

Chloroprene; CASRN: 126-99-8

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Chloroprene

File First On-Line 09/30/2010

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	message	09/30/2010
Inhalation RfC (I.B.)	yes	09/30/2010
Carcinogenicity Assessment (II.)	yes	09/30/2010

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name – Chloroprene
CASRN – 126-99-8
Section I.A. Last Revised – 09/30/2010

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at <http://www.epa.gov/iris/backgrd.html> for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of

substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

There was no previous oral RfD for chloroprene on IRIS.

I.A.1. CHRONIC ORAL RfD SUMMARY

There are no human data involving oral exposure to chloroprene. The only lifetime oral study in animals exposed rats to chloroprene at one dose (50 mg/kg/day) and only qualitatively reported noncancer effects ([Ponomarkov and Tomatis, 1980](#)).

Critical Effect	Point of Departure	UF	Chronic RfD
No oral studies available	N/A	N/A	Not derived

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Not applicable

I.A.3. UNCERTAINTY FACTORS

Not applicable

I.A.4. ADDITIONAL STUDIES/COMMENTS

Not applicable

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.8 \(PDF\)](#).

I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Not applicable

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document – ([U.S. EPA, 2010](#))

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to the EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Chloropene* (U.S. EPA, 2009). [To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition \(PDF\)](#).

I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name – Chloroprene
CASRN – 126-99-8
Section I.B. Last Revised – 09/30/2010

The RfC is 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. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarrespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. A summary of the evaluation of potential human carcinogenicity of chloroprene is contained in Section II of this file.

An inhalation assessment for chloroprene was not previously available on IRIS.

I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfC
Co-critical effects: increase in incidence of olfactory atrophy, alveolar hyperplasia, and splenic hematopoietic proliferation in male F344/N rats, female F344/N rats, and female B6C3F ₁ mice, respectively (NTP, 1998)	BMDL _{HEC} : 2 mg/m ³	100	2 × 10 ⁻² mg/m ³

*Conversion Factors and Assumptions. For the purposes of deriving an RfC for chloroprene, effects observed in male and female rats and male and female mice were evaluated from the 2 year chronic study by NTP (1998, 042076). Due to the nature and severity of the nasal degenerative effects (i.e., olfactory atrophy and necrosis), and the proximity of the BMDL₁₀ values to the observed LOAEL compared to other endpoints (Table 5-2), a BMR of 5% was considered appropriate for these olfactory endpoints. The nature of the observed nasal lesions potentially included the loss of Bowman's glands and olfactory axons in more severe cases. Effects that occur in the underlying lamina propria and basal layer of the olfactory epithelium may be indicative of more marked nasal tissue injury. For all other endpoints, a BMR of 10% was chosen as the response level. For the endpoints - olfactory atrophy, alveolar hyperplasia, and splenic hematopoietic cell proliferation - after rounding to one significant figure, the PODADJ resulted in a value of 2 mg/m³, which was used as the POD for deriving the RfC (U.S. EPA, 1995, 005992; U.S. EPA, 2000, 052150). The POD_{HEC} or BMDL_{HEC} was calculated by applying a DAF of 1.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

There is a limited body of information on the nonneoplastic toxicological consequences to humans who are exposed to chloroprene. Chloroprene has been reported to cause respiratory, eye, and skin irritation, chest pains, temporary hair loss, dizziness, insomnia, headache, and fatigue in occupationally exposed workers ([Nystrom, 1948](#)). Other effects reported include changes in the nervous system (lengthening of sensorimotor response to visual cues and increased olfactory thresholds), cardiovascular system (muffled heart sounds, reduced arterial pressure, and tachycardia), and hematological parameters (reduced RBC counts, decreased hemoglobin, erythrocytopenia, leucopenia, and thrombocytopenia) ([Sanotskii, 1976](#)).

In animals, toxicity in multiple organ systems, including respiratory tract, kidney, liver, spleen, and forestomach effects, was observed in short-term, subchronic, and chronic inhalation studies ([NTP \(1998\)](#)) [also reported by [Melnick et al. \(1999\)](#) and [Trochimowicz et al \(1998\)](#)].

From the available chronic studies, the [NTP \(1998\)](#) study was chosen as the principal study for the derivation of the RfC. This study utilized 50 animals per sex, per exposure group, a range of exposure concentrations based on the results of preliminary, shorter-duration studies (16 day and 13 weeks), and thoroughly examined chloroprene's observed toxicity in two species (Fischer rats and B6C3F₁ mice). [Trochimowicz et al. \(1998\)](#) was not chosen as the principal study due to concerns regarding high mortality observed in the low dose male and female rats due to the failure in the exposure chamber ventilation system. The high mortality in this dose group prevented histopathological examination of most organ systems (except for liver samples) and precluded any firm conclusions on dose-response characteristics from being drawn. Also, a lack of adverse effects at similar exposure levels as the [NTP \(1998\)](#) study ([Trochimowicz et al. \(1998\)](#); see Section 4.7.2.2 for discussion of potential causes of differences in observed toxicity between the NTP and Trochimowicz studies) was observed and influenced the choice to not select the [Trochimowicz et al. \(1998\)](#) as the principal study.

In the 2-year ([NTP, 1998](#)) inhalation study of chloroprene in male and female rats and mice, groups were exposed to target concentrations of 0, 12.8, 32, and 80 ppm chloroprene. Actual chamber concentrations achieved were 0, 12.8 ± 0.4, 31.7 ± 1.1, and 79.6 ± 1.6 and 0, 12.7 ± 0.4, 31.9 ± 0.9, and 79.7 ± 1.7 ppm chloroprene for rats and mice, respectively. All animals were observed twice daily, and body weights were recorded initially, weekly through week 12, approximately every 4 weeks from week 15 through week 91, and every 2 weeks until the end of the study. Clinical findings were recorded initially at weeks 4, 8, 12, and 15, every 4 weeks through week 91, and every 2 weeks until the end of the study. Complete necropsy and microscopic examinations were performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, heart, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidney, liver, lung, lymph nodes (bronchial,

mandibular, mediastinal, and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. A LOAEL of 12.8 ppm was identified from this study based on the observation of nonneoplastic lesions in multiple organ systems in animals exposed to the lowest exposure concentration.

From the [NTP \(1998\)](#) study, all nonneoplastic lesions that were statistically increased in rats or mice at the low- or mid-exposure concentration (12.8 or 32 ppm) compared to chamber controls, or demonstrated a suggested dose-response relationship in the low- or mid-exposure range in the absence of statistical significance, were considered candidates for the critical effect. The candidate endpoints included: alveolar epithelial hyperplasia, olfactory chronic inflammation, olfactory necrosis, olfactory epithelium atrophy, olfactory basal cell hyperplasia, olfactory metaplasia, and kidney (renal tubule) hyperplasia in rats; and bronchiolar hyperplasia, olfactory suppurative inflammation, kidney (renal tubule) hyperplasia, forestomach epithelial hyperplasia, and splenic hematopoietic cell proliferation in mice.

Methods of Analysis. This assessment used benchmark dose (BMD) methodology, where possible, to estimate a POD for the derivation of an RfC for chloroprene. Data for some endpoints were not amenable to BMD modeling; therefore the NOAEL/LOAEL approach was used for these data. A BMR of 10% extra risk is typically chosen as a standard response level for dichotomous data and is recommended for the BMR when using dichotomous models to facilitate a consistent basis of comparison across assessments and endpoints ([U.S. EPA, 2000](#)). For the data from the [NTP \(1998\)](#) study, a BMR of 10% extra risk was used initially. In addition to the incidence of the endpoints, the [NTP \(1998\)](#) study also reported the severity scores for individual animals in each dose group, thus making it possible to determine whether the endpoints were increasing in severity as well as incidence with dose.

Due to the nature and severity of the nasal degenerative effects (i.e., olfactory atrophy and necrosis), and the proximity of the BMDL₁₀ values to the observed LOAEL compared to other endpoints (Table 5-2), a BMR of 5% was considered appropriate for these olfactory endpoints. The nature of the observed nasal lesions potentially included the loss of Bowman's glands and olfactory axons in more severe cases. Effects that occur in the underlying lamina propria and basal layer of the olfactory epithelium may be indicative of more marked nasal tissue injury. For all other endpoints, a BMR of 10% was chosen as the response level.

Using BMD modeling, duration and dosimetric adjustments, increased incidence of olfactory atrophy, alveolar hyperplasia, and splenic hematopoietic cell proliferation in male F344/N rats, female F344/N rats, and female B6C3F₁ mice, respectively, were identified as co-critical

effects. For these endpoints the $BMDL_{HEC}$ resulted in a value of 2 mg/m^3 , which was used as the point of departure for deriving the RfC.

I.B.3. UNCERTAINTY FACTORS

$$UF = 100 = 3 (UF_A) \times 10 (UF_H) \times 1 (UF_S) \times 1 (UF_L) \times 3 (UF_D)$$

An UF of 3 ($10^{1/2} = 3.16$, rounded to 3) was applied for interspecies extrapolation (UF_A) to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability). This uncertainty factor is comprised of two separate and equal areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, toxicokinetic uncertainty was accounted for by the calculation of a human equivalent concentration by the application of a dosimetric adjustment factor as outlined in the RfC methodology ([U.S. EPA, 1994](#)). As the toxicokinetic differences are thus accounted for, only the toxicodynamic uncertainties remain, and a UF of 3 is retained to account for this residual uncertainty.

An UF of 10 was applied to account for variation in susceptibility among members of the human population (i.e., interindividual variability; UF_H). Only limited information is available to assess potential variability in human susceptibility, such as data regarding the human variability in expression of enzymes involved in chloroprene metabolism (e.g., metabolic activation via p450 isoform CYP2E1) ([Bernauer et al., 2003](#)). No data is currently available on the toxicodynamic variability within the human population. Therefore, in accordance with EPA policy ([U.S. EPA, 2002](#)), the default 10-fold UF_H is applied and presumed to account for variations in susceptibility within the human population.

An UF_S was not needed to account for subchronic-to-chronic extrapolation because a chronic inhalation study is being used to derive the chronic RfC. An UF for LOAEL-to-NOAEL extrapolation was not applied because the current approach is to address this factor as one of the considerations in selecting a BMR for benchmark dose modeling. In this case, a BMR of 5% change in olfactory atrophy and a BMR of 10% change in alveolar hyperplasia and splenic hematopoietic cell proliferation was selected under an assumption that these BMR levels represent a minimal biologically significant change for these endpoints.

An UF of 3 was applied to account for deficiencies in the database. The major strength of the database is the observation of exposure-response effects in multiple organ systems in a well-designed chronic inhalation study that utilized 50 animals per sex per dose group, a range of doses based on the results of preliminary, shorter-duration studies (16 day and 13 weeks), and thorough examination of the toxicity of chloroprene in two species (rat and mouse). The database further contains another chronic inhalation bioassay investigating outcomes in

another species (hamster), and well-designed embryotoxicity, teratological, and reproductive toxicity studies. The database also contains subchronic studies and chronic studies observing potential neurotoxic and immunotoxic effects. A limitation in the database is the lack of a full two-generation reproductive toxicity study ([the Appelman and Dreef van der Meulen \(1979\)](#) unpublished study exposed F₀ and F₁ rats to chloroprene, but did not allow the F₁ rats to mate).

I.B.4. ADDITIONAL STUDIES/COMMENTS

The results of BMD modeling indicated that olfactory atrophy in the male rat, alveolar hyperplasia in the female rat, and splenic hematopoietic cell proliferation in the female mouse were the most sensitive endpoints, with a POD_{ADJ} values of 2.3, 2.1, and 2.1 mg/m³, respectively. For these endpoints, after rounding to one significant figure, the POD_{ADJ} resulted in a value of 2 mg/m³, which was used as the point of departure for deriving the RfC.

Chloroprene is a relatively water-insoluble, nonreactive gas, with an approximate blood:air partition coefficient of less than 10 (see Table 3-1), that induces a range of nasal, thoracic, and systemic noncancer effects. Water-insoluble, nonreactive chemicals typically do not partition greatly into the aqueous mucus coating of the upper respiratory system. Rather, they tend to distribute to the lower portions of the respiratory tract where larger surface areas and the thin alveolar-capillary barrier facilitate uptake ([Medinsky and Bond, 2001](#)). The observation of systemic (i.e., nonrespiratory) effects resultant from chloroprene exposure clearly indicates the compound is absorbed into the bloodstream and distributed throughout the body. Further, the distribution of lesions (olfactory effects, but no respiratory mucosal damage) is indicative of a critical role for blood borne delivery and *in situ* metabolic activation. The absence of respiratory mucosal injury suggests that direct reactivity of the parent compound is not likely involved. Rather, the pattern of respiratory effects seen following chloroprene exposure is consistent with what is known about its metabolism and the expression of cytochrome P450 enzymes in the olfactory mucosa and lower respiratory tract in rats. The proposed mode of action of chloroprene involves the conversion of the parent compound into its reactive epoxide metabolite by P450 isoform CYP2E1. The olfactory mucosa of rats has been shown to specifically express CYP2E1 at levels more similar to hepatic levels than any other nonhepatic tissue examined ([Thornton-Manning and Dahl, 1997](#)). [Himmelstein et al. \(2004\)](#) observed that the microsomal fraction of rat lung homogenates was active in the metabolic oxidation of chloroprene into (1-chloroethenyl)oxirane at levels between 10-30% that of liver microsomes. *In situ* conversion of chloroprene into its highly reactive epoxide metabolite in the olfactory epithelia and lower respiratory tract may facilitate its uptake in these tissues and explain a portion of its biological activity in those regions. Evidence for metabolic activation in the respiratory tract combined with the observation that chloroprene induces effects in organ systems distal to the portal-of-entry, consistent with the parent compound's water-insoluble

and nonreactive chemical properties, suggest that chloroprene's principal mode of action does not involve direct reactivity of the parent compound at the portal of entry.

Consequently, the selected critical effects, olfactory atrophy, alveolar hyperplasia, and splenic hematopoietic cell proliferation, are assumed to primarily result from systemic distribution and the human equivalent concentration (HEC) for chloroprene was calculated by the application of the appropriate dosimetric adjustment factor (DAF) for category 3 gases (in this case 1 for systemic effects), in accordance with the U.S. EPA RfC methodology ([U.S. EPA, 1994](#)).

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.8 \(PDF\)](#).

I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Study – High

Database – Medium to High

RfC – Medium to High

Confidence in the principal study ([NTP, 1998](#)) is judged to be high as it was a well-designed study using two test species (rats and mice) with 50 animals per dose group. This study appropriately characterizes a range of chloroprene-induced nonneoplastic and neoplastic lesions, as determined by independent, external peer review. In addition, the key histopathological lesions observed are appropriately described, and suitable statistical analysis is applied to all animal data.

The co-critical noncancer effects, olfactory atrophy in the male rat, alveolar hyperplasia in the female rat, and splenic hematopoietic cell proliferation in the female mouse, is consistent with what is known about the metabolism and systemic distribution of chloroprene.

Confidence in the overall database specific to chloroprene is medium to high. The major strength of the database is the observation of dose-response effects in multiple organ systems in a well-designed chronic inhalation study that utilized 50 animals per sex per dose group, a range of doses based on the results of preliminary, shorter-duration studies (16 day and 13 weeks), and thorough examination of toxicity of chloroprene in two species (rat and mouse). The database further contains another chronic inhalation bioassay investigating outcomes in another species (hamster), and well-designed embryotoxicity, teratological, and reproductive toxicity studies. The database also contains subchronic studies and chronic studies observing potential neurotoxic and immunotoxic effects. A major limitation in the database is the lack of a complete two-generation reproductive toxicity study.

Therefore, confidence in the RfC is judged to be medium to high.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6](#) (PDF).

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document – ([U.S. EPA, 2010](#))

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Chloroprene* ([U.S. EPA, 2010](#)). ***[To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition](#) (PDF)***

I.B.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name – Chloroprene
CASRN – 126-99-8
Section II. Last Revised – 09/30/2010

This section provides information on the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005](#)) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* ([U.S. EPA, 2005](#)). The quantitative risk estimates are derived from the application of a low-

dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The “oral slope factor” is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a “unit risk” is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per µg/m³ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

A cancer assessment for chloroprene was not previously available on IRIS.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005](#)), there is evidence that chloroprene is “*likely to be carcinogenic to humans*” based on: (1) statistically significant and dose-related information from an [NTP \(1998\)](#) chronic inhalation bioassay demonstrating the early appearance of tumors, development of malignant tumors, and the occurrence of multiple tumors within and across animal species; (2) evidence of an association between liver cancer risk and occupational exposure to chloroprene; (3) suggestive evidence of an association between lung cancer risk and occupational exposure; (4) the proposed mutagenic mode of action; and (5) structural similarities between chloroprene and known human carcinogens, butadiene and vinyl chloride.

According to [NTP \(1998\)](#), there is clear evidence of carcinogenicity in the F344/N rat and B6C3F₁ mouse due to lifetime inhalation exposure to chloroprene. In rats, increased incidences of neoplastic lesions primarily occurred in the oral cavity (both sexes), lung (males only), kidney (both sexes), and mammary gland (females). In mice, increased incidences in neoplasms occurred in the lungs (both sexes), circulatory system (all organs, both sexes), Harderian gland (both sexes), forestomach (both sexes), liver (females only), skin (females only), mammary gland (females only), and kidney (males only).

Among epidemiological studies investigating the association between cancer mortality and chloroprene exposure in eight occupational cohorts, four studies observed statistically significant associations (i.e., two- to five-fold increased risk) between liver/biliary passage cancer cases and chloroprene exposure ([Bulbulyan et al., 1998](#); [Bulbulyan et al., 1999](#); [Leet and Selevan, 1982](#); [Li et al., 1989](#)). An increased risk of lung cancer incidence and mortality was observed in a few studies ([Bulbulyan et al., 1998](#); [Colonna and Laydevant, 2001](#); [Leonard et al., 2007](#); [Li et al., 1989](#); [Pell, 1978](#)), although few statistically significant associations were reported.

Compelling evidence for the hypothesized mutagenic mode of action for chloroprene includes: 1) chloroprene, like butadiene and isoprene, is metabolized to epoxide intermediates ([Bartsch et al., 1979](#); [Cottrell et al., 2001](#); [Himmelstein et al., 2001](#); [Hurst and Ali, 2007](#)); 2) chloroprene forms DNA adducts via its epoxide metabolite ([Munter et al., 2007](#); [Munter, et al., 2002](#)), and is a point mutagen in vitro (in some but not all bacterial assays) and in vivo ([Bartsch et al., 1979](#); [Drevon and Kuroki, 1979](#); [Foureman et al., 1994](#); [Himmelstein et al., 2001](#); [NTP, 1998](#); [Shelby and Witt, 1995](#); [Vogel, 1979](#); [Westphal et al., 1994](#); [Willems, 1978](#); [Willems, 1980](#)); 3) observation of the genetic alterations (base-pair transversions) in proto-oncogenes in chloroprene-induced lung, Harderian gland, and forestomach neoplasms in mice ([NTP, 1998](#); [Sills et al., 1999](#); [Sills et al., 2001](#); [Ton et al., 2007](#)); and 4) similarities in tumor sites and sensitive species between chloroprene and butadiene in chronic rodent bioassays ([NTP \(1998\)](#) and [Melnick et al. \(1999\)](#), respectively).

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.8 \(PDF\)](#).

II.A.2. HUMAN CARCINOGENICITY DATA

A number of occupational cohort studies have examined cancer mortality and incidence among workers exposed to chloroprene monomer and/or polychloroprene latex in the United States, Russia (Moscow), Armenia, France, China, and Ireland ([Bulbulyan et al., 1998](#); [Bulbulyan et al., 1999](#); [Colonna and Laydevant, 2001](#); [Leet and Selevan, 1982](#); [Li et al., 1989](#); [Marsh et al., 2007](#); [Marsh et al., 2007](#); [Pell, 1978](#); [Romazini et al., 1992](#)).

Despite these differences in occupational exposure to chloroprene and other chemicals, four of the cohorts with observed liver/biliary passage cancer cases showed statistically significant associations (i.e., two- to five-fold increased risk) with chloroprene exposure. Four mortality studies reported SMRs of 339, 240, 242, 571 when compared to external populations ([Bulbulyan et al., 1998](#); [Bulbulyan et al., 1999](#); [Leet and Selevan, 1982](#); [Li et al., 1989](#)). Although sample size and statistical power were limited (thus limiting the precision of risk estimates), [Bulbulyan et al. \(1998; 1999\)](#) observed significantly elevated relative risk estimates for liver cancer incidence and mortality among intermediate and highly exposed workers. The study involving four plants (including the Louisville Works plant included in the [Leet and Selevan \(1982\)](#) study) by [Marsh et al. \(2007\)](#), which had the largest sample size and most extensive exposure assessment, also observed increased relative risk estimates for liver cancer in relation to cumulative exposure in the plant with the highest exposure levels (trend p value = 0.09, RRs 1.0, 1.90, 5.10, and 3.33 across quartiles of exposure, based on 17

total cases). Although not statistically significant, these findings are consistent in magnitude with results (RR range: 2.9-7.1) detected in two other studies for high and intermediate cumulative exposures ([Bulbulyan et al., 1998](#); [Bulbulyan et al., 1999](#)).

The EPA guidelines for carcinogen risk assessment ([U.S. EPA, 2005](#)) advocate the use of “criteria” proposed by [Hill \(1965\)](#) to assess causality. There exist a number of methodological limitations in the chloroprene epidemiologic studies that may preclude drawing firm conclusions regarding those criteria: lack of control of personal confounders and risk factors associated with the outcomes in question, imprecise exposure ascertainment resulting in crude exposure categories, incorrect enumeration of cases leading to misclassification errors, limited sample sizes, and the healthy worker effect. However, the temporality of exposure prior to occurrence of liver cancer, strength of association, consistency, suggestive biological gradient, and biological plausibility provide some evidence for carcinogenicity of chloroprene in humans.

II.A.3. ANIMAL CARCINOGENICITY DATA

There is clear evidence of carcinogenicity in the F344/N rat and B6C3F₁ mouse due to lifetime inhalation exposure to chloroprene ([NTP, 1998](#)). The mouse is regarded as the most sensitive species because tumor incidence and multisite distribution were greater than with the rat. There was decreased survival in chloroprene-exposed rats and mice, and survival in mice was significantly associated with the burden of neoplastic lesions. Mortality in rats was likely due to overt toxicity across many organ systems. In rats, statistically significantly increased incidences of neoplastic lesions occurred in the oral cavity (papillomas or carcinomas, males and females), kidney (renal tubule adenomas or carcinomas, males), thyroid gland (adenomas or carcinomas, males) and mammary gland (fibroadenomas, females). In mice, increased incidences in neoplasms occurred in the lungs (adenomas or carcinomas, males and females), circulatory system (hemangiomas or hemangiosarcomas, all organs, males and females), Harderian gland (adenomas or carcinomas, males and females), liver (adenomas or carcinomas, females), skin and mesentery (sarcomas, females), mammary gland (carcinomas, females), and kidney (renal tubule adenomas or carcinomas, males). The observation of that chloroprene is more potent in inducing tumors in B6C3F₁ mice compared to F344/N rats may be due to species differences in metabolism. The activity of liver or lung microsomal oxidation of chloroprene and the formation of (1-chloroethenyl)oxirane was higher in the mouse than the rat ([Himmelstein et al. \(2004\)](#)). Additionally, the activity of epoxide hydrolase in liver microsomes was greater in the rat compared to the mouse (epoxide hydrolase activity was approximately equal in lung microsomes). The observation that formation of the reactive epoxide metabolite of chloroprene is greatest in the mouse lung may explain the observation that chloroprene exposure induces lung tumors in mice, but not rats.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

The inhalation study by [Dong et al. \(1989\)](#) found that a 7-month exposure of the Kunming strain of albino mice, a strain reported to have a low spontaneous rate of lung tumor formation, resulted in a chloroprene-associated increase in lung tumors. Although quality assurance procedures regarding histopathology were not reported, these study results are considered to support the findings in the B6C3F₁ mice in the [NTP \(1998\)](#) chronic bioassay.

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

II.B.1. SUMMARY OF RISK ESTIMATES

II.B.1.1. ORAL SLOPE FACTOR

In the only long-term oral cancer study (an F₁ generation of inbred BD-IV rats given weekly doses of 50 mg/kg chloroprene by gavage), no significant neoplastic effects were reported ([Ponomarkov and Tomatis, 1980](#)). The number of tumor-bearing animals was similar to controls. Therefore, no oral slope factor was derived for chloroprene.

II.B.1.2. DRINKING WATER UNIT RISK

N/A

II.B.1.3. EXTRAPOLATION METHOD

N/A

II.B.2. DOSE-RESPONSE DATA

N/A

II.B.3. ADDITIONAL COMMENTS

N/A

II.B.4. DISCUSSION OF CONFIDENCE

N/A

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1. SUMMARY OF RISK ESTIMATES

II.C.1.1. INHALATION UNIT RISK

Given the multiplicity of tumor sites observed in female mice exposed to chloroprene for 2 years (NTP, 1998), the derivation of the inhalation unit risk of 3.0×10^{-4} per $\mu\text{g}/\text{m}^3$ is based on the incidence of tumors in multiple organ systems: alveolar/bronchiolar adenoma or carcinoma; hemangioma/hemangiosarcoma (all organs); mammary gland adenocarcinoma, carcinoma, or adenoacanthoma; forestomach squamous cell papilloma or carcinoma; hepatocellular adenoma or carcinoma; Harderian gland adenoma or carcinoma; skin sarcoma; and Zymbal's gland carcinoma (NTP, 1998), (NTP, 1998), (NTP, 1998), (NTP, 1998). The dose metric used in the current estimate of the human equivalent concentration (HEC) is the applied or external dose because the only PBPK model available (Himmelstein et al., 2004) was determined to be inadequate for application for calculation of internal dose metrics or interspecies dosimetry extrapolations. As there is evidence that chloroprene and/or its metabolite are distributed systemically (i.e., the observation of tumors in multiple organ systems), there is the potential that chloroprene is redistributed to the lungs. For this reason, and because of chloroprene's low water solubility, low reactivity and distribution of lesions, it is most appropriately treated as a Category 3 gas for which blood-borne delivery plays a critical role. Hence, as was done for noncancer lesions, all tumors were treated as systemic effects and, since the blood:air partition coefficient for chloroprene is greater in rats than in humans, a DAF of 1.0 was applied. (see Section 5.2.3 of the *Toxicological Review of Chloroprene* (U.S. EPA, 2010) for additional discussion).

The initial composite unit risk of 2.7×10^{-4} per $\mu\text{g}/\text{m}^3$ is based from individual unit risks derived from BMDL_{HEC} values from the individual tumor types observed in female mice. The BMDL_{HEC} values are the 95% lower bound on the exposure associated with a defined extra cancer risk. The individual unit risks were calculated by dividing the risk (as a fraction) by the BMDL_{HEC} , and represent an upper bound, continuous lifetime exposure risk estimate. For example, for hepatocellular adenoma or carcinomas:

$\text{BMDL}_{\text{HEC}10}$, lower 95% bound on exposure at 10% extra risk: $1.58 \times 10^3 \mu\text{g}/\text{m}^3$

$\text{BMD}_{\text{HEC}10}$, central estimate of exposure at 10% extra risk: $2.73 \times 10^3 \mu\text{g}/\text{m}^3$

The individual unit risk for this tumor: $0.1/1.58 \times 10^3 \mu\text{g}/\text{m}^3 = 6.3 \times 10^{-5}$ per $\mu\text{g}/\text{m}^3$

The initial composite risk was calculated using the following steps (detailed in Section 5.4.4 and Appendix C of the *Toxicological Review of Chloroprene* ([U.S. EPA, 2010](#)):

- It was assumed that the tumor types associated with chloroprene exposure were statistically independent - that is, that the occurrence of a hemangiosarcoma, for example, was not dependent on whether there was a forestomach tumor. This assumption cannot currently be verified and if not correct could lead to an overestimate of risk from summing across tumor sites. However, [NRC \(1994\)](#) argued that a general assumption of statistical independence of tumor-type occurrences within animals was not likely to introduce substantial error in assessing carcinogenic potency from rodent bioassay data.
- The models previously fitted to estimate the BMDs and BMDLs were used to extrapolate to a lower level of risk (R) where the BMDs and BMDLs were in a linear range. For these data a 1×10^{-2} risk (R = 0.01) was generally the lowest risk necessary. Although this step appears to differ from the explicit recommendation of the cancer guidelines ([U.S. EPA, 2005](#)) to estimate cancer risk from a POD “near the lower end of the observed range, without significant extrapolation to lower doses,” this method is recommended in the cancer guidelines as a method for combining multiple extrapolations. A sensitivity analysis considering risks nearer the lower end of the observed ranges for each tumor type (data not shown) indicated that the composite risk was essentially the same (to 2 significant digits) whether or not the individual risks were estimated in the region of 10^{-2} risk or near the PODs.
- The central tendency estimates of unit potency (that is, risk per unit of exposure) at each BMD_{01} , estimated by $0.01/\text{BMD}_{01}$, were summed across the sites listed in Table 5-6 for male mice and similarly across the sites for female mice listed in Table 5-7 (see Appendix C, Table C-5 of the *Toxicological Review of Chloroprene* ([U.S. EPA, 2010](#))).
- The composite unit risk, which is a 95% upper confidence limit (UCL), was calculated by assuming a normal distribution for the individual risk estimates and deriving the variance of the risk estimate for each tumor site from its 95% UCL ($0.01/\text{BMDL}_{01}$) and MLE ($0.01/\text{BMD}_{01}$) according to the following formula:

$$\begin{aligned} 95\% \text{ UCL} &= \text{MLE} + 1.645 \times \text{SD} \text{ or} \\ 0.01/\text{BMDL}_{01} &= 0.01/\text{BMD}_{01} + 1.645 \times \text{SD} \end{aligned}$$

rearranged to:

$$\text{SD} = (0.01/\text{BMDL}_{01} - 0.01/\text{BMD}_{01})/1.645$$

where 1.645 is the t-statistic corresponding to a one-sided 95% confidence interval and >120 degrees of freedom, and the standard deviation (SD) is the square root of the variance of the MLE. The variances (variance = SD^2) for each site-specific estimate were summed across tumor sites to obtain the variance of the sum of the MLEs. The 95% UCL on the sum of the individual MLEs was calculated from expression (1) using the variance of the MLE to obtain the relevant SD ($SD = \text{variance}^{1/2}$).

The resulting composite unit risk for all tumor types for female mice was 2.7×10^{-4} per $\mu\text{g}/\text{m}^3$. The recommended composite upper bound estimate on human extra cancer risk from continuous lifetime exposure to chloroprene is 3×10^{-4} per $\mu\text{g}/\text{m}^3$, rounding the composite risk for female mice above to one significant digit. This unit risk should not be used with continuous lifetime exposures greater than $600 \mu\text{g}/\text{m}^3$ ($0.6 \text{ mg}/\text{m}^3$), the human equivalent POD for the female lung tumors, because the observed dose-response relationships do not continue linearly above this level and the fitted dose-response models better characterize what is known about the carcinogenicity of chloroprene.

Because a mutagenic mode of action for chloroprene carcinogenicity is supported by in vivo and in vitro data and relevant to humans (see Section 4.7.3.1 in the *Toxicological Review of Chloroprene* ([U.S. EPA, 2010](#)), and in the absence of chemical-specific data to evaluate the differences in susceptibility, increased early-life susceptibility is assumed and the age-dependent adjustment factors (ADAFs) should be applied, as appropriate, along with specific exposure data in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility From Early-Life Exposure to Carcinogens* ([U.S. EPA, 2005](#)). The inhalation unit risk of 3×10^{-4} per $\mu\text{g}/\text{m}^3$, calculated from data for adult exposures, does not reflect presumed early-life susceptibility for this chemical. Example evaluations of cancer risks based on age at exposure are given in Section 6 of the *Supplemental Guidance*.

The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current default 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, 2005](#)). The 10-fold and threefold adjustments in slope factor are to be combined with age specific exposure estimates when estimating cancer risks from early life (< 16 years age) exposure to chloroprene.

To illustrate the use of the ADAFs established in the *Supplemental Guidance* ([U.S. EPA, 2005](#)), sample calculations are presented for a lifetime risk estimate for continuous exposure from birth with a life expectancy of 70 years. The ADAFs are first applied to obtain risk estimates for continuous exposure over the three age groups:

Risk for birth through < 2 yr = 3×10^{-4} per $\mu\text{g}/\text{m}^3 \times 10 \times 2\text{yr}/70\text{yr} = 8.6 \times 10^{-5}$ per $\mu\text{g}/\text{m}^3$

Risk for ages 2 through < 16 = 3×10^{-4} per $\mu\text{g}/\text{m}^3 \times 3 \times 14\text{yr}/70\text{yr} = 1.8 \times 10^{-4}$ per $\mu\text{g}/\text{m}^3$

Risk for ages 16 until 70 = 3×10^{-4} per $\mu\text{g}/\text{m}^3 \times 1 \times 54\text{yr}/70\text{yr} = 2.3 \times 10^{-4}$ per $\mu\text{g}/\text{m}^3$

To calculate the lifetime risk estimate for continuous exposure from birth for a population with default life expectancy of 70 years, the risk associated with each of the three relevant time periods is summed:

$$\text{Risk} = 8.6 \times 10^{-5} + 1.8 \times 10^{-4} + 2.3 \times 10^{-4} = 5.0 \times 10^{-4} \text{ per } \mu\text{g}/\text{m}^3$$

II.C.1.2. AIR CONCENTRATIONS AT SPECIFIED RISK LEVELS

Air concentrations at specified risk levels are not provided for chloroprene. Since chloroprene is carcinogenic by a mutagenic mode of action and increased susceptibility is assumed for early-life exposures (<16 years of age), the concentrations at specified risk levels will change based on the age of the individuals in the exposed group. Risk assessors should use the unit risk and current EPA guidance to assess risk based on site-specific populations and exposure conditions. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/.

II.C.1.3. EXTRAPOLATION METHOD

Time-to-tumor Modeling. For the estimation of unit risk values, the multistage Weibull model was used with linear extrapolation from the POD(BMDLHEC) associated with a defined extra cancer risk (e.g., 10%, 5%, or 1%). The multistage Weibull model incorporates the time at which death-with-tumor occurred. The multistage Weibull model has the following form:

$$P(d) = 1 - \exp[-(b_0 + b_1d + b_2d^2 + \dots + b_kd^k) \times (t - t_0)^c]$$

where $P(d)$ represents the lifetime risk (probability) of cancer at dose d (i.e., human equivalent exposure in this case); parameters $b_i \geq 0$, for $i = 0, 1, \dots, k$; t is the time at which the animal's tumor status, either no tumor, tumor, or unknown (e.g., missing or autolyzed) was observed; and c is a parameter estimated in fitting the model, which characterizes the change in response with age. The parameter t_0 represents the time between when a potentially fatal tumor becomes observable and when it causes death and is generally set to 0 because of a lack of data to estimate the time reliably, such as interim sacrifice data. Parameters were estimated using the method of maximum likelihood estimation (MLE).

II.C.2. Dose-Response Data

Tumor type – multiple (see above)
Test species – female B6C3F₁ mice
Route – Inhalation
References – [NTP \(1998\)](#)

Tumor incidence in female B6C3F₁ mice exposed to chloroprene via inhalation					
Tissue		Chloroprene concentration (ppm)			
		Control	12.8	32	80
All organs: hemangioma or hemangiosarcoma	Unadjusted rate	4/50	6/49	18/50	8/50
	First incidence (days)	541	482	216	523
Lung: alveolar/bronchiolar adenoma or carcinoma	Unadjusted rate	4/50	28/49	34/50	42/50
	First incidence (days)	706	447	346	324
Liver: hepatocellular adenoma or carcinoma	Unadjusted rate	20/50	26/49	20/50	30/50
	First incidence (days)	493	440	503	384
Skin: sarcoma	Unadjusted rate	0/50	11/49	11/50	18/50
	First incidence (days)	-	285	524	462
Mammary gland: carcinoma or adenoacanthoma	Unadjusted rate	3/50	6/49	11/50	14/50
	First incidence (days)	527	440	394	336
Forestomach: squamous cell papilloma or carcinoma	Unadjusted rate	1/50	0/49	0/50	4/50
	First incidence (days)	734	-	-	576
Harderian gland ^a : adenoma or carcinoma	Unadjusted rate	2/50	5/50	3/50	9/50
	First incidence (days)	527	621	524	467
Zymbal's gland ^a : carcinoma	Unadjusted rate	0/50	0/50	0/50	3/50
	First incidence (days)	-	-	-	565

^a Harderian gland and Zymbal's gland were examined histopathologically only if a lesion was observed grossly at necropsy

Source: [NTP \(1998\)](#).

Dose-response modeling summary for female mouse tumors associated with inhalation exposure to chloroprene

Tumor type*	Power Parameter c ^a	BMR	Point of departure ^b				Unit risk ^d /($\mu\text{g}/\text{m}^3$)	Composite unit risk ^{e,f} /($\mu\text{g}/\text{m}^3$)
			Modeled from bioassay (ppm)		Continuous, Human equivalent ^c ($\mu\text{g}/\text{m}^3$)			
			MDL	MD	BMDL	BMD		
Lung: alveolar/ bronchiolar adenoma or carcinoma	3.8	0.1	0.88	1.20	5.69×10^2	7.71×10^2	1.8×10^{-4}	
All organs: hemangio-sarcomas, hemangiomas ^{f,g}	5.9	0.1	5.75	10.1	3.71×10^3	6.52×10^3	2.7×10^{-5}	
All organs: hemangio-sarcomas, hemangiomas ^{f,h}	1.0	0.1	11.1	14.9	7.13×10^3	9.62×10^3	1.4×10^{-5}	
Mammary gland: carcinoma or adenocanthoma	1.0	0.1	14.1	20.4	9.06×10^3	1.32×10^4	1.1×10^{-5}	
Forestomach: squamous cell papilloma or carcinoma	4.1	0.1	46.3	67.8	2.98×10^4	4.37×10^4	3.4×10^{-6}	2.7×10^{-4}
Liver: hepatocellular adenoma or carcinoma	4.2	0.1	2.45	4.24	1.58×10^3	2.73×10^3	6.3×10^{-5}	
Harderian gland: adenoma or carcinoma	2.9	0.1	12.6	27.1	8.13×10^3	1.75×10^4	1.2×10^{-5}	
Skin: sarcoma	1.6	0.1	7.18	9.49	4.63×10^3	6.11×10^3	2.2×10^{-5}	
Zymbal's gland: carcinoma	1.1	0.05	22.5	80.5	1.45×10^4	5.19×10^4	3.5×10^{-6}	

Dose-response modeling summary for female mouse tumors associated with inhalation exposure to chloroprene

^aMultistage-Weibull model: $P(d) = 1 - \exp[-(b_0 + b_1d + b_2d^2 + \dots + b_kd^k) \times (t-t_0)^c]$, coefficients estimated in terms of ppm as administered in bioassay; lower stage b_i not listed were estimated to be zero. See Appendix C for modeling details.

^bBMD = Concentration at specified extra risk; BMDL = 95% lower bound on concentration at specified extra risk.

^cContinuous equivalent estimated by multiplying exposures by $(6 \text{ hours})/(24 \text{ hours}) \times (5 \text{ days})/(7 \text{ days})$.

^dUnit risk estimated by dividing the BMR by the BMDL.

^eOverall unit risk estimate, across all sites listed; see text for method.

^fHighest exposure group dropped in order to better characterize low-dose responses.

^gTreatment of early deaths (prior to final sacrifice) with hemangiosarcomas as fatal, with all other hemangiomas and hemangiosarcomas as incidental to death.

^hAll hemangiosarcomas (and hemangiomas) were considered incidental.

* Tumor incidence data from [NTP \(1998\)](#).

II.C.3. ADDITIONAL COMMENTS

Supplementary information not required.

II.C.4. DISCUSSION OF CONFIDENCE

Human population variability. The extent of inter-individual variability in chloroprene metabolism has not been characterized. A separate issue is that the human variability in response to chloroprene is also poorly understood. The effect of metabolic variation, including potential implications for differential toxicity, has not been well studied. Although a mutagenic MOA indicates increased early-life susceptibility, there are no data exploring whether there is differential sensitivity to chloroprene carcinogenicity across human life stages. This lack of understanding about potential differences in metabolism and susceptibility across exposed human populations thus represents a source of uncertainty.

Choice of low-dose extrapolation approach. The MOA is a key consideration in clarifying how risks should be estimated for low-dose exposure. A multistage Weibull time-to-tumor model was the preferred model because it can account for differences in mortality and other competing risks between the exposure groups in the mouse bioassay; however, it is unknown how well this model predicts low-dose extrapolated risks for chloroprene. Cause of death information was not available for this model; if available, risk estimates would tend to be slightly higher. For example, treatment of early deaths (prior to final sacrifice) with hemangiosarcomas as fatal, with all other hemangiomas and hemangiosarcomas as incidental

to death, led to unit risks up to twofold higher than unit risks treating all hemangiosarcomas (and hemangiomas) as incidental.

Dose metric. Chloroprene is metabolized to intermediates with carcinogenic potential, most likely an epoxide. However, data sufficient to estimate quantities were not available. Under the assumption that the carcinogenic form(s) of chloroprene are produced in proportion to low-exposures of chloroprene, the derived unit risk is an unbiased estimate.

Choice of bioassay/species/gender. The NTP inhalation bioassay followed an accepted protocol, was well conducted, and extensively peer reviewed. The carcinogenic response occurs in both species and sexes of rodents (as well as in humans, as observed in occupational epidemiologic cohorts). The calculated combined unit risk is based on the most sensitive endpoint (risk of any tumor type) in the most sensitive species and gender (female mouse). There is no information on chloroprene to indicate that the observed rodent tumors are not relevant to humans. Further, no data exist to guide quantitative adjustment for differences in sensitivity among rodents and humans. While site concordance generally is not assumed across species, e.g., due to potential differences in pharmacokinetics, DNA repair, other protective systems across species and tissues ([U.S. EPA, 2005](#)), it is notable that human-mouse site concordance was observed for liver tumors. In addition, rat and mouse tumor types overlapped but included different tumor types observed for each species/sex combination. Human data were insufficient to rule out the occurrence of these additional tumor types in humans.

Cross-species scaling. Another source of uncertainty comes from the interspecies extrapolation of risk from mouse to human. The two rodent species for which bioassay data were available— mouse and rat—vary in their carcinogenic responses to chloroprene, in terms of both site specificity and magnitude of response (see Section 4). Ideally, a PBPK model for the internal dose(s) of the reactive metabolite(s) would decrease some of the quantitative uncertainty in interspecies extrapolation; however, current PBPK models are inadequate for this purpose (Section 3). Existing pharmacokinetic models cannot yet adequately explain the species differences in carcinogenic response, and it is possible that there are pharmacodynamic as well as pharmacokinetic differences between the mouse and rat with respect to their sensitivities to chloroprene.

While concordance of specific sites between rodents and humans (e.g., liver tumors) tends to support the relevance of rodent species to humans, lack of specific site concordance (other tumors) does not diminish concern for human carcinogenic potential. The mouse was the more sensitive species to the carcinogenic effects of chloroprene exposure. Although the derivation took into account some known differences between mice and humans in tissue

dosimetry ([U.S. EPA, 1994](#)) differences in anatomy of the upper respiratory tract and resulting differences in absorption or in local respiratory system effects are sources of uncertainty.

Statistical uncertainty at the Point of Departure (POD). Parameter uncertainty within the chosen model reflects the limited sample size of the cancer bioassay. For the multistage-Weibull model applied to this data set, there is a reasonably small degree of uncertainty at the 10% extra risk level (the POD for linear low-dose extrapolation). Central estimates of risk differed from their upper bounds by about 1.2-fold for lung tumors and for the composite risk estimates.

HEC derivation. A source of uncertainty in the derivation of the HEC comes from whether or not chloroprene induces lung tumors due to portal-of-entry or systemic effects. Systemic distribution of chloroprene is evidenced by the induction of tumors in multiple organs and suggests that chloroprene may be redistributed back to the lungs and may primarily act as a systemically delivered carcinogen. However, the contribution of either route of delivery (i.e., inhalation versus bloodstream) to the induction of lung tumors is currently unknown. Treating lung tumors as systemic effects returns the highest combined unit risk (approximately 60% greater than if lung tumors are treated as portal-of-entry effects).

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document – ([U.S. EPA, 2010](#))

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Chloroprene* ([U.S. EPA, 2010](#)). [*To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition \(PDF\)*](#).

II.D.2. EPA REVIEW

Agency Completion Date -- 09/30/2011

II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]

IV. [reserved]

V. [reserved]

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CASRN – 126-99-8

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VII. REVISION HISTORY

Chloroprene
CASRN – 126-99-8
File First On-Line – 09/30/2010

Date	Section	Description
09/30/2010	I, II, VI, VII, VIII	RfC and cancer assessment added, RfD message added

VIII. SYNONYMS

Chloroprene
CASRN – 126-99-8
Section VIII. Last Revised – 09/30/2010

- 2-chlorobuta-1,3-diene
- 2-chloro-1,3-butadiene
- chlorobutadiene

- 2-chlorobutadiene
- 2-chlorobutadiene-1,3
- beta-chloroprene