculated from a life-table analysis of adult-exposure-only and then rescaled as discussed for the adult-based unit risk estimates in Section 5.2.4.
[b]See Section 5.2.4 for a discussion of the ADAF adjustments and how to apply the ADAFs for less-than-lifetime exposure scenarios.
[c]Adult-based (rescaled) BMR/EC estimate for NPC intended for the application of ADAFs (see Sectionn5.2.4).

Sources of Uncertainty Associated with the Inhalation Unit Risk

In general, the major areas of uncertainty in unit risk estimates arise from limitations in the database, e.g., limitations resulting in the need for interspecies and high- to low-dose extrapolation and limitations in information on human variability, including especially sensitive populations. The ideal database would provide sufficient data for the direct calculation of robust cancer (incidence) estimates for the general population at environmental levels of exposure.

The availability of suitable human data from which to derive unit risk estimates eliminates one of the major sources of uncertainty inherent in most unit risk estimates—the uncertainty associated with interspecies extrapolation. The NCI study used as the basis for the selected unit risk estimate is considered a well-conducted study for the purposes of deriving unit risk estimates. The NCI study is a large longitudinal cohort study that developed individual worker exposure estimates using detailed employment histories and formaldehyde concentration measurements. In addition to the detailed exposure assessment, the study used internal analyses and carefully considered potential confounding or modifying variables. Moreover, the NCI study comprises a large cohort that has been followed for a long time. Nonetheless, uncertainties in derived unit risk estimates are inevitable. The sources of uncertainty related to these limitations include use of a single study to derive the unit risk estimate, the inability to derive unit risk estimates for all potential cancer sites, and the derivation of (incidence) unit risk estimates for the general population from an occupational mortality study.

Overall confidence in the selected unit risk estimate is **medium**. Although some uncertainty exists with respect to the low-exposure extrapolation, the estimate is based on human data on NPC from a large, high-quality epidemiological study. Furthermore, the estimate is similar to the estimate derived for nasal cancers from rodent data. Notably, the IUR is an underestimate due to

the inability to quantitatively incorporate the risks posed for sinonasal cancers and myeloid leukemia.

Use of a single study to derive unit risk

A major limitation in the human database for formaldehyde is that there was only one independent[72] epidemiology study, the NCI study (Beane Freeman et al., 2009; Beane Freeman et al., 2013), with adequate exposure estimates for the derivation of unit risk estimates, as discussed above. Although the unit risk estimation from human data used data from one epidemiological study, it is a large longitudinal cohort study that included workers from 10 different industrial plants, in different states, that produced or used formaldehyde in different products. These factors decrease the likelihood that the results are overly influenced by uncontrolled confounding related to either location or production process. The NCI study developed individual worker exposure estimates using detailed employment histories and formaldehyde concentration measurements. In addition to the detailed exposure assessment, the study used internal comparisons of risk from exposure and gave careful consideration to potential confounding or modifying variables. Thus, although the unit risk estimates are based on a single study, there is *high* confidence in that study.

Inability to derive unit risk estimates for all potential cancer sites

The IUR is based on results for NPC from the NCI study; however, the NCI study did not support the computation of unit risk estimates for all the cancer sites with an evidence integration judgment of **evidence demonstrates** based on the totality of the evidence (i.e., sinonasal cancer and myeloid leukemia risk are unaddressed by the IUR), and the contribution by these cancers to the total cancer risk associated with formaldehyde inhalation is unknown. However, the potential impact by myeloid leukemia suggested by the best available unit risk estimate (myeloid leukemia plus other/unspecified leukemia) might increase the ADAF-adjusted IUR by almost four-fold.

Derivation of incidence estimates from mortality data

The NCI study is a retrospective mortality study, and cancer incidence data are unavailable for the cohort. Using mortality risk would markedly underestimate incidence for NPC because survival for this cancer type is relatively high. This limitation was addressed quantitatively in the calculation of cancer incidence risk estimates using the dose-response relationships from the mortality study, although as discussed above, it was necessary to make certain assumptions. It was assumed that cancer incidence and mortality have the same exposure-response relationship for formaldehyde exposure, which is reasonable for NPC at the low induction rates observed. Despite the uncertainties introduced, the incidence-based estimates are believed to be better estimates of cancer incidence risk than the mortality-based estimates, given the high survival rates for these

[72]Another study, by (Marsh et al., 1996; Marsh et al., 2002; Marsh et al., 2007a), also derived exposure estimates for the individual workers; however, it examined one of the 10 plants included in the NCI study, and thus, is not an independent study.

cancers. The estimates may under- or overpredict the true risk, although the quantitative impact would be relatively low because the incidence estimates are constrained by the relative incidence: mortality rates and necessarily bounded by the mortality estimates, which are about 50% of the incidence estimates.

Generalizability of estimates from a worker population

The NCI data represent an industrial worker cohort that is generally healthier than the U.S. population at large. Therefore, the unit risk estimates derived from the NCI worker cohort data could underestimate the cancer risk for the general population to an unknown extent, although the impact is expected to be relatively low for the majority of the population.

Industrial workers can also differ from the general population in factors other than health status. In terms of representing the general population in other ways, the NCI cohort was somewhat diverse, but the workers were predominantly white males (81%), then white females (12%), black males (7%), and black females (<1%), and they were all adults. Thus, for example, cancer risk in the general population could be underestimated if females are more susceptible than males, or overestimated if males are more susceptible than females. The potential for increased early-life susceptibility is addressed explicitly in Section 5.2.4.

High- to low-dose extrapolation

The availability of human data from this occupational epidemiology study for the derivation of quantitative cancer risk estimates removes the need to extrapolate from the findings of rodent bioassays, a major source of uncertainty in most risk assessments. However, another major source of uncertainty inherent in most unit risk estimates remains—the uncertainty associated with extrapolation from high (in this case occupational) exposures to lower (environmental or typical nonoccupational indoor) exposures. One factor contributing to uncertainty in the low dose-response comes from the potential for endogenous formaldehyde levels in respiratory tissue to reduce the uptake of the inhaled gas at low doses, as demonstrated in modeling efforts by Schroeter et al. (2014) and Campbell Jr et al. (2020). This would be expected to result in an overprediction of the true risk.

Although the actual exposure-response relationship at low-exposure levels is unknown, the use of linear low-dose extrapolation is supported by evidence that formaldehyde has a mutagenic MOA for NPC. The linear low-dose extrapolation from the 95% lower bound on the exposure level associated with the extra risk level serving as the benchmark response is considered to be a plausible upper bound on the risk at lower exposure levels. Use of the upper bound is a health-protective practice recommended in EPA guidelines (U.S. EPA, 2005a).

Additional Sources of Uncertainty Stemming from the NCI Study and Its Analysis

Other sources of uncertainty arise from the key epidemiological study and its analysis (Beane Freeman et al., 2013), including the retrospective estimation of formaldehyde exposures in

the cohort, the modeling of the epidemiological exposure-response data, the exposure metric for exposure-response analysis, and potential confounding or modifying factors.

Exposure estimates

With respect to exposure estimation, the NCI investigators (Stewart et al., 1986) conducted a detailed retrospective exposure assessment to estimate the individual worker exposures. Formaldehyde exposures were estimated for specific jobs/tasks based on monitoring data, discussions with workers and plant managers, and assessment by industrial hygienists. Individual worker estimates were derived for a variety of exposure metrics based on work histories. This exposure assessment was a major undertaking, involving over 100 person-months. Hauptmann et al. (2004) suggested that employment of such a detailed exposure assessment would tend to minimize exposure misclassification for average and cumulative exposure and duration of exposure but that peak exposure estimates could be more susceptible to misclassification because they were defined more qualitatively. In addition, the follow-up study did not account for exposures after 1980. Beane Freeman et al. (2013) suggest that any underestimation of total exposure resulting from the 1980 cutoff would be small because only 3.5% of all person-years were contributed by workers who were 65 years or younger and in exposed jobs in 1980 and because exposure levels were believed to have been much lower after 1980 than in earlier years.

Marsh et al. (1996) also estimated individual worker exposures at one of the 10 plants (Wallingford, Connecticut) studied by the NCI team. The Marsh et al. (1996) exposure estimates were about 10-fold lower than those derived by the NCI for the workers at the Wallingford plant. Marsh et al. (2002) hypothesized that "the NCI used data from several facilities to estimate exposures in a single facility." However, the NCI investigators maintain that they estimated exposures for each plant separately. While the exact reasons for such a large discrepancy are unclear, some differences in the assessment procedures which could have resulted in substantial differences in the estimates are apparent. First, according to Marsh et al. (1996), 91.7% of the white male Wallingford plant workers were specified as being exposed to formaldehyde in the NCI study, while only 83.3% were considered to have been exposed in the Marsh et al. (1996) analysis (it should be noted that these two cohorts of the Wallingford plant are not identical). Second, the NCI investigators (Stewart et al., 1986; Stewart et al., 1987) did their own exposure monitoring at all the plants, including the Wallingford facility, to standardize the data provided by the plants as well as to fill data gaps for certain jobs. There is no indication that Marsh et al. (1996) made any additional measurements themselves. Third, although the (Marsh et al., 1996; Marsh et al., 2002) papers are not entirely consistent on this point, those investigators apparently assumed that the job-specific exposures at the plant were essentially constant over the history of the plant, whereas the NCI team, based on interviews with plant personnel knowledgeable about equipment and process changes, assumed that past exposures were higher.

In any event, despite the discrepancies in the absolute exposure values, the relative exposures for both the (Marsh et al., 1996; Marsh et al., 2002) and NCI studies, as reflected in the

exposure-response relationships, are less subject to misclassification and are considered to be reliable. The Wallingford plant is just one of the 10 plants in the NCI study (representing 4,389 of the 25,619 workers in the NCI cohort), but if the Marsh et al. (1996) exposure estimates, which are roughly 10-fold lower than the NCI estimates, are closer to the actual exposures for those workers, then the true potency of formaldehyde could be greater than that suggested by the unit risk estimates calculated above based on the NCI data. Furthermore, if the NCI exposure values were significantly overestimated across all 10 plants, then the actual potency could be higher still.

In summary, EPA has high confidence in the NCI exposure assessment because of the large effort and high degree of expertise that NCI devoted to developing their detailed exposure estimates. Nonetheless, errors in retrospective exposure assignments are inevitable, and as a result, the unit risk estimates based on the NCI study could overpredict or underpredict the true risks to an unknown extent, although the discrepancy with the independently derived Marsh et al. (1996) exposure estimates suggests that the risks might be underestimated.

Exposure-response modeling

With respect to the exposure-response model, the log-linear Poisson regression model used by the investigators (Beane Freeman et al., 2009; Beane Freeman et al., 2013) for their trend tests (i.e., $RR = e^{\beta X}$) is generally an appropriate model for the analyses of epidemiological cancer data.[73] As discussed above, when age is well characterized and adjusted for, as it was in the NCI study, the results of the Poisson regression model should be essentially the same as results from the Cox proportional hazards model (Callas et al., 1998). The investigators reported efforts to check for deviations from log-linearity by adding a quadratic term to their models; none of these additional terms was statistically significant. However, the "true" underlying exposure-response relationships are unknown.

Even if the correct exposure-response model for NPC was known, there would be substantial uncertainty in estimating the model parameters because there are only 10 NPC deaths to model. Additionally, a 15-year lag was used for all the NCI solid cancer models. The actual best lag interval is unknown; the NCI investigators reported that lag intervals between 2 and 20 years yielded similar results.

Exposure metrics

Another potentially significant source of uncertainty is associated with the exposure metrics. With the log-linear model used for modeling the occupational data, the peak exposure metric gave the strongest exposure-response relationship between formaldehyde exposure and increased risk of NPCs. However, as discussed above, there are limitations in the peak exposure metric, and it is unclear how to extrapolate RR estimates based on peak exposure estimates to

[73]EPA relied on the results of the NCI exposure-response analyses and did not investigate other possible exposure-response models beyond those conducted by NCI.

meaningful estimates of lifetime extra risk of cancer from environmental exposure (i.e., extra risk from lifetime continuous low-level environmental exposures). The cumulative exposure metric also yielded nearly statistically significant exposure-response relationships (p = 0.07) and was used for the cancer risk calculations in this assessment. The "true" exposure metric best describing the toxicologically relevant dose of formaldehyde for carcinogenesis is unknown. If a peak-exposure type of metric is the best representative of the toxicologically relevant dose, this suggests that there are dose-rate effects in the exposure-response relationship for formaldehyde and cancer. If this is the case, the unit risk estimates presented here, which are based on a linear low-dose extrapolation, could overpredict the true risks.

Influence of confounding or effect modification

Beane Freeman et al. (2013) provided a detailed description of their evaluation of potential confounding and modifying factors in their analyses. The important factors of age, race, sex, calendar year, and pay category were taken into account in the Poisson regression and trend analyses. Furthermore, they used the low-exposure person-years, rather than the unexposed person-years, as their referent group to minimize any potential confounding effects resulting from differences in socioeconomic or other characteristics between exposed and unexposed workers. When the slope estimate (i.e., regression coefficient) for the exposed person-years only was used in the analyses, the unit risk estimate was essentially identical to that calculated from the slope estimate for all person-years (see Section 5.2.1).

In addition, these investigators evaluated routine respirator use, exposure to formaldehyde-containing particulates, durations of exposure to 11 other chemicals/substances in the plants (antioxidants, asbestos, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, wood dust, and benzene), and duration of employment as a chemist or laboratory technician. Only 133 workers ever routinely used a respirator (Hauptmann et al., 2003). RR estimates reportedly did not change substantially when adjusted for exposure to any of the other 10 chemicals/substances in the NPC (with cumulative exposure) analyses (Beane Freeman et al., 2013). Only one of the workers who died of NPC was identified as being exposed to wood dust, a recognized nasopharynx carcinogen. Adjusting for duration of time spent working as a chemist or laboratory technician did not substantially alter the results for NPC (Beane Freeman et al., 2013).

Beane Freeman et al. (2013) reported that their analyses showed no evidence of plant heterogeneity for the solid tumor results. In addition, six of the 10 deaths with NPC on the death certificate were from the Wallingford plant also studied by Marsh et al. (2007b).[74] Marsh et al. (2007a) hypothesized that the excess NPCs in the Wallingford plant could be due to external employment in metal-working industries. However, as noted by Beane Freeman et al. (2013), when

[74]In the previous follow-up of the NCI cohort by Hauptmann et al. (2004), 10 NPCs were reported on death certificates and included in NCI's SMR analyses, but one of these cases was apparently misclassified on the death certificate, so only nine cases were used to estimate the RRs in the internal comparison analyses; the misclassified case was not from the Wallingford plant (Beane Freeman et al., 2013).

Marsh et al. (2007a) adjusted for metal-working, the associations of NPC with formaldehyde for different metrics of exposure did not decrease.

Although smoking data were not available for the cohort, smoking is unlikely to explain the excesses in NPCs because there was no consistent increase for tobacco-related diseases, including lung cancer, across the same exposure metrics. No information was available on Epstein-Barr virus infections, a major risk factor for NPC, in the cohort.

In the reporting of the previous follow-up, Hauptmann et al. (2004) noted that each of the seven formaldehyde-exposed workers who had died of NPC was also exposed to particulates and neither of the two workers who died of NPC but were not exposed to formaldehyde was exposed to particulates. Due to the complete collinearity of formaldehyde and particulate exposures, one cannot estimate the exposure-response slope in workers exposed only to formaldehyde. The exposure-response relationships observed for formaldehyde within the NCI cohort and the associations observed between formaldehyde exposure and NPC in workers not exposed to particulates indicate that there is a formaldehyde effect independent of particulates; however, one cannot rule out a possible modifying effect of particulates, which might, for example, enhance delivery of formaldehyde to the nasopharynx.

In summary, uncontrolled confounding could theoretically result in unit risk estimates that are either under- or overestimated; nevertheless, given the careful consideration paid to potential confounding, any quantitative impacts are expected to be minimal. However, a possible modifying effect of particulate exposure on NPC cannot be ruled out, which could overestimate the risk from formaldehyde alone to an unknown extent.

Perspective on uncertainty in extrapolation using background cancer incidence and internal dose of endogenous and exogenous formaldehyde

EPA has considered estimates derived by Swenberg et al. (2011) and Starr and Swenberg (Starr and Swenberg, 2016) that are referred to by the authors as a "bottom-up" approach, to bound low-dose human cancer risks from formaldehyde exposure in a manner that only uses information regarding background incidence in the U.S. population of nasopharyngeal cancers (NPC), leukemia, and Hodgkin lymphoma; background (endogenous) metrics of internal formaldehyde dose in laboratory animals; and exogenous exposure to formaldehyde expressed in terms of an internal dose. The results in Starr and Swenberg (Starr and Swenberg, 2016) are updates, based on newer data, to those presented earlier in (Starr and Swenberg, 2013); however, the approach remains unchanged.

The data for the internal dose in these calculations were obtained from measurements in rats and monkeys of formaldehyde-induced DNA adducts experiments based on a highly sensitive mass spectrometry (MS) method using [$^{13}CD_2$]-formaldehyde (Yu et al., 2015a; Moeller et al., 2011; Lu et al., 2010a; Lu et al., 2011). The authors of these experiments conclude that their method can be used to distinguish whether formaldehyde-induced hydroxymethyl-DNA monoadducts, in particular the N^2-hydroxymethyl-dG (N2-hmdG) adduct, originate from endogenous or exogenous

sources of formaldehyde. The experiments quantified this mono adducts formed from both sources in various tissues of rats and monkeys: nasal cavity, bone marrow, mononuclear WBCs, spleen, and thymus (rats); nasal cavity and bone marrow (monkeys). These adduct measurements and data on the background incidences of NPC, Hodgkin lymphoma, and leukemia in the U.S. population were then used (Starr and Swenberg, 2016) to develop cancer risk estimates by attributing all the background incidences to endogenous formaldehyde, using the measured endogenous N2-hmdG adducts formed by formaldehyde in specific tissues as a biomarker of exposure. Their risk model assumes a linear relation between cancer incidence and N2-hmdG adduct levels over the concentration range of endogenous adducts as well as in the low-exposure range for exogenous adducts.

Risk estimates from this approach are claimed by the authors to produce conservative upper bounds primarily on the grounds that: (a) the method attributes all of the background risks of specific cancers to endogenous formaldehyde (based on N2-hmdG adducts); (b) lower confidence bounds on measured adduct levels are used; and (c) a linear relation is assumed between cancer incidence and N2-hmdG adduct levels over the endogenous range as well as in the low-exposure range of interest for exogenous exposure. Starr and Swenberg (2016) updated their previous estimates using better estimates of tissue specific endogenous and exogenous formaldehyde-DNA adducts in monkeys and an improved estimate of the DNA adduct elimination half-life in rats obtained by Yu et al. (2015a). The revised bottom-up estimates of risk at 1 ppm exposure concentration in (Starr and Swenberg, 2016) were 2.69×10^{-4} for NPC and $<1.24 \times 10^{-6}$ for leukemia. The authors then compared these values with the risk estimates in EPA's 2010 draft Toxicological Review that were derived by dose-response modeling of the epidemiological data and linearly extrapolating to lower doses from a POD (a lower bound on the concentration associated with the benchmark response). The authors determined that the 2010 draft EPA upper-bound risk estimates at 1ppm were higher than the adduct-based bottom-up estimates by 40-fold for NPC and over 45,000-fold for leukemia.

There is considerable uncertainty in extrapolating downward from high-dose animal or occupational data, particularly in the case of a dose-response that is highly curvilinear; thus, an approach that allows an upward linear extrapolation in lieu of the traditional downward extrapolation is appealing. The bottom-up approach uses cancer incidence in the general population and is independent of the tumor dose-response data (other than to identify the type of tumors of concern for analysis); therefore, it can potentially provide a perspective on the likely contribution of a specific MOA and on the uncertainty in risk estimates derived from higher dose data where other phenomena such as significant cytotoxicity and impact on DNA repair prior to mutations may be occurring.

EPA evaluated this bottom-up approach and identified scenarios under which this approach would yield an underestimate of the total (endogenous plus exogenous) risk for a specific cancer type, thereby concluding that the method does not necessarily provide an upper bound on the slope

of the dose-response at low exogenous exposures. Therefore, the approach in Starr and Swenberg (Starr and Swenberg, 2016) is not carried forward in the candidate unit risks presented in this assessment. Further details are elaborated in Appendix D.2.4. A critique of the approach in (Starr and Swenberg, 2013) along with a response by the authors were published by (Crump et al., 2014) and (Starr and Swenberg, 2014) respectively.

5.2.6. Previous IRIS Assessment: Inhalation Unit Risk

In the previous assessment (last updated in 1991), an inhalation unit risk of 1.3×10^{-5} per $\mu g/m^3$ was developed based on nasal SCCs in F344 rats from Kerns et al. (1983). The data were modeled from the estimates of the probability of death with tumor and its variance using a linearized multistage procedure.

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