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2 Acetaldehyde

This chapter summarizes the relevant epidemiologic and toxicologic studies of acetaldehyde. Selected chemical and physical properties, toxicokinetic and mechanistic data, and inhalation-exposure levels from the National Research Council and other agencies are also presented. The committee considered all that information in its evaluation of the U.S. Navy's 1-h, 24-h, and 90-day exposure guidance levels for acetaldehyde. The committee's recommendations for acetaldehyde exposure levels are provided at the end of this chapter with a discussion of the adequacy of the data for defining the levels and the research needed to fill the remaining data gaps.

PHYSICAL AND CHEMICAL PROPERTIES

Acetaldehyde is a colorless, flammable liquid with a pungent, fruity odor (HSDB 2005). Ruth (1986) reported an odor threshold ranging from 0.0001 to 2.3 ppm and an irritating concentration of 50 ppm. Selected physical and chemical properties are shown in Table 2-1.

OCCURRENCE AND USE

Acetaldehyde is used primarily as a chemical intermediate in the production of such products as herbicides, insecticides, fungicides, pharmaceuticals, flavors, fragrances, dyes, plastics, and synthetic rubber (IARC 1985). Small quantities are used as a food additive. It is an intermediate in the respiration of higher plants and thus a natural component of many fruits and vegetables (EPA 2007). It is also a metabolite of ethanol and sugar metabolism in humans, and it is endogenously produced in humans from amino acid metabolism and from anaerobic metabolism of glucose by intestinal microflora (NRC 1994). Acetaldehyde is eliminated in expired air of fasted humans at 17 μg/h (NRC 1994).

Acetaldehyde is a component of tobacco smoke. The amount of acetaldehyde generated depends on the type of cigarette. Results of several studies indicate a range in the amount of acetaldehyde in the smoke of 400-1,400 μg/cigarette (IARC 1985; Hoffmann and Hecht 1990), although results of one study indicate a much lower emission of acetaldehyde from low-tar cigarettes (90-270 μg/cigarette; IARC 1985). Acetaldehyde is also a component of automobile exhaust and is generated by the combustion of wood and plastics (IARC 1985). Several studies have measured acetaldehyde concentrations in ambient air in the United States; results range from nondetectable to 69 ppb (IARC 1985).

Acetaldehyde concentrations have been measured on nuclear-powered submarines. Raymer et al. (1994) reported the results of air sampling at three locations over 6 h during the missions of two submarines. Acetaldehyde concentrations ranged from 78 to 130 ppb on an attack submarine and from 210 to 250 ppb on a ballistic-missile submarine. Holdren et al. (1995) reported the results of a similar sampling exercise (two submarines, three locations, and sampling duration of 6 h). Concentrations ranged from 46.6 to 97.2 ppb on a nuclear-powered attack submarine and from 103.9 to 118.0 ppb on a ballistic-missile submarine. Hagar (2008) reported data representing 228,960 h (318 patrols) on 23 attack submarines and 77,760 hours (108 patrols) on 10 ballistic-missile submarines. Acetaldehyde concentrations were determined with passive monitoring and averaged 16 ppb (range, 1-110 ppb) on the attack submarines and 5 ppb (range, 1-16 ppb) on the ballistic-missile submarines. The most recent data (Hagar 2008) collected on three attack submarines indicated an acetaldehyde concentration of 250-350 ppb. Few details on collection of the data were provided.

SUMMARY OF TOXICITY

Acetaldehyde toxicity has been reviewed in several publications (IARC 1985, 1999; EPA 1987; NRC 1994; WHO 1995; Heck 1997; Environment Canada and Health Canada 2000; ACGIH 2001; EC 2004; HEI 2007; NASA, unpublished material, 2007; Dorman et al. 2008). Mucosal irritation is the sensitive effect of acute exposure to acetaldehyde; eye irritation is more sensitive than nose or throat irritation. Eye irritation has been reported in human volunteers at concentrations as low as 50 ppm, whereas concentrations greater than 100-200 ppm are typically required for nose or throat irritation (Silverman et al. 1946; Sim and Pattle 1957; Muttray et al. 2009). Increasing air concentrations result in deeper penetration of acetaldehyde vapor in the respiratory system, which causes bronchiolitis obliterans (as reported after accidental high-dose occupational exposures) or bronchoconstriction in asthmatics. Acetaldehyde, like formaldehyde and acrolein, is chiefly a portal-of-entry toxicant that targets the upper respiratory mucosa, but it is considerably less potent than these two other aldehydes.

No systemic effects or effects on the olfactory epithelium or other portions of the respiratory tract were reported after repeated subchronic exposure of rats at 50 ppm (Dorman et al. 2008). Continuous 24-h exposure of mice at 125 ppm for 14 days (Oyama et al. 2007) and repeated subchronic exposure of rats to acetaldehyde at 150 ppm or greater result in nasal lesions and increasing olfactory neuron loss and degeneration and thinning of the olfactory epithelium with increasing concentration and exposure duration. Repeated subchronic exposure of rats at higher concentrations (such as those greater than 500 ppm) has also resulted in inflammation, hyperplasia, and squamous metaplasia of the respiratory epithelium; moderate to severe lesions of the olfactory epithelium with neuronal loss and hyperplasia result at 1,500 ppm (Dorman et al. 2008).

Chronic exposure of rats at 750 ppm or greater for 2 years is carcinogenic to the nasal mucosa (Woutersen et al. 1986). Data on humans are inadequate to assess carcinogenicity of inhaled acetaldehyde (EPA 1991; NTP 2005). Some evidence indicates that humans with genetic polymorphisms for reduced aldehyde dehydrogenase activity may be at higher risk for oral and esophageal cancers from consuming alcohol because the acetaldehyde from metabolism of the alcohol is not readily oxidized (NTP 2005; Baan et al. 2007).

Concentrations of toxicologic concern are related to resulting epithelial tissue concentrations, which depend on the rates of tissue absorption and metabolism of acetaldehyde by acetaldehyde dehydrogenases (Morris 1997a; Environment Canada and Health Canada 2000). High airborne concentrations result in saturation of acetaldehyde metabolism, which leads to apparent nonlinear increases in nasal tissue concentration, tissue damage, and penetration of acetaldehyde beyond the nasal cavity to the larynx and trachea (Heck 1997; Morris 1997b).

Effects in Humans

Accidental Exposures

As noted above, acetaldehyde is a component of food flavorings and is added to various products, such as fruit juices and soft drinks. Its concentration in foods is generally up to 0.047% (IARC 1985). In a food-flavoring manufacturing facility using high concentrations of acetaldehyde, an index case of bronchiolitis obliterans was reported (Lockey et al. 2002); exposure involved the manual pouring of concentrated acetaldehyde into open mixing tanks (J. Lockey, University of Cincinnati, personal commun., July 11, 2009).

Experimental Studies

Human subjects were exposed to various individual chemicals for 15 min, including acetaldehyde at 25, 50, and 200 ppm (Silverman et al. 1946).[1] Several subjects strenuously objected to the vapor at 25 ppm, although whether this was because of odor or irritation is not stated. Silverman et al. (1946), however, stated that eye irritation appeared at 50 ppm with the majority of subjects reporting some eye irritation at that concentration. Those not reporting eye irritation had bloodshot eyes and reddened eyelids at 200 ppm. Nevertheless, the majority of subjects said that they would be willing to work an 8-h day at 200 ppm. Exposure to acetaldehyde at 134 ppm for 30 min resulted in mild upper respiratory irritation in 14 men (Sim and Pattle 1957). Data on sensory irritants, such as acrolein, indicate that a constant level of irritation is eventually reached. For example, in humans, the eye irritancy of acrolein increased from

15 to 40 min of exposure at 0.3 ppm and stayed constant from 40 to 60 min (Weber-Tschopp et al. 1977, cited in NRC 1994).

In a recent study (Muttray et al. 2009), 20 volunteers were exposed to acetaldehyde at 50 ppm and to ambient air using a crossover design for 4 h in an exposure chamber. Subjects reported no increase in irritating symptoms after exposure to acetaldehyde as measured by questionnaire. There was a nonsignificant increase in mucociliary transport time, but no change in olfactory threshold. In addition, there was no increase in the concentration of interleukins in nasal secretion and no increase in mRNA levels of inflammatory factors in nasal epithelial cells.

An oral ethanol provocation test using a solution (300 mL) that contained ethanol at 10% and glucose at 5% was performed in Japanese asthmatics (Matsuse et al. 2007). Bronchoconstriction was noted in 21 of 46 asthmatics and corresponded with increased blood histamine and acetaldehyde concentrations and decreased enzymatic activity of acetaldehyde dehydrogenase 2 (ALDH2). An investigation of the direct effect of increasing concentrations of aerosolized acetaldehyde solutions (5, 10, 20, and 40 mg/mL) administered with a nebulizer was conducted in asthmatics with and without pretreatment with the antihistamine terfenadine and in healthy controls (Myou et al. 1993). Asthmatics had a significant decrease (more than 20%) in FEV_1 compared with healthy subjects and asthmatics pretreated with terfenadine. There was a significant correlation between the acetaldehyde concentration and the methacholine concentration needed to cause a 20% decrease in FEV_1. The authors concluded that acetaldehyde causes bronchoconstriction in asthmatics indirectly through histamine release (Myou et al. 1993). A later study demonstrated that acetaldehyde administered by nebulizer can increase nonspecific bronchial hyperresponsiveness as measured by methacholine provocation in asthmatics independently of histamine release (Myou et al. 1994). Various additional studies have shown the sensitivity of the asthmatic population to acetaldehyde exposure (Myou et al. 1995; Fujimura et al. 1999; Sanchez-Toril et al. 2000; Prieto et al. 2000, 2002a,b).

OEHHA (2008) converted the concentrations of inhaled acetaldehyde delivered by nebulizer in the various studies in milligrams per milliliter to approximate air concentrations in parts per million. The authors noted the uncertainty in the conversions related to inconsistencies in nebulizer delivery systems. Given the limitations, the acetaldehyde concentration producing a 20% reduction in FEV_1 in adult asthmatics was estimated to range from 286 to 692 ppm (geometric means). The lowest individual concentration was 59 ppm. Although the inhalation-challenge studies are difficult to relate to exposure to airborne acetaldehyde because of the method of administration (inhalation of nebulized solutions through the mouth), the studies indicate sensitivity to bronchoconstriction in asthmatics, particularly those with genetic impairment in ALDH2 activity. The calculated concentrations, however, overestimate the concentration that would reach the middle to lower respiratory tract in normal airborne exposures because the method of administration bypasses the upper respiratory tract and does not account for uptake there.

Occupational and Epidemiologic Studies

Mucous-membrane irritation was measured in workers exposed to two suppliers' cutting fluids that contained acetaldehyde and formaldehyde. The incidence of nasal irritation ranged from less than 10% after exposure to one of the cutting fluids to 30-40% after exposure to the other, but there was no consis tent correlation between reported symptoms and aldehyde concentrations in the fluids or in the ambient air according to the limited air-monitoring data (Jarvholm et al. 1995).

In a study of acetaldehyde-production workers, total cancer incidence was higher than in the background German population (Bittersohl 1974, cited in NRC 1994). Concentrations in the factory workroom after equipment leakages were 0.56-3.88 ppm (Bittersohl 1975, cited in ACGIH 2001). Of the nine cancers in the cohort of 220 workers, the incidences of oral cancer (two cases) and bronchial cancer (five cases) were highest (Bittersohl 1974, cited in NRC 1994). Major deficiencies of the study were the small number of subjects, the 100% smoking rate in those with cancer, and the presence of various confounding exposures, which made it impossible to evaluate the carcinogenic potential of acetaldehyde (Bittersohl 1974, cited in NRC 1994).

Effects in Animals

Acute Toxicity

Appelman et al. (1982) reported a 4-h LC_{50} in rats of 13,300 ppm, whereas a higher LC_{50} in rats of 20,000 ppm was reported for a 30-min exposure (Skog 1950, cited in ACGIH 2001). At 5,000 ppm for the first 30 min of exposure, rats showed dyspnea and excitation (Appelman et al. 1982). ALDH2-/- transgenic mice (representing ALDH2-deficient humans) demonstrated greater sensitivity to acetaldehyde after a 4-h exposure at 5,000 ppm than wild-type (ALDH2+/+) mice (Isse et al. 2005). ALDH2+/+ mice showed flushing, whereas ALDH2-/-mice showed tears, straggling gait, prone position, pale skin, abnormal deep respiration, dyspnea, and one death. Both types of mice showed crouching, bradypnea, and piloerection.

Studies of acute effects in laboratory animals have noted mucosal and sensory irritation, breathing-rate decreases mediated by the trigeminal nerve reflex (Alarie 1973), ciliostasis (Dalhamn and Rosengren 1971, cited in NRC 1994), and DNA-protein cross-link formation in the respiratory and olfactory mucosa (Lam et al. 1986). The acetaldehyde concentration resulting in a 50% reduction in respiratory rate (RD_{50}) in two mouse strains was reported to be about 2,800-2,900 ppm in 10 min compared with formaldehyde at about 3-5 ppm and acrolein at 1-1.4 ppm (Steinhagen and Barrow 1984). The RD_{50} in rats exposed to acetaldehyde vapor for the first 3 min was 3,046 ppm compared with formaldehyde at 10 ppm and acrolein at 9 ppm (Cassee et al. 1996). At the lowest acetaldehyde concentration tested (2,800 ppm), the immediate decrease in respiratory rate (to about 55% of normal) in the first 3 min was followed by partial recovery to about 90% of normal over the remainder of the 30-min exposure period and nearly full to full recovery in the 10-min period after exposure (Cassee et al. 1996). Within 30 min, an acetaldehyde concentration of about 560 ppm produced stasis of cilia in rabbit tracheal explants (Dalhamn and Rosengren 1971, cited in NRC 1994). Acute exposure to acetaldehyde (for 6 h) resulted in increased DNA-protein cross-link formation in the nasal respiratory mucosa of rats at 1,000 and 3,000 ppm but not at 100 or 300 ppm (Lam et al. 1986). No such increase was found in the nasal olfactory mucosa after a single 6-h exposure, but a significant increase occurred at 1,000 ppm after repeated exposure 6 h/day for 5 days.

Repeated Exposure and Subchronic Toxicity

A 90-day inhalation study in hamsters used exposure concentrations of 390-4,560 ppm 6 h/day, 5 days/week (Kruysse et al. 1975). At the highest concentration, effects included severe histopathologic changes in the respiratory tract, irritation of the eyes and nose, growth retardation, increased numbers of erythrocytes, and increased heart and kidney weights. No toxic effects were reported at 390 ppm.

Rats exposed to acetaldehyde at 5,000 ppm 6 h/day, 5 days/week for 4 weeks showed growth reduction, more neutrophils and fewer lymphocytes in blood, reduced urine production with increased urine specific gravity, increased lung weights, and severe degeneration with hyperplasia and metaplasia of the nasal, laryngeal, and tracheal epithelium (Appelman et al. 1982). At 1,000 and 2,200 ppm, growth reduction and increased urine production in males was observed. Moderate to severe degeneration of the nasal olfactory epithelium with hyperplasia or metaplasia was observed in most animals at 2,200 ppm, whereas slight to moderate degenerative changes of the nasal olfactory epithelium without hyperplasia or metaplasia were observed in most animals at 1,000. Minimal epithelial changes of the larynx and trachea were also observed at 2,200 ppm. At 400 ppm, degeneration of the nasal olfactory epithelium was slight to moderate in most animals, without hyperplasia or metaplasia but with loss of microvilli, thinning and disarrangement of epithelial cells, and occasional loss of sensory cells. Thus, increasing acetaldehyde concentrations were associated with more severe epithelial lesions and effects deeper into the respiratory tract, going beyond the nasal cavity at 2,200 ppm.

A follow-up study examined the effect of variable vs fixed exposure concentrations of acetaldehyde in male rats (Appelman et al. 1986). Exposure concentrations were 110, 150, or 500 ppm 6 h/day, 5 days/week for 4 weeks. At the highest concentration, animals were divided into three groups, each of which was exposed to one of the following daily exposure regimens: (1) one 6-h exposure, (2) two 3-h exposures separated by 1.5 h with no exposure, or (3) same as regimen 2 but with four 5-min peak exposures (6 times the exposure concentration) during each 3-h exposure. Regimen 3 was used for the 110-ppm group of rats, and regimens 1 and 2 for the 150-ppm group. Rats exposed at 500

ppm showed degeneration of the olfactory epithelium with little difference among the three exposure regimens. The group exposed at peaks of 3,000 ppm showed irritation, excitation, a reduction in body-weight gain, and greater reduction in the phagocytotic index of lung macrophages. No effects related to acetaldehyde exposure were observed in the rats exposed at 150 ppm or exposed at 110 ppm with a peak of 660 ppm. The investigators concluded that the fixed, variable, or peak exposure regimens tested had little effect on the toxicity of acetaldehyde to nasal epithelial cells.

Another 4-week study examined pulmonary effects in nonsensitized or ovalbumin-sensitized guinea pigs that were challenged with an ovalbumin aerosol at the end of 4 weeks of exposure to acetaldehyde 6 h/day, 5 days/week (Lacroix et al. 2002). The acetaldehyde concentration was intended to be a low, environmentally relevant concentration of 200 ppb (0.2 ppm). However, the chamber concentration varied widely, and the exposure concentrations were lognormally distributed with a geometric mean of 149.9 ppb for the nonsensitized group and 221.9 ppb for the sensitized group, both with a geometric standard error of the mean of 0.6. Histopathology results were summarized briefly without details. Nonsensitized guinea pigs reportedly showed slight irritation (metaplasia or hyperplasia) of the respiratory epithelium of the nasal cavity, trachea, and lungs. Sensitized guinea pigs showed moderate irritation of the trachea and lungs. Nonsensitized guinea pigs also showed a significant increase in alveolar macrophages, which indicated pulmonary inflammation.

The results of the Lacroix et al. study are inconsistent with the rest of the literature. No other studies report histopathologic lesions beyond the nasal cavity into the trachea and lungs after exposure to a concentration as low as 0.2 ppm. Observations in the control (ambient-air) group are not described, so it is not possible to evaluate fully whether the effects were related to acetaldehyde exposure, husbandry conditions, or other factors. In addition to the wide variation in chamber concentrations, the sample-collection and analytic methods are described incompletely with respect to sample validation (such as collection efficiency and method for generating standard curves) and limits of detection. Thus, the results do not appear to be reliable for setting an exposure guidance level.

A subchronic study in rats (Dorman et al. 2008) investigated the concentration-response relationship for acetaldehyde-induced nasal lesions, nasal epithelial cell proliferation, and DNA-protein cross-link formation. Rats were exposed to acetaldehyde at 0, 50, 150, 500, or 1,500 ppm 6 h/day, 5 days/week for up to 65 days of exposure. No treatment-related systemic toxicity or effects on body-weight gain or on the trachea or lungs were observed. Histologic examinations of the olfactory epithelium showed no effects at 50 ppm, relatively little olfactory neuronal loss at 150-500 ppm, and moderately severe lesions at 1,500 ppm. The severity of olfactory neuronal loss increased with exposure duration from 4 to 65 days. Increased olfactory epithelial cell proliferation was also reported at the highest concentration. Exposures at 500 and 1,500 ppm resulted in inflammation, hyperplasia, and squamous metaplasia of the respiratory epithelium (Dorman et al. 2008). In contrast with the observations of Lam et al. (1986) at 1,000 ppm, no effect of acetaldehyde on DNA-protein cross-link formation was observed, even at 1,500 ppm.

Oyama et al. (2007) exposed wild-type (ALDH2+/+) and ALDH2-/-knockout mice to acetaldehyde at 0, 125, and 500 ppm 24 h/day for 14 days. ALDH2-/- mice, particularly at the highest concentration, showed greater erosion of the nasal respiratory epithelium; hemorrhage of the nasal subepithelium; hemorrhage of the nasal cavity; degeneration of the respiratory epithelium in larynx, pharynx, and trachea; erosion of the dorsal skin; and higher acetaldehyde blood concentration than the wild-type mice. Relatively few effects on the olfactory epithelium were reported; one of five wild-type and knockout mice showed slight degeneration of cells at 500 ppm. Some of the effects were increased in wild-type mice compared with controls, primarily at 500 ppm. Fewer effects were reported in the mice compared with controls at 125 ppm, and knockout and wild-type mice were more similar in response.

Chronic Toxicity

Feron (1979, cited in EPA 1991 and ACGIH 2001) conducted a 52-week study in hamsters exposed to acetaldehyde at 1,500 ppm 7 h/day, 5 days/week. Treatment-related effects included epithelial hyperplasia, metaplasia of the nasal mucosa, inflammation of the nasal cavity and trachea, growth retardation, slight anemia, increased urinary glutamic-oxaloacetic transaminase activity, increased protein content, and increased kidney weights without pathologic

changes. No evidence of carcinogenicity was reported. Because only one concentration was used, no evaluation of a dose-response relationship or no-effect level was possible.

In a 52-week study (7 h/day, 5 days/week) in hamsters, acetaldehyde concentrations were gradually reduced from 2,500 ppm to 1,650 ppm (Feron et al.1982, cited in EPA 1991 and ACGIH 2001). The combined tumor incidence in the larynx (carcinoma in situ, squamous cell carcinoma, and adenosquamous carcinoma) was significantly higher in the exposed group than in the controls. Simultaneous exposure to acetaldehyde and benzo[a]pyrene (administered intratracheally) increased malignant respiratory tract tumors over those in animals exposed to air or acetaldehyde alone by a factor of 3-5.

Woutersen et al. (1986) exposed rats to acetaldehyde at 0, 750, and 1,500 ppm for up to 28 months. They also exposed rats at 3,000 ppm but gradually decreased this concentration over the course of the study to about 1,000 ppm by day 359 because of signs of morbidity (such as severe growth reduction) and early mortality. All treatment groups showed non-neoplastic changes (degeneration, hyperplasia, and metaplasia) and adenocarcinomas of the olfactory epithelium. The two highest-exposure groups also showed squamous cell carcinomas of the respiratory epithelium and hyperplasia and keratinized squamous metaplasia of the laryngeal epithelium. In addition, the highest-exposure group showed rhinitis and sinusitis.

Reproductive Toxicity in Males

No studies that reported male reproductive toxicity of acetaldehyde were located.

Immunotoxicity

The immune system is not reported to be a critical target of acetaldehyde toxicity. No immunologic effects are reported below concentrations that cause respiratory toxicity (Environment Canada and Health Canada 2000). Mice showed an 8% increase in bactericidal activity of alveolar macrophages after a single 3-h exposure to acetaldehyde at 204 ppm but a 15% reduction after repeated exposure at 180 ppm 3 h/day for 5 days (Aranyi et al. 1986). Neither exposure regimen affected mortality from streptococcal infection. Various in vitro tests have indicated effects on immune-system cells, but concentrations used in the cell cultures are much higher than what would result in the body from air concentrations causing initial upper respiratory system effects (reviewed by WHO 1995).

The study by Lacroix et al. (2002) investigated the potential for acetaldehyde to increase pulmonary allergic responses in guinea pigs. Ovalbumin-sensitized guinea pigs exposed to acetaldehyde at 200 ppb 6 h/day, 5 days/week for 4 weeks showed no changes in biologic measures associated with inflammatory or allergic responses. As noted above, inconsistency with other studies and insufficient description of methods and results limit the usefulness of that study.

Genotoxicity

According to reviews by WHO (1995), NRC (1994), HEI (2007), and Morris (1997a), acetaldehyde is mutagenic in mammalian cells in several (although not all) in vitro systems without exogenous metabolic activation (for example, chromosomal aberrations and sister-chromatid exchanges). Addition of NAD^+ and ALDH to human lymphocyte cultures reduces sister-chromatid exchanges induced by acetaldehyde (Obe et al. 1986, cited in WHO 1995), presumably by oxidizing acetaldehyde. The available evidence indicates that acetaldehyde primarily produces clastogenic effects and sister-chromatid exchanges, but evidence indicating that acetaldehyde causes genetic mutations is sparse (Morris 1997a). A study using an in vitro system involving separated alleles in yeast indicated that acetaldehyde may play a role in mutations of tumor-suppressor gene *TP53*, which is involved in human esophageal cancers (Paget et al. 2008).

In vivo, acetaldehyde induced sister-chromatid exchanges in bone marrow of hamsters after intraperitoneal injection (HEI 2007) and increased micronucleus frequency in reticulocytes in mice after inhalation of acetaldehyde vapor (Kunugita et al. 2008) but did not increase micronucleus frequency in mouse early spermatids after intraperitoneal injection (WHO 1995). Although several in vitro studies indicate that acetaldehyde can react with DNA in forming

DNA-protein and DNA-DNA cross-links (Morris 1997a), studies demonstrating such formation in vivo are few and required high concentrations of acetaldehyde. The in vivo study in rats by Lam et al. (1986) suggested that acetaldehyde at 1,000 ppm can react with DNA and proteins to form stable adducts (Lam et al. 1986; WHO 1995). Dorman et al. (2008) and Stanek and Morris (1999), however, did not observe DNA-protein cross-link formation at 1,500 ppm in rats. Inhibition of ALDH had no effect in inducing DNA-protein crosslink formation at 1,500 ppm (Stanek and Morris 1999).

Standard bacterial test systems (Ames) with or without exogenous metabolic activation have generally had negative or equivocal results for genotoxicity, although acetaldehyde has resulted in reverse mutations in some tests that used *Escherichia coli* (IARC 1985; WHO 1995).

Carcinogenicity

The International Agency for Research on Cancer (IARC) listed acetaldehyde as possibly carcinogenic in humans (category IIB) on the basis of evidence from animal studies. Increased incidences of oral, throat, and esophageal cancers were found after heavy alcohol intake by people who had genetic polymorphisms of an enzyme involved in the metabolism of acetaldehyde (IARC 1999). As a metabolite of alcohol, acetaldehyde was discussed at an IARC meeting about the carcinogenicity of alcoholic beverages. On the basis of mechanistic evidence, the IARC working group concluded that acetaldehyde derived from alcoholic beverages contributed to causing malignant esophageal tumors in humans who are deficient in ALDH2 (Baan et al. 2007; Lachenmeier and Sohnius 2008).

The U.S. Environmental Protection Agency (EPA 1991) has also classified acetaldehyde as a B2 or probable human carcinogen by inhalation on the basis of sufficient animal data (nasal tumors in rats and laryngeal tumors in hamsters). The human evidence was judged to be inadequate on the basis of the epidemiologic study of workers by Bittersohl (1974, cited in EPA 1991) because of the lack of age adjustment of the incidence and several other methodologic limitations, such as exposures to other chemicals, smoking (all the incident cases were in smokers, according to Bittersohl 1975, as cited in ACGIH 2001), “short duration, small number of subjects, and lack of information on subject selection, age, and sex distribution.” EPA (1991) relied on the finding of significantly increased laryngeal tumors in hamsters exposed to acetaldehyde at a time-weighted average concentration of 2,028 ppm 7 h/day, 5 days/week for 52 weeks (Feron et al. 1982, cited in EPA 1991) and on exposure-related increases in multiple types of nasal-cavity tumors in rats exposed to acetaldehyde at 0, 750, or 1,500 ppm or at an initial concentration of 3,000 ppm that was gradually decreased to 1,000 ppm 6 h/day, 5 days/week for up to 28 months (Woutersen et al. 1986). Squamous cell carcinomas of the nasal respiratory epithelium showed clear concentration-related increases, whereas adenocarcinomas of the olfactory epithelium were highest in the middle-concentration group, possibly because of high mortality and competing squamous cell carcinomas in the high-concentration group.

TOXICOKINETIC AND MECHANISTIC CONSIDERATIONS

Toxicokinetic and mechanistic data on acetaldehyde have been reviewed in several publications (WHO 1995; Morris 1997a; Environment Canada and Health Canada 2000; EC 2004; HEI 2007; Deitrich et al. 2007). As a highly reactive, electrophilic compound, acetaldehyde readily binds with tissues and with sulfhydryl moieties of free proteins and nonprotein sulfhydryl groups, such as cysteine and glutathione. Acetaldehyde binding to intracellular thiols (cysteine and glutathione) may prevent binding to proteins, peptides, and DNA. Conjugation with thiols can result in various intermediates and later elimination of thioethers and disulfides in the urine. Inhaled acetaldehyde is largely retained at the initial site of contact with little increase in blood concentrations except at high airborne concentrations that exceed the capacity of respiratory tissues for binding and metabolism. Once aldehydes are absorbed after inhalation or ingestion, their primary reported metabolism and detoxification pathway is oxidation to acetate via the NAD^+-dependent enzyme, ALDH. Acetate is further metabolized to carbon dioxide and water or enters the two-carbon pool for molecular synthesis reactions.

Of the 19 known ALDH enzymes in humans, only a few are involved in aldehyde oxidation for which genetic polymorphisms can result in hereditary defects in metabolism of normal endogenous substrates (Deitrich et al. 2007).

Most notably, polymorphism in the ALDH2 gene affects the mitochrondrial enzyme primarily responsible for oxidation of ethanol-derived acetaldehyde. A common polymorphism of that gene inhibits enzymatic activity, and this has resulted in reduced clearance of acetaldehyde in both homozygotic and heterozygotic people. Such people are protected from alcohol abuse (because of the unpleasant effects of acetaldehyde accumulation) but may be more at risk for esophageal, pharyngeal, and oral cancer (Deitrich et al. 2007; Kunugita et al. 2008). The frequency of polymorphisms for slow clearance of acetaldehyde may be as high as 50% in some populations (for example, Japanese) (Kunugita et al. 2008).

Other enzymes (such as aldehyde oxidase, xanthine oxidase, cytochrome P450 oxidase, and glyceraldehyde-3-phosphate dehydrogenase) may also play a role in acetaldehyde metabolism, but their contribution to total metabolic activity is small (Deitrich et al. 2007).

Although the liver is the primary location of ALDH activity, it is also present in other tissues. ALDH has been shown to be present in the noses of rats, hamsters, mice, and guinea pigs and is thought to be a detoxification pathway for inhaled aldehydes (Morris 1997a,b). ALDH activity in the respiratory tract of rats is primarily in the nasal respiratory epithelium (particularly in ciliated epithelial cells) and in Clara cells of the lower bronchioles; there is low activity in the tracheal epithelium and virtually no activity in the olfactory epithelium (Bogdanffy et al. 1986). Morris (1997b) reported that in all four rodent species studied, uptake of acetaldehyde in the upper respiratory tract was 2-3 times more efficient at 1-10 ppm than at 1,000 ppm; this suggests a saturable process for acetaldehyde removal in the tissues. The rank order among mice, rats, hamsters, and guinea pigs in scrubbing efficiency of acetaldehyde in the upper respiratory tract differed between high and low concentrations, and this makes extrapolation of toxicity from high to low concentrations in rodents complex. Capacity limitation of nasal metabolism occurs when the rate of acetaldehyde delivered to the nasal tissues exceeds the total metabolic capacity of the tissues (Morris 1997b) or such protective mechanisms as binding to intracellular thiols (Environment Canada and Health Canada 2000). Thus, above some critical concentration, tissue concentrations of acetaldehyde increase as deposition exceeds metabolism (Heck 1997). Morris and Blanchard (1992) noted that the acetaldehyde deposition rate exceeds the rate of metabolism at 100 ppm and 1,000 ppm but not at 1 ppm or 10 ppm. A decrease in mucosal absorption in the upper airways also results in more penetration to lower airways.

Much of the observed decrease in the efficiency of uptake of acetaldehyde in rats between 10 and 100 ppm is thought to be attributed to saturation of metabolism because the concentration dependence disappears after pretreatment with an ALDH inhibitor (Morris 1999). Humans with the inactive variant of ALDH2 may have a lower critical concentration for saturation of acetaldehyde removal, which results in increased tissue concentrations in the upper respiratory tract, greater potential for systemic absorption, and deeper penetration at lower concentrations than in those with the active form of this enzyme. Using a knock-out-gene mouse model to represent ALDH2-deficient humans, Oyama et al. (2007) showed greater effects on the upper respiratory tract and higher blood acetaldehyde concentrations in ALDH2-/- mice than in wild-type mice after exposure to acetaldehyde at 125 ppm or 500 ppm for 24 h/day for 14 days. At 125 ppm, blood acetaldehyde concentrations measured in three ALDH2-/- mice were about 1.4 times higher than those in three wild-type mice; however, at 500 ppm, blood acetaldehyde concentrations were 5 times higher in ALDH2-/- mice than in wild-type mice. In a previous study by the same group (Isse et al. 2005), the difference in blood acetaldehyde concentrations after exposure at 5,000 ppm for 4 h was about a factor of 2. Although blood acetaldehyde concentrations were not reported for the control (clean-air) group, blood acetaldehyde concentrations in wild-type mice were relatively unchanged between 125 and 500 ppm (1.65 μM and 1.72 μM, respectively) (Oyama et al. 2007). After the 4-h exposure at 5,000 ppm, blood acetaldehyde concentrations in wild-type mice ranged from 80 to 227 μM (Isse et al. 2005), indicating saturation of acetaldehyde metabolism and tissue binding in the respiratory tract and greater systemic absorption at this higher concentration.

The difference in blood acetaldehyde concentrations between wild-type and ALDH2-deficient mice appears to be nonlinear over the air acetaldehyde concentration range examined. At the lower concentration of 125 ppm, the difference is less than a factor of 2, but it increases to a factor of 5 at 500 ppm, reflecting a reduced capacity of removal of acetaldehyde in ALDH2-/- mice because of impaired metabolic activity (Oyama et al. 2007). At the high

concentration (5,000 ppm), the difference in blood acetaldehyde concentration decreases to a factor of 2 as the metabolic capacity of the respiratory tissues is also exceeded in the wild-type mice (Isse et al. 2005).

Related research by Kunugita et al (2008) showed that exposure to acetaldehyde at 125 and 500 ppm for 2 weeks resulted in higher mutagenicity (micronucleus frequency in reticulocytes) in the ALDH2-deficient mice than in the wild-type mice and controls. Micronucleus frequencies were similar between wild-type mice and controls at both concentrations and about 1.5 times higher and 1.75 times higher in deficient mice at 125 and 500 ppm, respectively.

Using the cytokinesis-block micronucleus assay on peripheral lymphocytes from blood samples from 47 healthy Korean subjects, Kim et al. (2005) showed that application of 0 mM, 0.5 mM, and 1.5 mM of acetaldehyde to lymphocytes in vitro increased the micronucleus frequencies in a dose-dependent manner. At the highest concentration, a 2-fold increase in micronucleus frequency over baseline (0 mM) was observed in lymphocytes from subjects with wild-type genotype ($ALDH2^1$) compared with a 3-fold increase in micronucleus frequency in lymphocytes from heterozygotes ($ALDH2^1/ALDH2^2$) and a 3.5-fold increase in micronucleus frequency in lymphocytes from homozygotes ($ALDH2^2/ALDH2^2$). The relative difference between the homozygotes and the wild-type was thus about 1.75 fold.

INHALATION EXPOSURE LEVELS FROM THE NATIONAL RESEARCH COUNCIL AND OTHER ORGANIZATIONS

A number of organizations have established or proposed acceptable exposure limits or guidelines for inhaled acetaldehyde. Selected values are shown in Table 2-2.

COMMITTEE RECOMMENDATIONS

The committee's recommended EEGLs and CEGL for acetaldehyde are shown in Table 2-3. The current U.S. Navy values (R. Hagar, Naval Sea Systems Command, personal commun., August 5, 2008) are provided for comparison.

1-Hour EEGL

The 1-h EEGL is based on human ocular and nasal irritation. As discussed above, Muttray et al. (2009) evaluated the protectiveness of the German occupational level for acetaldehyde and exposed 20 human subjects to acetaldehyde at 50 ppm for 4 h. They found no self-reported increase in irritating symptoms, a nonsignificant increase in mucociliary transport time but no change in olfactory threshold, no increase in the concentration of interleukins in nasal secretion, and no increase in mRNA levels of inflammatory factors in nasal epithelial cells. Their results differed from those in the study of Silverman et al. (1946), in which several subjects objected to acetaldehyde at 25 ppm (reason not specified) and most of the subjects (about 12) reported some eye irritation at 50 ppm. However, the recent study used a stronger crossover design, included various clinical and subclinical measures of irritation or inflammatory effects, and involved more people. It is possible that neither study included people who were more sensitive, such as those who were ALDH2-deficient.

ALDH2-deficient people may be more sensitive because of decreased acetaldehyde metabolism in epithelial tissues. Therefore, an uncertainty factor of 2 was applied to the 50-ppm exposure level to yield a 1-h EEGL of 25 ppm. The uncertainty factor is based on the difference between blood acetaldehyde concentrations in ALDH2-deficient and wild-type mice at low air concentrations (a factor of about 1.4 at 125 ppm; Oyama et al. 2007), evidence of micronucleus formation in reticulocytes of ALDH2-deficient and wild-type mice (a factor of about 1.5 at 125 ppm; Kunugita et al. 2008), and in vitro evidence in human lymphocytes from people who were ALDH2-deficient and people who had normal ALDH activity levels (a factor of about 1.75; Kim et al. 2005). Although those measures of the effect of ALDH2 deficiency are more systemic, ALDH activity in some epithelial tissues will affect the rate of acetaldehyde removal and thus the degree of irritation. Evidence from the above studies showing a reduction in the difference between impaired and normal ALDH2 activity with a decrease in air acetaldehyde concentration indicates that the difference may be even lower than a factor of 1.4-1.5 at 50 ppm compared with that at 125 ppm. Thus, an

uncertainty factor of 2 should help to account for other potential differences in sensitivity among individuals. Any potential irritation at 25 ppm would be expected to be mild and not to interfere with duties during a 1-h emergency.

24-Hour EEGL

The basis of the 24-h EEGL is the study conducted by Oyama et al. (2007) in which ALDH2-deficient and wild-type mice were exposed to acetaldehyde 24 h/day for 14 days. The lowest exposure concentration used in the study (125 ppm) was associated primarily with nasal epithelial lesions, which tended to be more severe in the ALDH2-deficient mice (that is, ALDH wild-type mice showed fewer effects in terms of number of tissues, types of pathologic effects, and number of animals showing effects). Lesions after 1 day are expected to be minimal compared with those after 2 weeks of exposure, and the variation in response between rats and humans with respect to such direct irritation was expected to be less than a full factor of 10. Therefore, an uncertainty factor of 3 to extrapolate from a lowest observed-adverse-effect level (LOAEL) to a no-observed-adverse-effect level (NOAEL) and an interspecies uncertainty factor of 3 to extrapolate from rats to humans were used to yield a total uncertainty factor of 10. An additional intraspecies uncertainty factor for variation within humans was not included because the sensitive ALDH2-deficient mice were used. The resulting 24-h EEGL is 12.5 ppm, which is half the 1-h EEGL based on irritation in humans and one-fourth of the NOAEL for eye irritation in the human study by Muttray et al. (2009). Furthermore, the 24-h EEGL should be protective against nasal lesions, which develop at higher exposures associated with greater irritation and more prolonged exposure.

90-Day CEGL

The subchronic study in rats by Dorman et al. (2008) was selected as the basis of a 90-day CEGL because of the study's comprehensive evaluation of the lower dose-response range and modeling of corresponding tissue concentrations to relate to 24-h continuous air concentrations for humans. The study showed a NOAEL of 50 ppm for olfactory epithelial effects.

Dorman et al. (2008) estimated a reference concentration for acetaldehyde based on the 50-ppm NOAEL in rats (see Figure 2-1). According to EPA (1994) guidelines, a reference concentration is intended to be protective in continuous exposure up to a lifetime for the general public, including sensitive populations. EPA's reference concentration for acetaldehyde includes a conversion of the air exposure concentration in rats to a human-equivalent concentration in an attempt to address the anatomic and physiologic differences between rats and humans (EPA 1991). Rather than using the EPA default cross-species ratio for reactive gases, Dorman et al. (2008) used a physiologically based pharmacokinetic (PBPK) model in rats to relate the NOAEL concentration of 50 ppm to a nasal tissue concentration in rats. The rat tissue concentration was divided by an uncertainty factor of 30 to extrapolate it to a human nasal tissue concentration. Dorman et al. (2008) then used a PBPK model for humans to provide the corresponding acetaldehyde concentration in air for a 24-h daily exposure (0.4 ppm). Dorman et al. (2008) also calculated the reference concentration by converting the rat nasal tissue concentration to a human-equivalent air concentration by using the PBPK model in humans and then applying the uncertainty factor of 30 (see Figure 2-1). That approach yielded approximately the same reference concentration as calculated by the other approach. Dorman et al. (2008) did not apply an additional uncertainty factor for extrapolating subchronic to chronic exposure because no additional damage would be expected for a longer duration of exposure at the NOAEL for epithelial tissue injury (D. Dorman, North Carolina State University College of Veterinary Medicine, personal commun., December 4, 2008).

The reference concentration derived by Dorman et al. (2008) is intended to be protective of the general public. The uncertainty factor used to extrapolate to human exposures may differ between submariners and the general population. Dorman et al. (2008) used a combined uncertainty factor of 30 composed of a factor of 3 for pharmacodynamic differences between rats and humans (the model accounted for pharmacokinetic differences) and a factor of 10 for variation among humans (D. Dorman, North Carolina State University College of Veterinary Medicine, personal commun., December 4, 2008). However, because the submariner population is considered to be healthier and less susceptible than the general population, the committee used a factor of 2 instead of 10 for variation in humans based on the ALDH2-deficient polymorphism. Differences in human sensitivity to acetaldehyde are expected to be less

variable at low air concentrations because it is associated with direct tissue effects at the site of entry rather than systemic effects. The combined uncertainty factor is 6 on the basis of a factor of 3 for pharmacodynamic differences between rats and humans and a factor of 2 for intraindividual variation.

Because Dorman et al. (2008) found little difference between application of the uncertainty factor to the rat tissue concentration calculated by the PBPK model in rats and application of the uncertainty factor to the human-equivalent air concentration calculated by the PBPK model in humans, the committee used the human-equivalent air concentration as a starting point to calculate the CEGL to avoid the need to rerun the model. Thus, an uncertainty factor of 6 was applied to the human-equivalent air concentration of 12.51 to yield a CEGL of 2 ppm.[2]

CARCINOGENICITY ASSESSMENT

EPA (1991) calculated an inhalation unit risk factor for assessing risks to the general public with the linearized multistage model based on the data on nasal cavity tumors in rats (Woutersen and Appelman 1984, cited in EPA 1991; Woutersen et al. 1985, cited in EPA 1991; Woutersen et al. 1986). The resulting unit risk value is 2.2×10^{-6} per microgram of acetaldehyde per cubic meter, assuming 24-h daily exposure for a lifetime. Implicit in that risk value is the assumption of no threshold dose below which the cancer risk is negligible. Given a total exposure time for a submariner over his career of 5 years and the U.S. Navy's acceptable cancer risk of 1×10^{-4} (NRC 1986), the corresponding acetaldehyde concentration is 0.35 ppm.[3]

That concentration is about 0.18 the calculated 90-day CEGL based on noncancer effects. The EPA cancer risk assessment is based on the assumption that the tumors observed in animals at high doses can be extrapolated to lower doses with no threshold for negligible cancer risk. However, as for formaldehyde (NRC 2007), considerable evidence indicates that the mechanism of action for tumor formation at high concentrations is related to cytotoxicity, hyperplasia, and cellular proliferation in the nasal cavity. Given the mutagenicity of acetaldehyde, lower doses could be associated with a risk of cancer through some genotoxic mechanism, although no specific models have been developed to assess such risk for acetaldehyde. Lower doses would not have cell proliferation to amplify the genotoxic effects and therefore would be associated with a substantially lower risk of tumor formation. The toxicokinetic and mechanistic evidence suggests that the dose-response relationship for acetaldehyde toxicity may also be nonlinear as the activity of ALDH becomes saturated; this would allow tissue concentrations to increase more rapidly. As a result, the cancer risk at lower doses would be less than predicted based on extrapolation from high doses. DNA-protein cross-link formation, which has been used to model low-dose formaldehyde cancer risk (Conolly et al. 2003), was not shown to demonstrate a dose-response relationship for acetaldehyde concentrations of 50-1,500 ppm (Dorman et al. 2008). Stanek and Morris (1999) likewise found no evidence of increased DNA-protein cross-link formation in rats exposed at 1,500 ppm even with administration of an ALDH inhibitor.

Dorman et al. (2008) note that rats and mice may be more predisposed to nasal lesions (and thus nasal tumors) than humans. Rats and mice are obligate nose breathers in which a larger portion of the nasal cavity (50% vs 10% in humans) is lined with olfactory mucosa. The network of ethmoid turbinates in the caudal region of the nasal cavity in rats also greatly expands the surface area of the olfactory mucosa and decreases air flow. Those factors in combination increase the concentration of acetaldehyde delivered to the olfactory mucosa. Lower ALDH activity in the olfactory epithelium in rats (Bogdanffy et al. 1986) would also make this tissue more susceptible to injury from acetaldehyde. Consequently, the 90-day CEGL based on protection of submariners from noncancer effects of acetaldehyde should also be protective against cancer.

DATA ADEQUACY AND RESEARCH NEEDS

Although data for assessing NOAELs for the different acetaldehyde guidance levels are available, uncertainties in setting exposure limits for submariners include the relative paucity of studies available for defining the lower limits for eye irritation, the relative effect of ALDH2 polymorphisms in increasing sensitivity to irritation, and the chronic injury at low airborne concentrations of acetaldehyde. More research on carcinogenic mechanisms of inhaled acetaldehyde at low doses is needed to evaluate the potential carcinogenic risk at low concentrations.

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Footnotes

1 Silverman et al. (1946) exposed different subjects to a number of chemicals at various concentrations but did not report the specific number of subjects for each chemical exposure. They reported that an average of 12 subjects of both sexes were used for each solvent exposure.

2 The committee notes that a peer-reviewed HEC value was used here to derive the CEGL, whereas HEC values were not used in other EEGL and CEGL derivations because no other peer-reviewed values were available and only a default method would have been available to calculate the values.

3 $[1 \times 10^{-4}\ (1\ \mu g/m^3 / 2.2 \times 10^{-6})]\ (70/5) = 636\ \mu g/m^3$ or $0.636\ mg/m^3$ (0.35 ppm).

Figures

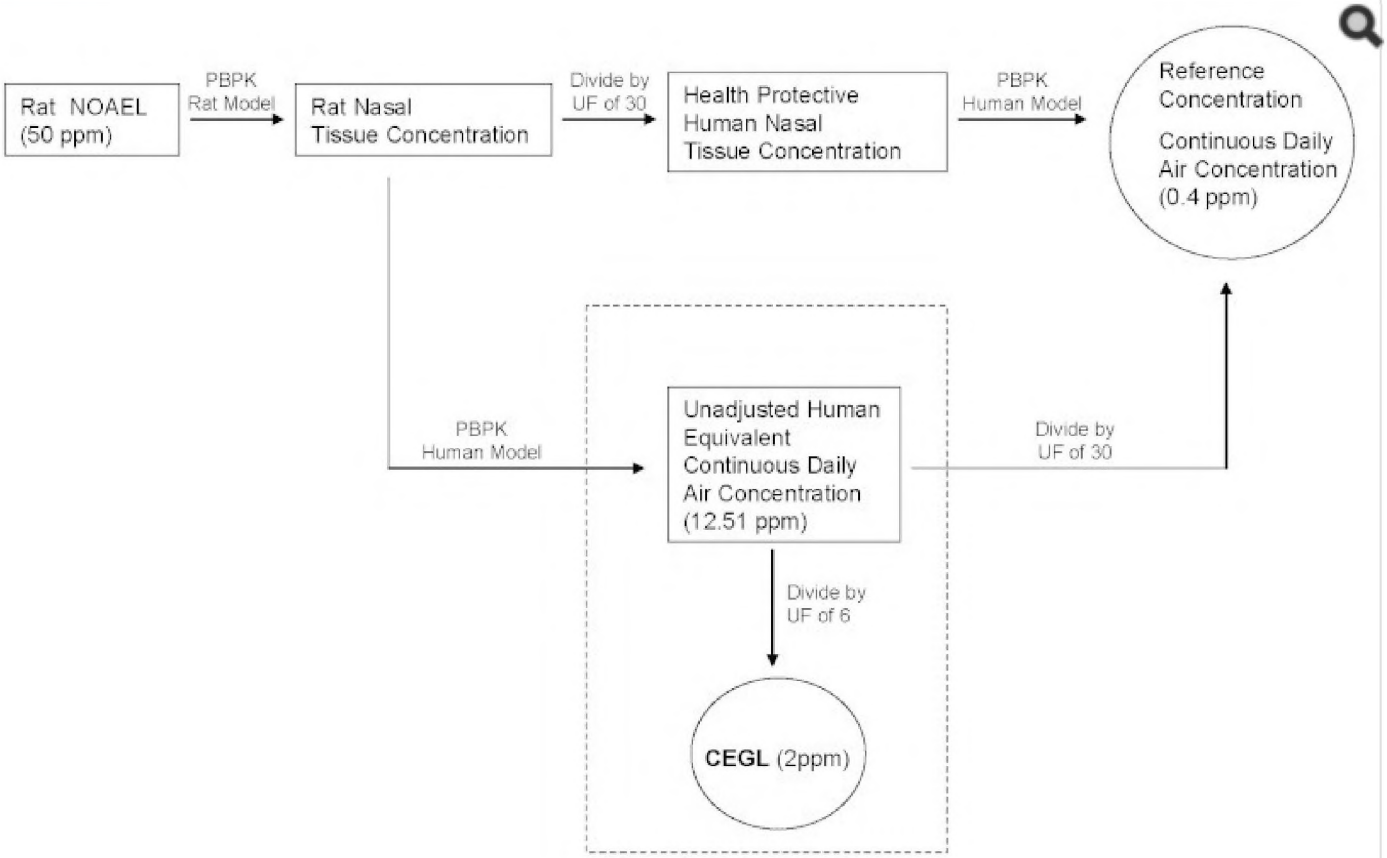

FIGURE 2-1

Calculation of the acetaldehyde reference concentration by Dorman et al. (2008). The pathway in the box shows the committee's calculation of the CEGL.

Tables

Table 2-1 Physical and Chemical Properties of Acetaldehyde

Synonyms	Acetic aldehyde, ethanal, ethyl aldehyde
CAS registry number	75-07-0
Molecular formula	CH_3CHO
Molecular weight	44.05
Boiling point	21°C
Melting point	−23.5°C
Flash point	−38.9°C (closed cup)
Explosive limits	Lower limit, 4.1%; upper limit, 55% by volume
Specific gravity	0.788 at 16°C
Vapor pressure	902 mmHg at 25°C
Solubility	Miscible with water and most common organic solvents
Conversion factors	1 ppm = 1.8 mg/m^3; 1 mg/m^3 = 0.56 ppm

Sources: Budavari et al. 1989, HSDB 2005.

TABLE 2-2 Selected Inhalation Exposure Levels for Acetaldehyde from the National Research Council and Other Agencies[a]

Organization	Type of Level	Exposure Level (ppm)	Reference
Occupational			
ACGIH	TLV-ceiling	25	ACGIH 2001
NIOSH	REL	Ca[b]	NIOSH 2005
OSHA	PEL-TWA	200	29 CFR 1910.1000
Spacecraft			
NASA	SMAC		NRC 1994
	1-h	10	
	24-h	6	
	30-day	2	
	180-day	2	
General public			
NAC (interim)	AEGL-1 (1-h)	45	EPA 2006
	AEGL-2 (1-h)	270	
	AEGL-1 (8-h)	45	
	AEGL-2 (8-h)	110	

a Comparability of EEGLs and CEGLs with occupational-exposure and public-health standards or guidance levels is discussed in Chapter 1 ("Comparison with Other Regulatory Standards or Guidance Levels").

b Potential occupational carcinogen.

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AEGL, acute exposure guideline level; NAC, National Advisory Committee; NASA, National Aeronautics and Space Administration; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; SMAC, spacecraft maximum allowable concentration; TLV, Threshold Limit Value; TWA, time-weighted average.

TABLE 2-3 Emergency and Continuous Exposure Guidance Levels for Acetaldehyde

Exposure Level	Current U.S. Navy Values (ppm)	Committee Recommended Values (ppm)
EEGL		
1-h	10	25
24-h	6	12.5
CEGL		
90-day	2	2

Abbreviations: CEGL, continuous exposure guidance level; EEGL, emergency exposure guidance level.

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