Acetaldehyde; CASRN 75-07-0

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 Acetaldehyde

File First On-Line 06/30/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	10/01/1991
Carcinogenicity Assessment (II.)	yes	06/30/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Acetaldehyde
CASRN — 75-07-0

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Acetaldehyde
CASRN — 75-07-0
Last Revised — 10/01/1991

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this 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.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Degenration of olfactory epithelium **Short-term Rat Inhalation Studies** **Appleman et al., 1986;1982**	NOAEL: 273 mg/cu.m (150 ppm) NOAEL:(ADJ): 48.75 mg/cu.m NOAEL(HEC): 8.7 mg/cu.m LOAEL: 728 mg/cu.m (400 ppm) LOAEL(ADJ): 130 mg/cu.m LOAEL(HEC): 16.9 mg/cu.m	1000	1	9E-3 mg/cu.m

*Conversion Factors -- MW = 44.5. Appleman et al., 1986: Assuming 25C and 760 mmHg, NOAEL(mg/cu.m) = 150 ppm x 44.5/24.45 = 273. NOAEL(ADJ) = 273 mg/cu.m x 6 hours/day x 5 days/7 days = 48.75 mg/cu.m. The NOAEL(HEC) was calculated for a gas:respiratory effect

in the ExtraThoracic region. MVa = 0.23 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm, Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.18. NOAEL(HEC) = NOAEL(ADJ) x RGDR = 8.7 mg/cu.m.

Appleman et al., 1982: Assuming 25C and 760 mmHg, LOAEL(mg/cu.m) = 400 ppm x 44.5/24.45 = 130. LOAEL(ADJ) = 728 mg/cu. m x 6 hours/day x 5 days/7days = 130 mg/cu.m. The LOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.17 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm., Sh(ET) = 177 sq.cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.13. LOAEL(HEC) = LOAEL(ADJ) x RGDR = 16.9 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Appleman, L.M., R.A. Woutersen, V.J. Feron, R.N. Hooftman and W.R.F. Notten. 1986. Effect of variable versus fixed exposure levels on the toxicity of acetaldehyde in rats. J. Appl. Toxicol. 6(5): 331-336.

Appleman, L.M., R.A. Woutersen, and V.J. Feron. 1982. Inhalation toxicity of acetaldehyde in rats. I. Acute and subacute studies. Toxicology. 23: 293-297.

Two short-term studies conducted by the same research group are the principal studies used. While these studies are short-term in duration, together they establish a concentration-response for lesions after only 4 weeks of exposure. These same types of lesions appear at longer exposure times and higher exposure levels in chronic studies (Wouterson et al., 1986; Wouterson and Feron, 1987; Kruysse et al., 1975). Under other circumstances, studies of short duration may not be considered appropriate, but for this chemical the observed effects are consistent with pathology seen in long-term studies. The 150-ppm exposure level was therefore established as the NOAEL from the Appleman et al. (1986) study and the LOAEL from the Appleman et al. (1982) study.

Appleman et al. (1986) conducted two inhalation studies on male Wistar rats (10/group) exposing them 6 hours/day, 5 days/week for 4 weeks to 0, 150, and 500 ppm (0, 273 and 910 mg/cu.m, respectively). Duration-adjusted concentrations are 0, 48.75, and 162.5 mg/cu.m, respectively. One group was exposed without interruption, a second group was interrupted for 1.5 hours between the first and second 3-hour period, and a third group was interrupted as described with a superimposed peak exposure profile of 4 peaks at 6-fold the basic concentration per 3-hour period. The purpose was to test intermittent and peak exposure effects. Urine samples were collected from all rats and lung lavage performed on 4-5 per group at the end of the experiment. Cell density, viability, number of phagocytosing cells, and phagocytic index were determined on the lavage fluid. Microscopic examination was performed on the nasal cavity, larynx, trachea with bifurcation and pulmonary lobes of all rats of all groups.

Continuous and interrupted exposure to 500 ppm did not induce any visible effect on general condition or behavior, but peak exposures at this level caused irritation. No behavioral differences were noted in the other groups. Mean body weights of the group exposed to 500 ppm with interruption and with peak exposures were statistically significantly lower than those of the controls. Body weights were similar to controls in the other exposure groups. Mean cell density and cell viability were significantly decreased in the group exposed to 500 ppm with or without peak exposures. The mean percentage of phagocytosing cells and the phagocytic index were significantly lower than controls in all groups exposed to 500 ppm, especially the group exposed to superimposed peaks. Histopathological changes attributable to exposure were found only in the nasal cavity. Degeneration of the olfactory epithelium was observed in rats exposed to 500 ppm. Interruption of the exposure or interruption combined with peak exposure did not visibly influence this adverse effect. No compound-related effects were observed in rats interruptedly or uninterruptedly exposed to 150 ppm during the 4-week exposure period; therefore, the NOAEL is 150 ppm. The NOAEL(HEC) based on effects on the olfactory epithelium in the extrathoracic region is 8.7 mg/cu.m.

Appelman et al. (1982) exposed Wistar rats (10/sex/group) for 6 hours/day, 5 days/week for 4 weeks to 0, 400, 1000, 2200, or 5000 ppm acetaldehyde (0, 728, 1820, 4004 and 9100 mg/cu.m, respectively). Duration-adjusted concentrations are 0, 130, 325, 715 and 1625 mg/cu.m, respectively. The general condition and behavior of the rats were checked daily. Blood picture (Hb, Hct, RBC, total and differential WBC, and plasma protein) and chemistry were examined at the end of the treatment period. Activities of plasma glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, and alkaline phosphatase were also determined. Urine was analyzed for density, volume, pH, protein, glucose, occult blood, ketones, and appearance. The kidneys, lungs, liver, and spleen were weighed. Microscopic examination was performed on the lungs, trachea, larynx, and nasal cavity (3 transverse sections) of all animals and on the kidneys, liver, and spleen of all control and high- concentration groups.

During the first 30 minutes of each exposure at the 5000-ppm level, rats exhibited severe dyspnea that gradually became less severe during the subsequent exposure period. Two animals died at this level (1 female, 1 male) and one male died at the 2200-ppm level, but the cause of death could not be determined due to autolysis or cannibalism. Growth was retarded in males at the three highest exposure concentrations and in females at the 5000-ppm level. The percentage of lymphocytes in the blood was lower and the percentage of neutrophilic leukocytes higher in males and females of the 5000-ppm group than in controls. There were a few statistically significant differences in several blood chemistry parameters between the exposure groups and the control group but none of them were concentration-related. Statistically significant changes in organ-to-body weight ratios included decreased liver weights in both sexes and increased lung weights in males at the 5000-ppm level. Males in the 5000-ppm level produced less urine, but it was of higher density. Compound-related histopathological changes were observed only in the

respiratory system. The nasal cavity was most severely affected and exhibited a concentration-response relationship. At the 400-ppm level, compound-related changes included: slight to severe degeneration of the nasal olfactory epithelium, without hyper- and metaplasia, and disarrangement of epithelial cells. At the 1000- and 2200-ppm levels, more severe degenerative changes occurred, with hyperplastic and metaplastic changes in the olfactory and respiratory epithelium of the nasal cavity. Degeneration with hyperplasia/metaplasia also occurred in the laryngeal and tracheal epithelium at these levels. At 5000 ppm changes included severe degenerative hyperplastic and metaplastic changes of the nasal, laryngeal, and tracheal epithelium. Based on the degenerative changes observed in the olfactory epithelium, the 400-ppm level is designated as a LOAEL. The LOAEL(HEC), based on the ventilation rates for female rats, is 16.9 mg/cu.m. No NOAEL was identified.

Woutersen et al.(1986) exposed Wistar rats (105/sex/group) for 6 hours/day, 5 days/week for up to 28 months to 0, 750, 1500 and 3000/1000 ppm (0, 1365, 2730, 5460/1820 mg/cu.m, respectively). The highest concentration was gradually decreased because of severe growth retardation, occasional loss of body weight, and early mortality in this group. The duration-adjusted concentrations are 0, 244, 488, and 975/325 mg/cu.m, respectively. The general condition and behavior of the rats were checked daily. Samples of a wide range (otherwise not specified) of tissues, including the nasal cavity, trachea with main bronchi, and lungs were examined by light microscopy. The rats in the high-exposure concentration showed excessive salivation, labored respiration, and mouth breathing. The respiratory distress was still observed when the concentration was reduced to 1000 ppm, although fewer were dyspneic. Only a few rats died during the first 6 months of the study but thereafter a sharp increase in the numbers of deaths occurred in the high-concentration group. All top concentration rats had died by 25 months. When the study was terminated, only a few animals remained alive in the mid-concentration group. The cause of early death or moribund condition was nearly always partial or complete occlusion of the nose by excessive amounts of keratin and inflammatory exudate. Several showed acute bronchopneumonia occasionally accompanied by tracheitis. Growth retardation occurred in males of each test group and in females of the two highest concentrations. The only exposure- related histopathology occurred in the respiratory system and showed a concentration-response relationship. The most severe abnormalities were found in the nasal cavity. Basal cell hyperplasia of the olfactory epithelium was seen in the low- and mid-concentration rats. The decrease in these changes in the olfactory epithelium was attributed to the incidence of adenocarcinomas at the higher levels. The respiratory epithelium of the nasal cavity was involved (hyperplasia and squamous metaplasia with keratinization) at the mid and high concentrations. Hyperplasia and squamous metaplasia, occasionally accompanied by keratinization, occurred in the larynx of rats exposed at the mid and high concentrations. The tracheal epithelium was not visibly affected at any exposure level. Adenocarcinomas occurred at all exposure concentrations and squamous cell carcinoma at the mid and high concentrations only. It thus appeared that the nasal tumors could be distinguished into two major types:

adenocarcinomas from olfactory epithelium, and squamous cell carcinoma from the respiratory epithelium. The lowest exposure concentration, 750 ppm, is clearly a LOAEL based on the above changes in the olfactory epithelium. The LOAEL(HEC) is 56 mg/cu.m. No NOAEL was identified.

Woutersen and Feron (1987) conducted an inhalation study in which Wistar rats (30 rats/sex/group) were exposed to 0, 750, 1500, or 3000/1500 ppm acetaldehyde (0, 1365, 2730, 5460/2730 mg/cu.m, respectively) for 6 hours/day, 5 days/week for 52 weeks with a 26- or 52-week recovery period. The highest concentration was gradually decreased because of severe growth retardation, occasional loss of body weight, and early mortality. Duration-adjusted concentrations are 0, 244, 488, and 975/488 mg/cu.m, respectively. The general condition and behavior of the rats were checked daily. Histopathology was performed as described for Wouterson et al. (1986).

At the end of the 52-week exposure period, most of the animals in the high-concentration group exhibited labored respiration and mouth breathing. The respiratory distress diminished during the recovery period but did not disappear completely. Adenocarcinoma and squamous cell carcinoma occurred at the mid and high concentrations. Degeneration of the olfactory epithelium was similar in rats terminated after 26 weeks of recovery and rats killed immediately after exposure termination. Histopathological changes found in the respiratory epithelium were comparable with, but less severe than, those observed immediately after exposure termination. After 52 weeks of recovery, the degeneration of the olfactory epithelium was still visible to a slight degree in animals from all exposure groups. Animals in the high-concentration group did not show restoration of the olfactory epithelium. At the low concentration, normal olfactory epithelium was present in some animals but replacement of olfactory epithelium by respiratory epithelium was frequently seen. Histopathological changes in the respiratory epithelium of the two females of the high-concentration group examined were essentially comparable with those found in rats terminated after 26 weeks of recovery. These data suggest that there is incomplete recovery of olfactory and respiratory epithelium changes induced at all exposure concentrations for periods as long as 52 weeks after exposure termination.

Kruysse et al. (1975) conducted a 90-day inhalation study in hamsters (10/sex/concentration). The hamsters were exposed to acetaldehyde vapor at concentrations of 0, 390, 1340, or 4560 ppm (0, 127, 435.5 or 1482 mg/cu.m, adjusted for duration, respectively), for 6 hours/day, 5 days/week for 90 days. Histopathological changes attributable to exposure were observed only in the respiratory tract. At 4560 ppm, body weights were significantly reduced and the relative weights of heart, kidney, brain, testicle, and lung were significantly increased. Histopathological changes of the nasal cavity, larynx, trachea, and bronchi included necrosis, inflammatory changes, and hyperplasia and metaplasia of the epithelium. Mild effects observed at 1340 ppm consisted of statistically significant increased kidney weight in males, and small areas of

stratified epithelium in the trachea in both sexes (30% of the animals). At 390 ppm, with the exception of a tiny focus of metaplastic epithelium in the trachea of 1 out of the 20 animals examined, no adverse effects were observed. The 390-ppm concentration was identified by the authors as a NOAEL. The study by Appelman et al. (1982) identified a similar level (400 ppm) as a LOAEL [LOAEL(HEC) = 16.9 mg/cu.m] for Wistar rats, but surface area values in hamsters are not available so that a comparison on HEC values could not be made to determine the relative sensitivities of the species to acetaldehyde. The LOAEL for the extrarespiratory effects (effect on kidney weight) is 1340 ppm and the NOAEL also at 390 ppm. The NOAEL(HEC) for extrarespiratory effects is 127 mg/cu.m.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — An uncertainty factor of 10 was applied to account for sensitive human populations. A factor of 10 was applied for both uncertainty in the interspecies extrapolation using dosimetric adjustments and to account for the incompleteness of the database. A factor of 10 was applied to account for subchronic to chronic extrapolation.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

Saldiva et al. (1985) exposed male Wistar rats (12/group) to 0 or 243 ppm (442 mg/cu.m) of acetaldehyde 8 hours/day, 5 days/week for weeks. Duration- adjusted values are and 105/cu.m., respectively. The animals were evaluated pulmonary mechanics before after exposure period, gross paraffin-embedded sample observations made exposure, especially respiratory system. Increases in RF, FRC, RV, TLC significantly different from control values. Damage distal airways was suggested since functional tests elasticity severe obstruction not demonstrated. Histopathological investigation showed an intense inflammatory reaction with olfactory epithelium hyperplasia polymorphonuclear mononuclear infiltration submucosa. Cannulation precluded evaluation tracheal effects no differences between observed lower tract. Although this study presents pathology data only a descriptive fashion, it identifies LOAEL nasal/cu.m (HEC = 13.7 that is consistent principal studies. LOAEL(HEC) thoracic on function 220.5/cu.m.

Saldiva et al. (1985) exposed male Wistar rats (12/group) to 0 or 243 ppm (442 mg/cu.m) of acetaldehyde 8 hours/day, 5 days/week for 5 weeks. Duration- adjusted values are 0 and 105 mg/cu.m., respectively. The animals were evaluated for pulmonary mechanics before and after the exposure period, and gross and paraffin-embedded sample observations were made after exposure, especially of the respiratory system. Increases in RF, FRC, RV, and TLC were significantly different from control values. Damage to distal airways was suggested since functional tests for damage to elasticity or for severe obstruction were not demonstrated.

Histopathological investigation showed an intense inflammatory reaction with olfactory epithelium hyperplasia and polymorphonuclear and mononuclear infiltration of the submucosa. Cannulation precluded evaluation of tracheal effects and no differences between the control and exposed animals were observed for the lower respiratory tract. Although this study presents the pathology data in only a descriptive fashion, it identifies a LOAEL for nasal effects of 105 mg/cu.m (HEC = 13.7 mg/cu.m) that is consistent with the principal studies. The LOAEL(HEC) for thoracic effects on pulmonary function is 220.5 mg/cu.m.

Feron (1979) exposed Syrian golden hamsters (35 males/group) by inhalation to 1500 ppm acetaldehyde 7 hours/day, 5 days/week for 52 weeks. The duration- adjusted concentration is 487.5 mg/cu.m. Exposure to acetaldehyde vapor resulted in epithelial hyperplasia and metaplasia, accompanied by inflammation in the nasal cavity and trachea. No evidence of carcinogenicity was observed.

In an inhalation study Feron et al. (1982) exposed Syrian golden hamsters to 2500 ppm (948 mg/cu.m adjusted for duration) for the first 9 weeks, 2250 ppm, (853 mg/cu.m adjusted for duration) for weeks 10-20, 2000 ppm (758 mg/cu.m adjusted for duration) for weeks 21-29, 1800 ppm (682.5 mg/cu.m adjusted for duration) for weeks 30-44, and 1650 ppm (626 mg/cu.m adjusted for duration) for weeks 42-52, for 7 hours/day, 5 days/week for a total of 52 weeks. Compound-related changes included rhinitis, hyperplasia, and metaplasia of the nasal, laryngeal, and tracheal epithelium, and nasal and laryngeal carcinomas. No LOAEL was identified.

No inhalation studies for reproductive or developmental effects have been performed. No oral or inhalation developmental studies, nor any reproductive studies, exist.

Zorzano and Herrera (1989) studied the pattern of acetaldehyde appearance in maternal and fetal blood, maternal and fetal liver and placenta after oral ethanol administration or intravenous acetaldehyde administration (10 mg/kg) to pregnant Wistar rats. The study demonstrated that acetaldehyde was able to cross the placental barrier at high concentrations (fetal blood concentrations were only detectable when maternal blood concentrations were greater than 80 uM). The fetal oxidation capacity in liver and placenta was shown to be lower than that of the maternal liver. A threshold above which the removal capacity of acetaldehyde metabolism by the fetoplacental unit would be surpassed was estimated to be 80 uM (maternal blood concentration) in the 21-day pregnant rat and possibly lower at early pregnancy when aldehyde dehydrogenase is absent from fetal liver.

Retention of acetaldehyde in humans under "physiologic conditions" of breathing rate and tidal volume has been shown to be approximately 60% between 100 and 200 mg/cu.m for a few minutes (Egle, 1970), and retention was shown to decrease slightly at higher concentrations. Breathing rate and volume and exposure concentration were shown to influence retention.

Retention has not been determined at lower concentrations comparable with the HEC estimates derived here, however. Retention of acetaldehyde from cigarette smoke was shown to be 99% (Dalhamn et al., 1968). Acetaldehyde has been shown to be absorbed via inhalation at high concentrations (9000-10,000) for 1 hour (Watanabe et al., 1986). Binding and metabolism in blood and rat nasal mucosa have been demonstrated (Hagihara et al., 1981; Casanova-Schmitz et al., 1984). Casanova-Schmitz et al. (1984) observed that rats exposed to 700 ppm for 2 hours demonstrated only 0.7 mM in circulating blood 5 minutes after exposure termination, suggesting that binding in the respiratory tract and rapid metabolism significantly reduces systemic circulation at steady state.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Low
RfC -- Low

Confidence in the principal studies is medium since appropriate histopathology was performed on an adequate number of animals and a NOAEL and LOAEL were identified, but the duration was short and only one species was tested. Confidence in the database is low due to the lack of chronic data establishing NOAELs and due to the lack of reproductive and developmental toxicity data. Low confidence in the RfC results.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA documentation -- U.S. EPA, 1991

Agency Work Group Review — 05/18/1989, 04/25/1991

Verification Date — 04/25/1991

I.B.7. EPA Contacts (Inhalation RfC)

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 (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Acetaldehyde
CASRN — 75-07-0
Last Revised — 06/30/1988

Section II provides information on three aspects of 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 and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Based on increased incidence of nasal tumors in male and female rats and laryngeal tumors in male and female hamsters after inhalation exposure.

II.A.2. Human Carcinogenicity Data

Inadequate. The only epidemiological study involving acetaldehyde exposure showed an increased crude incidence rate of total cancer in acetaldehyde production workers as compared with the general population (Bittersohl, 1974). Because the incidence rate was not age adjusted, and because this study has several other major methodological limitations (including concurrent exposure to other chemicals and cigarette exposure, short duration, small number of subjects, and lack of information on subject selection, age and sex distribution) it is considered inadequate to evaluate the carcinogenicity of acetaldehyde.

II.A.3. Animal Carcinogenicity Data

Sufficient. Feron (1979) exposed groups of 35 male Syrian Golden hamsters to 0 or 1500 ppm acetaldehyde by inhalation 7 hours/day, 5 days/week, for 52 weeks. These animals were also exposed weekly by intratracheal instillation to increasing doses of benzo(a)pyrene (BaP) in 0.2 mL of 0.9% NaCl, or to NaCl alone. Animals were killed and autopsied after exposure and 26 weeks of recovery in air. No neoplastic effects due to acetaldehyde alone were found. The highest BaP dose (1 mg/week for 52 weeks) combined with acetaldehyde exposure produced twice the incidence of squamous cell carcinomas compared with the same dose of BaP alone. In the second part of this study, no respiratory tract tumors were found in groups of 25 male hamsters which were intratracheally instilled once a week with 0.2 mL of 2% or 4% acetaldehyde in 0.9% NaCl for 52 weeks.

Feron et al. (1982) studied male and female hamsters exposed by inhalation to acetaldehyde alone or in combination with intratracheally administered BaP or diethylnitrosamine. The animals were exposed for 7 hours/day, 5 days/week, for 52 weeks to a time weighted average concentration of 2028 ppm. They were killed and autopsied after a 29-week recovery period; that is, at week 81. A slight increase in nasal tumors and a significantly increased incidence of laryngeal tumors was observed in both male and female hamsters exposed to acetaldehyde alone. This study supported the observation of Feron (1979) that acetaldehyde treatment enhanced tumorigenicity (production of tracheobronchial carcinomas) of BaP.

The carcinogenicity of acetaldehyde was studied in 420 male and 420 female albino SPF Wistar rats (Woutersen and Appelman, 1984; Woutersen et al., 1985). After an acclimatization period of 3 weeks, these animals were randomly assigned to four groups of 105 males and 105 females each. The animals were then exposed by inhalation to atmospheres containing 0, 750, 1500, or 3000 ppm acetaldehyde for 6 hours/day, 5 days/week, for 27 months. The concentration in the highest dose group was gradually reduced from 3000 to 1000 ppm because of severe growth retardation, occasional loss of body weight and early mortality in this group. Interim sacrifices were carried out at 13, 26, and 52 weeks. One tumor was observed in the 52 week sacrifice group and none at earlier times. Exposure to acetaldehyde increased the incidence of tumors in an exposure-related manner in both male and female rats. In addition, there were exposure-related increases in the incidences of multiple respiratory tract tumors. Adenocarcinomas were increased significantly in both male and female rats at all exposure levels, whereas squamous cell carcinomas were increased significantly in male rats at middle and high doses and in female rats only at the high dose. The squamous cell carcinoma incidences showed a clear dose-response relationship. The incidence of adenocarcinoma was highest in the mid-exposure group (1500 ppm) in both male and female rats, but this was probably due to the high mortality and competing squamous cell carcinomas at the highest exposure level. In the low-exposure group, the adenocarcinoma incidence was higher in males than in females.

In a concurrent study, 30 animals of each sex were exposed to the same concentrations of acetaldehyde for 52 weeks followed by a recovery period of 26 weeks (10 animals) or 52 weeks (20 animals). Significant increases in nasal tumors were observed in male and female rats, including adenocarcinomas and squamous cell carcinomas, in both recovery groups. These findings indicate that after 52 weeks of exposure to acetaldehyde, proliferative epithelial lesions of the nose may develop into tumors even without continued exposure.

II.A.4. Supporting Data for Carcinogenicity

Acetaldehyde has been shown by several laboratories to induce sister chromatid exchange (SCE) in cultured mammalian cells (Obe and Ristow, 1977; Obe and Beer, 1979; deRaat et al., 1983; Bohlke et al., 1983; Ristow and Obe, 1978; Jansson, 1982; Norrpa et al., 1985). A recent study provided evidence that SCE-inducing lesions may be persistent for several cell generations (He and Lambert, 1985). The in vitro SCE response did not require metabolic activation. The induction of SCE by acetaldehyde has also been detected in bone marrow cells of mice and hamsters in vivo (Obe et al., 1979; Korte and Obe, 1981). Acetaldehyde caused chromosomal aberrations in mammalian cell culture (Bird et al., 1981; Bohlke et al., 1983) and plants (Rieger and Michaelis, 1960), but not in Drosophila (Woodruff et al., 1985). Chromosome gaps and breaks were found in rat embryos after a single intraamniotic injection on day 13 of gestation (Barilyak and Kozachuk, 1983). Acetaldehyde produced sex-linked recessive lethal gene mutations after injection in Drosophila (Woodruff et al., 1985), but has been negative in testing in Salmonella (Commoner, 1976, Laumbach et al., 1976; Pool and Wiesler, 1981., Marnett et al., 1985, Mortelmans et al., 1986). Acetaldehyde has been shown to produce crosslinks between protein and DNA in the nasal respiratory mucosa (Lam et al., 1986).

Acetaldehyde is similar in stucture to formaldehyde (classified B1) which also produces nasal tumors in animals exposed by inhalation.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 2.2E-6 per (ug/cu.m)

Extrapolation Method — Linearized multistage-variable exposure input form (extra risk)

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	5E+1 ug/cu.m
E-5 (1 in 100,000)	5E+0 ug/cu.m
E-6 (1 in 1,000,000)	5E-1 ug/cu.m

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type: nasal squamous cell carcinoma or adenocarcinoma
Test animals: rat/SPF Wistar, male
Route: inhalation
Reference: Woutersen and Appleman, 1984

Dose		Tumor Incidence
Lifetime Average Exposure		
Administered (ppm)	**Human Equivalent (ppm)**	
0	0	1/94
750	130	20/95
1500	255	49/95
1540	279	47/92

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Actual measured exposures on two occasions for the low and medium dose groups were 727/735 and 1438/1412 ppm, respectively. The highest dose administered is given as TWA. Low-dose extrapolation was performed using two forms of the linearized multistage model, the quantal model (Crump et al., 1977) and a form which allows analysis for a variable dose pattern, adjusts for intercurrent mortality, and is capable of estimating risk at any time from any dosing pattern (Crump and Howe, 1984). The latter model is referred to as the variable exposure form. Comparison of the results from the two models showed very little difference in the unit risk estimates. The variable exposure form was selected for the final unit risk estimate because it allows the combination of the lifetime study and the recovery study for risk estimation. The above estimates are from male rats; the unit risk calculated from data on female rats at 18 months was 1.6E-6 per (mg/cu.m). No difference was found in tumor incidence between animals exposed for a full lifetime and those exposed for 12 months and allowed to recover. At the end of 24 months, however, the tumor incidences in the recovery group were less than those in the lifetime exposure group.

The unit risk should not be used if the air concentration exceeds 5E+3 ug/cu.m, since above this concentration the unit risk may not be appropriate.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

An adequate number of animals was observed in a lifetime study. Increases in nasal tumors were observed in both male and female rats, and similar unit risks were obtained using these data.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1987

The 1987 Health Assessment Document is a final draft which has received both agency and external review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 01/13/1988

Verification Date — 01/13/1988

II.D.3. EPA Contacts (Carcinogenicity Assessment)

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 (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Acetaldehyde
CASRN — 75-07-0

VI.A. Oral RfD References

None

VI.B. Inhalation RfD References

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VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — Acetaldehyde
CASRN — 75-07-0

Date	Section	Description
10/01/1991	I.B.	Inhalation RfC summary on-line

VIII. Synonyms

Substance Name — Acetaldehyde
CASRN — 75-07-0
Last Revised — 06/30/1988

- 75-07-0
- ACETALDEHYD
- Acetaldehyde
- ACETIC ALDEHYDE
- ACETYLALDEHYDE
- ALDEHYDE ACETIQUE
- ALDEIDE ACETICA
- ETHANAL
- ETHYL ALDEHYDE
- NCI-C56326
- OCTOWY ALDEHYD
- RCRA WASTE NUMBER U001
- UN 1089