|  |  |
| --- | --- |
| **ACETALDEHYDE**CASRN: 75-07-0Update: December 8, 2014 |    |
| **Massachusetts Air Guidelines**[[1]](#footnote-1),**:** **AAL = 0.4 ug/m3** (0.2 ppb) [[2]](#footnote-2) (annual average concentration)**TEL = 30 ug/m3** (20 ppb) (24 hour average concentration) |
| **Chemical Properties:** (HSDB 2014 ) |
| Odor Characteristics: | Green, sweet, fruity (Ruth 1986) |
| Odor Threshold: | 0.2 ug/m3 (Ruth 1986) |
| Irritant:  | Yes, to respiratory tract, eyes, skin  |
| Sensitizer: | No information |
| Chemical Class: | Colorless volatile liquid or gas above 20oC |
| Boiling Point: | 20.1oC |
| Melting Point: | -123.37oC |
| Vapor Pressure: | 902 mm Hg at 25oC |
| Molecular Weight: | 44.05 |
| Unit Conversion factor:  | 1.8 ug/m3 per ppb at 25oC |
| **Critical Effects**[[3]](#footnote-3)**:*** Irritation, inflammation and injury to nose, larynx and trachea, including degeneration, hyperplasia and metaplasia of the mucosal tissues.
* Target organ systems affected include the upper respiratory tract, eyes, and skin.
* Probable human carcinogen.
 |
| **Potentially Susceptible Populations:*** Infants, children, people with asthma or a compromised respiratory system may be susceptible members of the population. Exposure to high concentrations has caused bronchoconstriction in people with asthma.
* People with exposure to other sources of acetaldehyde, e.g., cigarettes and alcohol.
* People with variants of aldehyde dehydrogenase (ALDH) that increase internal concentration of acetaldehyde, including a variant common in people of Asian descent.
 |
| **TEL Basis for Criteria:**Available chronic inhalation noncancer toxicity values:RfC 9 ug/m3 (USEPA 1991)REL 140 ug/m3 (CalEPA 2008)The REL of 140 ug/m3 derived by CalEPA (2008) was selected as the basis of the TEL. A relative source contribution factor (RSC) of 0.2 is incorporated into the final value.TEL = 140 ug/m3 x 0.2 (RSC) = 28 ug/m3, rounded to 30 ug/m3The USEPA RfC and CalEPA REL are more than an order of magnitude from each other. Because they are more than a factor of 3 from each other, both values were evaluated as described in MassDEP (2011). USEPA and CalEPA used different methods for estimating the human equivalent concentration for the point of departure and different uncertainty factors. The CalEPA (2008) REL was selected as the basis of the TEL because it used a chemical specific animal to human extrapolation method and dose response modeling to estimate the point of departure.The USEPA RfC and CalEPA REL are based on the same two subchronic inhalation studies in Wistar rats by Appleman et al. (1982; 1986) where rats were exposed to acetaldehyde for 6 hours per day, 5 days per week for four weeks. Male and female rats were exposed to 400, 1000, 2200 or 5000 ppm acetaldehyde (728, 1820, 4004 or 9100 mg/m3) in the Appleman et al. (1982) study resulting in degeneration of olfactory nasal tissues at all exposure concentrations. As the exposure concentration increased, damage was observed deeper in the respiratory tract. Degeneration of nasal respiratory tissues was observed at the three highest exposure levels, tracheal and laryngeal lesions were observed at the two highest exposure levels, and mild injury to the lower respiratory tract was observed only at the highest exposure level (USEPA 1991; CalEPA 2008).The subsequent study by Appleman et al. (1986) exposed male rats to 150 or 500 ppm acetaldehyde (273 or 910 mg/m3) using the same experimental conditions as the earlier study. Degeneration of the olfactory nasal tissue was observed at the 500 ppm exposure level, but not at the 150 ppm exposure level. USEPA (1991) and CalEPA (2008) identified a NOAEL of 150 ppm (273 mg/m3) from Appleman et al. (1986) and a LOAEL of 400 ppm (728 mg/m3) from Appleman et al. (1982).Although the Appleman et al. (1982, 1986) studies only exposed the rats for 4 weeks, additional studies exposing rats (Wouterson et al. 1984a, Dorman et al. 2008) or hamsters (Kruyesse et al. 1975; Feron et al. 1982) for up to 28 months support the finding observed in the Appleman et al. (1982, 1986) studies. The nasal olfactory tissues were the most sensitive endpoint. In studies where exposures were selected such that a NOAEL *and* LOAEL were observed, LOAELs of 150 ppm (Dorman et al. 2008) and 390 ppm (Kruyesse et al. 1975) were identified. The study by Dorman et al. 2008 was not included as a critical study because there was no gradation of response with none of the animals affected at the NOAEL and all animals having nasal olfactory tissue lesions at the LOAEL (CalEPA 2008).USEPA (1991) used the methods described in the 1994 RfC guidance (USEPA 1994) citing a 1989 draft version to estimate the HEC from the NOAEL of 273 mg/m3 (150 ppm) observed in the Appleman et al. 1986 study. USEPA assumed that acetaldehyde is a highly reactive gas, Category 1, and calculated a regional gas dosimetry ratio[[4]](#footnote-4) (RGDRET) of 0.18 for the extrathoractic region (nose, larynx and pharynx) taking into account the relative surface area and ventilation rates of male rats and adult humans. The NOAEL of 273 mg /m3, duration adjusted from 6 hr/day, 5 day/week exposure to 24 hour/day, 7 day/week exposure to a NOAELadj of 48.75 mg/m3, was multiplied by the RGDRET of 0.18 to estimate the NOAELHEC of 8.7 mg/m3. The NOAELHEC was divided by a composite uncertainty factor of 1,000 (UFA=3, UFH=10, UFS=10, UFL=1, UFD=3) to derive an RfC of 8.7 ug/m3, rounded to 9 ug/m3.CalEPA (2008) used benchmark dose modeling to estimate the point of departure instead of the NOAEL used by USEPA. They used a scale, rating the severity of the olfactory epithelium degeneration in the individual animals at each exposure level, to convert incidence into a continuous measure. Responses at each exposure level were categorized into one of eight categories from a score of zero for no effect to a score of 7 for very severe degeneration with hyperplasia. The means and standard deviations for each dose group, male and female, from both Appleman et al. (1982, 1986) studies were evaluated together for dose response modeling. The point of departure was estimated using USEPA’s (2003) benchmark dose software (BMDS) models for continuous responses, averaging the lower confidence limit of the concentration expected to produce a response rate of 5% across the three best fitting model forms (CalEPA 2008). The BMCL05 was calculated to be 99 + 1.20 ppm (178 + 2.16 mg/m3).The output of the physiologically based pharmacokinetic (PBPK) model developed by Teeguarden et al. (2008) was used by CalEPA to extrapolate the rat exposure concentration (BMCL05) to an exposure concentration for humans that results in the same concentration in the olfactory epithelium in rats and humans. CalEPA used the ratio of the rat (8.41) and human (6.20) internal concentrations estimated for olfactory epithelia cells from the same external exposure concentration of acetaldehyde yielding a dosimetric adjustment factor (DAF) of 1.36.Acetaldehyde is metabolized by the enzyme aldehyde dehydrogenase (ALDH); a detoxifying pathway present in many tissues of rodents and humans (Teeguarden et al. 2008). Humans and rodents have two forms of this enzyme, low-affinity ALDH\*1 and high-affinity ALDH\*2. While ALDH\*2 has not been studied or measured specifically in human nasal tissues, given the similarity in tissue distribution in rodents and humans, it is plausible that it is expressed in human nasal tissues (CalEPA 2008). Humans are well known to vary in the activity of ALDH\*2, as the absence of its activity [in the liver] is the basis of alcohol sensitivity particularly in people of Asian descent (Teeguarden et al. 2008). Teeguarden et al. (2008) modeled the influence of ALDH\*2 activity, full, intermediate or zero, on the metabolism of acetaldehyde in nasal tissues and found very limited impact.The BMCL05 of 178 mg/m3 estimated from the rat studies (Appleman et al. 1982, 1986) was adjusted to a human equivalent concentration of 242.1 mg/m3 from animal to human using the DAF of 1.36 from the PBPK model of Teeguarden et al. (2008), and duration adjusted to a BMCLHEC of 43.2 mg/m3, where 43.2 mg/m3 = 242.1 mg/m3 x 6 hours/24 hours x 5 days/7 days. The BMCLHEC was divided by a composite uncertainty factor of 300.REL = 43.2 mg/m3 x 103 ug/mg = 144 ug/m3, rounded to 140 ug/m3 1 x 3 x 3 x 10 x 3***Uncertainty factors:***UFA-k (extrapolation from animals to humans toxicokinetics) = 1UFA-d (extrapolation from animals to humans toxicodynamics) = 3UFH-k (human population variability in kinetics) = 3UFH-d (human population variability in response) = 10to account for potential asthma exacerbation in childrenUFL (LOAEL to NOAEL) = 1UFS (subchronic to chronic) = 3UFD (combined data deficiencies) = 1 A DAF from the PBPK model of Teeguarden et al. (2008) was used to adjust the toxicokinetic portion of the interspecies uncertainty factor (UFA-k), so a value of one was used for UFA-k. Toxicodynamic differences across species are not known and the key studies are in non-primates, thus CalEPA (2008) used a factor of 3 for the toxicodynamic portion of interspecies uncertainty factor (UFA-d). A value of 3 was selected for the toxicokinetic portion of the intraspecies uncertainty factor (UFH-k) because acetaldehyde is a reactive substance with effects occurring at the portal of entry, thus CalEPA (2008) expects less kinetic differences between children and adults. A value of 10 was selected for the toxicodynamics portion of the intraspecies uncertainty factor (UFH-d) to account for the potential for greater susceptibility among children and people with asthma. |
| **Cancer Classification:**USEPA (1991): B2, probable human carcinogenIARC (1999): Group 2B, possibly carcinogenic to humans.NTP (2014): Reasonably anticipated to be a human carcinogen. |
| **NTEL Basis for Cancer Assessment:** Available estimates of cancer inhalation unit risks: 2.2x10-6 per ug/m3 derived in 1987 (USEPA 1991) 2.7x10-6 per ug/m3 derived in 1993 (CalEPA 2011)The UR of 2.2x10-6 per ug/m3 derived by USEPA (1991) was selected as the basis of the NTEL. The NTEL is the ambient air concentration estimated to be associated with a 1 in a million risk of cancer.NTEL = 1 x 10-6 / 2.2x10-6 per ug/m3 = 0.45 ug/m3, rounded to 0.4 ug/m3The two available cancer potency estimates are essentially the same and after rounding yield the same NTEL. The NTEL based on the CalEPA unit risk value, 2.7x10-6 per ug/m3, is 0.37 ug/m3, rounded to 0.4 ug/m3. USEPA and CalEPA based their values on animal studies conducted by the same researchers, but used different subsets of available data, different dose-response models, and different approaches for extrapolating from animal to human exposure concentrations. The similarity of the unit risk values lends confidence to the NTEL. While the updated AAL/TEL methodology (MassDEP 2011) indicates that the most recent value will be selected when values are less than 3-fold apart, in this case the values are so close that they result in the same AAL. The UR derived by USEPA was identified as the basis of the NTEL for consistency with USEPA. Cancer risk estimates are based on several studies conducted by the same group as described in Woutersen and Appleman (1984), and Woutersen et al. (1985). Briefly, summarized from USEPA (1991), groups of 105 male and female SPF Wistar rats were exposed to 0, 750, 1500 or 3000 ppm acetaldehyde by inhalation for 6 hours per day, 5 days per week, for 27 months. Incidence of respiratory tract tumors increased with increased exposure concentration in both male and female rats. Nasal adenocarcinomas were significantly increased in both males and female at all exposure concentrations. Nasal squamous cell carcinomas were significantly increased in male rats at middle and high concentrations, but only at the highest concentration in female rats. A clear dose dependent trend was observed for squamous cell carcinoma incidence in male rats (USEPA 1991).Incidence of nasal squamous cell carcinoma or adenoma in male rats, from the combined results of the lifetime and recovery studies, was 1/94, 20/95, 49/95 and 47/92 at exposure levels of 0, 750, 1500 and 3000 ppm acetaldehyde, respectively. Increased incidence of growth retardation and early mortality was observed in the highest exposure group. Thus, the 3000 ppm exposure concentration was decreased to 1000 ppm over the course of the study, yielding an average administered concentration of 1540 ppm. Exposure concentrations were duration adjusted from the measured administered concentrations of 0, 727/735, 1438/1412, 1540 ppm acetaldehyde to continuous exposure concentrations adjusting exposures by 5 days to 7 days per week, 6 hours/day to 24 hours/day, to 0, 130, 255, and 279 ppm. [Note: when administered concentration was measured twice, the two values are separated by a slash; unlike the RfC for acetaldehyde, no other adjustments were made to estimate the human equivalent concentration.] USEPA (1991) used the linearized multistage-variable exposure input form (extra risk)(Crump and Howe 1984) of the dose response model to derive a unit risk value of 2.2x10-6 per ug/m3.Cal EPA (2011) used the incidence of nasal carcinoma (Woutersen et al. 1986) in male rats to derive a unit risk value. After excluding the highest dose group (3000 ppm) due to the change in exposure concentration during the study, they fit a linearized, time-independent multistage model to the male rat carcinoma data using the GLOBAL86 program of Howe et al. (1986). The unit risk was adjusted to scale from rats to humans using body weight raised to the 2/3 power, yielding a unit risk value of 2.7x10-6 per ug/m3. [Note: it is not standard practice to scale using body weight for inhalation exposures, especially those affecting the respiratory tract.] |
| **References:** Appleman LM, Woutersen RA, Feron VJ. 1982. Inhalation toxicity of acetaldehyde in rats. I. Acute and subacute studies. Toxicology 23: 293-307(as cited in USEPA 1991, CalEPA 2008). Appleman LM, Woutersen RA, Feron VJ, Hooftman RN, Notten WRF. 1986. Effect of variable versus fixed exposure levels on the toxicity of acetaldehyde in rats. J. Appl. Toxicol. 6(5): 331-336 (as cited in USEPA 1991, CalEPA 2008).CalEPA (California Environmental Protection Agency). 2008. Air Toxics Hot Spots Program Technical Support Document for the Derivation of Noncancer Reference Exposure Levels, appendix D1. Office of Environmental Health Assessment (accessed September 4, 2014).CalEPA (California Environmental Protection Agency). 2011. Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures, Appendix D. Office of Environmental Health Assessment (accessed September 4, 2014).Crump KS, Howe RB. 1984. The multistage model with a time-dependent dose pattern: application to carcinogenic risk assessment. Risk Analysis. 4: 163-176 (as cited in USEPA 1991).Dorman DC, Struve MF, Wong BA, Gross EA, Parkinson C, Willson GA, Tan YM, Campbell JL, Teeguarden JG, Clewell HJ, 3rd, Andersen ME. 2008. Derivation of an inhalation reference concentration based upon olfactory neuronal loss in male rats following subchronic acetaldehyde inhalation. Inhal Toxicol 20(3): 245-56 (as cited in CalEPA 2008).Feron VJ, Kruysse A, Woutersen RA. 1982. Respiratory tract tumors in hamsters exposed to acetaldehyde vapour alone or simultaneously to benzo(a)pyrene or diethylnitrosamine. Eur. J. Cancer Clin. Oncol. 18: 13-31 (as cited in USEPA 1991, CalEPA 2008). Howe RB, Crump K, Van Landingham C. 1986. GLOBAL86. Clement Associates, Ruston, LA (as cited in CalEPA 2011).HSDB (Hazardous Substances Data Bank). 2014. Available: <http://toxnet.nlm.nih.gov> (accessed September 4, 2014). IARC (International Agency for Research on Cancer). 1999. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Monograph 71. Available: <http://monographs.iarc.fr/ENG/Preamble/index.php> (accessed September 4, 2014).Kruysse A, Feron, VJ, Til HP. 1975. Repeated exposure to acetaldehyde vapor. Arch. Environ. Health. 30: 449-452 (as cited in USEPA 1991).MassDEP (Massachusetts Department of Environmental Protection). 2011. Methodology for Updating Air Guidelines: Allowable Ambient Limits (AALs) and Threshold Effects Exposure Limits (TELs). Office of Research and Standards, Boston, MA.NTP (National Toxicology Program). 2014. Report on Carcinogens Thirteenth Edition; U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.Ruth JH. 1986. Odor thresholds and irritation levels of several chemical substances: a review. Am. Ind. Hyg. Assoc. 47A:142-151.Teeguarden JG, Bogdanffy MS, Covington TR, Tan C, Jarabek AM. 2008. A PBPK model for evaluating the impact of aldehyde dehydrogenase polymorphisms on comparative rat and human nasal tissue acetaldehyde dosimetry. Inhal. Toxicol. 20(4): 375-90.USEPA (U.S. Environmental Protection Agency). 1991. Acetaldehyde. Integrated Risk Information System (IRIS). Available: <http://www.epa.gov/iris/> (accessed September 4, 2014).USEPA (U.S. Environmental Protection Agency). 1994. Interim Methods for Development of Inhalation Reference Concentrations. Prepared by the Environmental Criteria and Assessment Office, Research Triangle Park, NC. October 1994. EPA/600/8-90/066A. (Final Draft) USEPA (U.S. Environmental Protection Agency). 2003. Benchmark Dose Software. National Center for Environmental Assessment, United States Environmental Protection Agency.Woutersen RA, Appelman LM. 1984. Lifespan inhalation carcinogenicity study of acetaldehyde in rats. III. Recovery after 52 weeks of exposure. Report No. V84.288/190172. CIVO-Institutes TNO, The Netherlands. Woutersen RA, Appelman LM, Feron VJ, Van der Heijden CA. 1984. Inhalation toxicity of acetaldehyde in rats. II. Carcinogenicity study: Interim results after 15 months. Toxicology 31(2): 123-133 (as cited in CalEPA 2008).Wouterson R, Van Garderen-Hoetmer A, Appelman LM. 1985. Lifespan (27 months) inhalation carcinogenicity study of acetaldehyde in rats. Report No. V85.145/190172. CIVO-Institutes TNO, The Netherlands.Woutersen RA, Appelman LM, Van Garderen-Hoetmer A, Feron VJ. 1986. Inhalation toxicity of acetaldehyde in rats. III. Carcinogenicity study. Toxicology 41(2): 213-231 (as cited in CalEPA 2008). |
| **Update History:**TEL/AAL first listed – 1995TEL/AAL updated and summary added 1/2015 |

1. The process used for selecting and deriving Threshold Effects Exposure Limits (TELs), Non-Threshold Effects Exposure Limits (NTELs) and Allowable Ambient Limits (AALs) is described in MassDEP (2011). [↑](#footnote-ref-1)
2. Guidance values are presented with 1 significant figure in units of ug/m3; for convenience, values in units of ppb are calculated based on the rounded guidance value in units of ug/m3 then rounded to 1 significant figure in units of ppb for presentation. [↑](#footnote-ref-2)
3. This summary document provides information about the toxicity data supporting the available toxicity values for this chemical and the rationale for selecting among values. It is not intended to be a comprehensive summary of all toxicity information for this chemical. [↑](#footnote-ref-3)
4. The regional gas dosimetry ratio (RGDRET) and dosimetric adjustment factor (DAF) serve an equivalent function for estimating the difference in applied dose between the test animal and humans. [↑](#footnote-ref-4)