

Acetaldehyde

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Acetaldehyde

INTRODUCTION

Acetaldehyde (CAS Registry Number 75-07-0, C₂H₄O, molecular weight = 44.1) (Figure 1), also known as ethanal, is ubiquitous in the environment and is a product of numerous natural, industrial, and combustion processes.

Acetaldehyde is present in many ripe fruits, such as apples, grapes, and citrus fruits, as well as in roasted coffee beans, essential oils, wine, and other foods. It is the main metabolite of ethanol, the alcohol found in alcoholic beverages. Indeed, such beverages are the general population's principal source of exposure to acetaldehyde.

Acetaldehyde is used extensively as a chemical intermediate in the production of plastics and resins, the manufacture of paper, and the synthesis of organic chemicals. It is released into the environment by numerous industrial sources as well as the combustion of hydrocarbons found, for example, in wood, tobacco, and fossil fuels used in vehicles.

At one atmosphere pressure and 25°C, 1 ppm acetaldehyde is equivalent to 1.82 mg/m³.

BENCHMARK LITERATURE

The following evaluation of research literature on acetaldehyde is based on data and source tables listed in Appendices B and D (available on the HEI Web site) of this report. Additional information was obtained from two large studies (Kinney et al. 2002; Weisel et al. 2005). Personal-exposure data also came from these two studies (Kinney et al. 2002; Weisel et al. 2005). Data summaries from the EPA Air Quality System database were used to calculate rural, suburban, and urban concentrations of acetaldehyde (EPA 2004a). Data used to assess exposures to acetaldehyde in ambient, outdoor, and indoor air were extracted from publications identified in Appendices B and D of this report. Evaluations of health endpoints were based on information from the International Agency for Research on Cancer (IARC 1999a), U.S. National Toxicology Program (NTP 2005), EPA (1999b, 2000b), and European Commission Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

(European Commission 2004) as well as various published papers cited as the findings are presented.

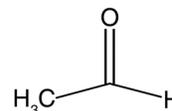


Figure 1. Structure of acetaldehyde.

EXPOSURE

SOURCES AND EMISSIONS

Acetaldehyde is ubiquitous in the environment. It is formed as a product of many processes, including the incomplete combustion of wood in fireplaces and woodstoves, the roasting of coffee beans, the combustion of gasoline and diesel fuel in motor vehicles, refining and waste processing in coal plants, the combustion of fossil fuels in power plants, the photochemical oxidation of hydrocarbons in the atmosphere, and (as an intermediate product) in respiration in plants (EPA 1994a, 2000b; Lakes Environmental Software 1998).

The National Air Toxics Assessment (NATA), conducted by the EPA, estimated that 32.4% of acetaldehyde emissions nationwide are from on-road mobile sources (including automobiles, trucks, and other vehicles) and that 40.8% and 19.1% of emissions are from on-road mobile sources in urban and rural areas, respectively (EPA 2006b). Acetaldehyde can also be produced photochemically in the atmosphere. It is estimated that 56% of ambient concentrations of acetaldehyde in California (in 1987) were from photochemical oxidation of organic precursors and that 44% were from direct-source emissions (California Environmental Protection Agency [California EPA] 1993). It is not known whether these findings are representative of other parts of the U.S.

Indoor sources of acetaldehyde are generally associated with combustion, such as smoke from tobacco or wood fires. Other indoor sources include building materials (e.g., polyurethane foams), cooking, certain consumer products (e.g., adhesives and nail-polish remover), volatilization from certain foods, and infiltration from ambient air sources (California EPA 1993; Lakes Environmental Software 1998).

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

Table 2 and Figure 2 show the range of mean and maximum concentrations of acetaldehyde in $\mu\text{g}/\text{m}^3$ measured in outdoor (including in-vehicle) locations, in indoor environments, and by personal monitoring. The literature on ambient and outdoor concentrations reports acetaldehyde measurements in six different environments (urban, urban roadside, urban in-vehicle, suburban, rural, and

combined urban–suburban–rural). Indoor concentrations are reported for three environments (residences, schools, and offices). One study reported personal-exposure concentrations among inner-city high school students (Sax et al. 2004); another reported personal-exposure concentrations for adults and children (Weisel et al. 2005).

Sampling times reported for ambient measurements ranged from 1 (Grosjean and Grosjean 2002) to 48 hours (Kinney et al. 2002), with concentration-averaging times

Table 2. Acetaldehyde Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures^a

Sample Location and Type	Observations (n)	Averaging Sampling Time	Concentration ($\mu\text{g}/\text{m}^3$)		Citations	Comments
			Mean	Maximum		
Outdoor Areas						
Urban						
	91 averages*	Yearly	2.8	25.5**	EPA 2004a	
	68	Yearly	1.5	3.8	California Air Resources Board 2003	
	73	Yearly	2.8	8.5	California Air Resources Board 2003	
	82	Yearly	0.7	2.7	California Air Resources Board 2003	
	67	Yearly	2.9	10.0	California Air Resources Board 2003	
	76	Yearly	1.2	3.6	California Air Resources Board 2003	
	71	Yearly	1.8	6.1	California Air Resources Board 2003	
	36	8 wk	4.2	—	Kinney et al. 2002	Summer
	36	8 wk	2.8	—	Kinney et al. 2002	Winter
	~ 60	Yearly	3.2	—	South Coast Air Quality Management District 2000	
	~ 60	Yearly	5.2	—	South Coast Air Quality Management District 2000	
	395	Yearly	6.9	25.9	Weisel et al. 2005	2 seasons
	—	—	1.58	—	EPA 2006b	Model
	~ 350	≤ 2 months	1.9–5.4	12.0	Zielinska et al. 1998	
Urban in-vehicle						
	20	Travel time	2.8–63.0	—	Riediker et al. 2003	Bus runs
	50	Travel time	9.0	31.0	Riediker et al. 2003	Car
	115	Travel time	25.2	—	Weisel et al. 2005	Car
Urban roadside						
	8	2 hr	1.5–5.5	—	Grosjean and Grosjean 2002	Tunnel
	10	2 hr	1.1–2.3	—	Grosjean and Grosjean 2002	Tunnel
Suburban						
	33 averages*	Yearly	2.6	19.4**	EPA 2004a	
Rural						
	—	Yearly	0.71	—	EPA 2006b	Model
	33 averages*	Yearly	2.0	15.6**	EPA 2004a	
Urban–suburban–rural combined						
	1875	Yearly	2.5	17.0	EPA 2004d	
	2479	Yearly	1.1	8.8	Pratt et al. 2000	

Table continues on next page

^a Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 10,515 measurements in EPA Air Quality System database (EPA 2004a);

** = maximum average.

ranging from a few days (e.g., Fitz et al. 2003) to 9 years (Pratt et al. 2000). The number of individual measurements per study ranged from a low of 20 for an in-vehicle study (Fitz et al. 2003) to a high of 10,515 for the combined urban–suburban–rural category (EPA 2004a). The 10,515 individual measurements contained in the largest combined data set (EPA 2004a) were acquired and concentrations were calculated for separate urban, suburban, and

rural categories. The number of averages were then arranged as urban, suburban, and rural, and reported as the mean of the number of reported averages for use in this report.

The two remaining combined-category studies (EPA 2004d; Pratt et al. 2000), each with more than 1880 observations, reported data for the combined urban–suburban–rural category. The mean rural concentration of 0.71 $\mu\text{g}/\text{m}^3$ and mean urban concentration of 1.58 $\mu\text{g}/\text{m}^3$, shown in

Table 2 (Continued). Acetaldehyde Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures^a

Sample Location and Type	Observations (n)	Averaging Sampling Time	Concentration ($\mu\text{g}/\text{m}^3$)		Citations	Comments
			Mean	Maximum		
Indoor Spaces						
Residences						
	30	100 min	18.0	38.0	Feng and Zhu 2004	75 homes
	6	—	—	43.0	Fortmann et al. 2001	Test house
	14	48 hr	12.1	18.0	Reiss et al. 1995	4 homes
	26	48 hr	9.2	30.0	Reiss et al. 1995	9 homes
	83	6 days	10.0	24.0	Sawant et al. 2004	Homes
	36	6 days	5.3	29.0	Zhang et al. 1994	6 homes
	40	2 days	15.0	36.0	Sax et al. 2004	Winter
	33	2 days	9.6	23.0	Sax et al. 2004	Fall
	41	2 days	15.0	92.0	Kinney et al. 2002; Sax et al. 2004	Summer
	37	2 days	16.0	54.0	Kinney et al. 2002; Sax et al. 2004	Winter
	398	Yearly	23.2	119.0	Weisel et al. 2005	2 seasons
Schools						
	—	School wk	6.8	25.0	Shendell et al. 2004	Heating and cooling in 20 classrooms
	28	6 days	12.0	25.0	Sawant et al. 2004	School rooms
Offices						
	199	6–8 hr	12.0	20.0	Whitmore et al. 2003b	201 classrooms in 67 schools
	23	2 years	5.0	—	Subramanian et al. 2000	Office building
Personal Exposures						
	38	2 days	13.0	—	Sax et al. 2004	Winter
	42	2 days	20.2	—	Sax et al. 2004	Summer
	409	2 days	22.9	86.1	Weisel et al. 2005	Adults
	169	2 days	24.9	112.0	Weisel et al. 2005	Children

^a Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 10,515 measurements in EPA Air Quality System database (EPA 2004a);

** = maximum average.

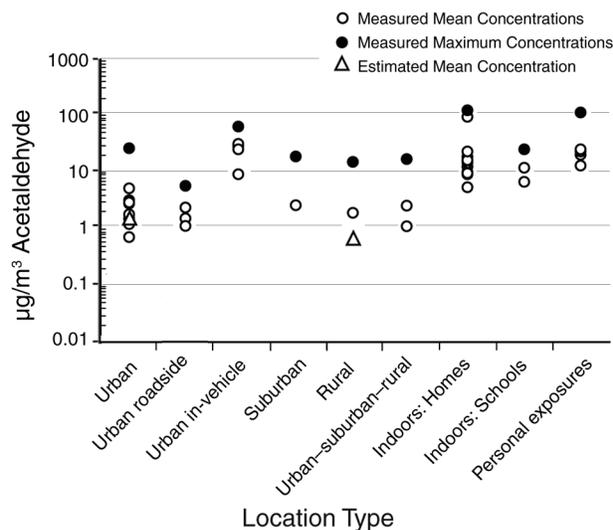


Figure 2. Concentrations of acetaldehyde (µg/m³) at various locations. Data for figure are from Table 2.

Table 2 and Figure 2, were estimated using the NATA model (EPA 2006b). Sampling times for indoor measurements ranged from 90 minutes (Feng and Zhu 2004) to 1 school week (Shendell et al. 2004), with comparable concentration-averaging times. The number of samples per study ranged from 6 for a test-house study, in which a house was rented for the study (which afforded a more controlled environment) (Fortmann et al. 2001), to 398 for a residential-home study (Weisel et al. 2005). The personal-monitoring study, conducted in New York over a winter and summer monitoring campaign, focused on inner-city high school students, with personal samples collected over 48-hour periods (Sax et al. 2004). The largest database on personal exposures to acetaldehyde was obtained from data on adults and children in Elizabeth, N.J., Los Angeles, Calif., and Houston, Tex. (Weisel et al. 2005).

Although there was great variability in the number of measurements, season of measurement, and geographic area of measurement, Table 2 and Figure 2 suggest a trend. Mean concentrations in individual categories of location types—urban, urban-roadside, suburban, rural, and combined urban-suburban-rural—tended to be similar and to range from approximately 1 to 7 µg/m³. Average urban in-vehicle concentrations tended to be higher than those in ambient air and were highly variable. Average home, school, and personal mean concentrations tended to be similar to each other (from 5 to 25 µg/m³) and to range from approximately 2 to 10 times ambient and outdoor levels (Zhang et al. 1994; Sax et al. 2004; Weisel et al. 2005). Personal exposures of adults and children were similar to each other in the one study for which data were available (Weisel et al. 2005) and were higher than indoor

residential levels. The highest average concentrations were measured inside vehicles in urban settings and ranged from 10 to more than 60 µg/m³. Residences and personal exposures had the highest maximum concentrations, at 92 µg/m³ (Kinney et al. 2002; Sax et al. 2004). The highest personal exposure, at 112 µg/m³, was measured for a child. In general, peak concentrations of acetaldehyde, independent of sampling location, were in the 10 to 100 µg/m³ range. Seasonal comparisons, though limited, indicated higher concentrations and exposures in summer than in winter. This is likely to be the result of increased atmospheric photochemical production of acetaldehyde in summer.

The NATA estimated the overall average ambient urban and rural mean concentrations for acetaldehyde to be 1.58 and 0.71 µg/m³, respectively (EPA 2006b). The one study for which rural ambient monitoring data were available (EPA 2004d) reported a mean concentration of 2.0 µg/m³. Several studies (Table 2 and Figure 2) reported mean urban concentrations for acetaldehyde in the range of 1 to 7 µg/m³. Although the available monitoring data were not collected with the express intention of validating NATA estimates, it appears that the NATA model slightly underestimates ambient concentrations in both urban and rural settings.

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

Average urban concentrations of acetaldehyde measured in several other countries are generally within the range of those for U.S. urban areas reported in Table 2 and Figure 2. Ambient concentrations in China, Japan, Denmark, Finland, France, Germany, Greece, Italy, and Sweden are in the range of those seen in the U.S. for urban, urban-roadside, suburban, and rural measurements (Kalabokas et al. 1988; Satsumabayashi et al. 1995; Slemr et al. 1996; Solberg et al. 1996; Granby et al. 1997; Ferrari et al. 1998; Christensen et al. 2000; Possanzini et al. 2000, 2002; Viskari et al. 2000; Nguyen et al. 2001; Sin et al. 2001; Ho et al. 2002; Bakeas et al. 2003; Feng et al. 2004, 2005; Hellén et al. 2004, 2005; Umweltbundesamt 1998).

Measurements in Mexico City (Baez et al. 1995, 2003) and Brazil (Tanner et al. 1988), however, show higher concentrations of acetaldehyde, in the range of 9.8 to 68 µg/m³ in urban settings and 11 to 439 µg/m³ in roadway tunnels (Nguyen et al. 2001; Grosjean et al. 2002; Vasconcellos et al. 2005). In recent years in Brazil, there has been increased use of oxygenated fuels, including hydrated ethanol and gasohol (a mixture of gasoline and 24% vol/vol ethanol), which currently account for more than 83% of the fuel used by vehicles in this country (Colón et al. 2001; Corrêa et al. 2003; Corrêa and Arbilla 2005). The use of natural gas in vehicles has been increasing by 20% per year in Brazil. The data from Brazil are of particular interest

because they demonstrate the effects of changes in fuel composition on atmospheric concentrations of aldehydes, such as acetaldehyde and formaldehyde. Montero and colleagues (2001) recorded average and peak acetaldehyde concentrations as high as $36.1 \mu\text{g}/\text{m}^3$ and $103.6 \mu\text{g}/\text{m}^3$, respectively, for São Paulo. The authors noted that while direct vehicle emissions appeared to be the primary source of both acetaldehyde and formaldehyde in the morning, photochemistry appeared to be the primary source at midday and in the evening. For Rio de Janeiro, average and peak acetaldehyde concentrations as high as $55.4 \mu\text{g}/\text{m}^3$ and $83.5 \mu\text{g}/\text{m}^3$, respectively, have been reported (Corrêa et al. 2003; Corrêa and Arbilla 2005). In general, the highest average and peak urban acetaldehyde concentrations in major Brazilian cities exceed those in U.S. urban areas by a factor of five. Recent increases in the use of natural gas in vehicles in Rio de Janeiro have had little effect on acetaldehyde concentrations but have resulted in a fourfold increase in formaldehyde concentrations and in the formaldehyde:acetaldehyde ratio (Corrêa and Arbilla 2005).

TEMPORAL TRENDS

Data that can be used to assess temporal trends in ambient concentrations of acetaldehyde are limited. Data on seasonal trends in ambient concentrations were reported for multiple sites in California's South Coast Air Basin from April 1998 through March 1999, as part of the Multiple Air Toxics Exposure Study (MATES-II) (South Coast Air Quality Management District 2000). Average concentrations were lowest during May ($< 1.8 \mu\text{g}/\text{m}^3$), rising to a maximum in August (approximately $5 \mu\text{g}/\text{m}^3$) and then gradually tailed off. The seasonal pattern observed for formaldehyde closely followed that for acetaldehyde. These seasonal patterns suggest direct-source and photochemically generated contributions to the atmospheric concentrations of both acetaldehyde and formaldehyde.

Mohamed and colleagues (2002), using data collected as part of the EPA urban air toxics monitoring program at 13 urban locations in the U.S., reported no common seasonal trend for carbonyls (including acetaldehyde, acrolein, and formaldehyde) at all locations. They noted that the variations in trends from location to location might be a function of complex sources, photochemical processes, and anthropogenic processes that vary by location. Seasonal trend results, however, were not reported specifically for acetaldehyde but for carbonyls as a class. Weisel and colleagues (2005) reported average concentrations of acetaldehyde in Houston that were twice as high in fall and winter (approximately $9 \mu\text{g}/\text{m}^3$) as in spring and summer. In this study, average concentrations measured in Elizabeth, N.J., were twice as high in spring, summer, and fall (increasing to approximately $10 \mu\text{g}/\text{m}^3$) as in winter.

No clear pattern was observed for Los Angeles. Sax and colleagues (2004) reported only a slight seasonal trend for acetaldehyde measured in New York and Los Angeles, where average concentrations were approximately $4 \mu\text{g}/\text{m}^3$ or lower.

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

The data on the biochemistry and metabolism of acetaldehyde were reviewed and summarized by Morris (1997), Health Canada (2000), and the European Commission (2004). Acetaldehyde is a highly reactive electrophilic compound and thus reacts readily with amino and sulfhydryl moieties of proteins and DNA to form DNA-protein crosslinks. After exposure and absorption via respiratory or oral routes, acetaldehyde is rapidly oxidized to acetic acid in the respiratory tract and liver by the enzyme NAD^+ -dependent aldehyde dehydrogenase (Figure 3). The reported half-life of acetaldehyde in circulating blood is less than 15 minutes. Acetic acid is either further metabolized to carbon dioxide and water or enters the body's two-carbon pool for molecular synthesis reactions.

Aldehyde dehydrogenase-mediated metabolism of acetaldehyde in nasal tissue is of particular importance in the toxicity of inhaled acetaldehyde. In the rat, aldehyde dehydrogenase is present in all epithelial cells of the respiratory mucosa except the olfactory mucosa, where it is present only in the basal cells and Bowman's glands (Bogdanffy et al. 1986). This distribution correlates with the susceptibility of the epithelial region to the toxic effects of acetaldehyde. In general, the activities of rat olfactory enzymes are equivalent to those of humans (Bogdanffy et al. 1998).

Acetaldehyde is also produced endogenously in humans during sugar metabolism and thus occurs in trace quantities in human blood. It is the major metabolite of ethanol (Figure 3) and can reach relatively high concentrations in the blood of people who drink alcoholic beverages, especially if they are deficient in certain isoenzymic forms of aldehyde dehydrogenase 1.

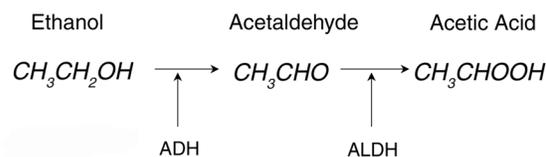


Figure 3. Metabolic pathway of acetaldehyde from ethanol. ADH = Alcohol dehydrogenase. ALDH = Aldehyde dehydrogenase.

NONCANCER HEALTH EFFECTS

Acute Effects

Data on acute toxicity summarized by the American Industrial Hygiene Association (AIHA 2004) show that acetaldehyde has low acute toxicity when inhaled or ingested. The 4-hour LC₅₀ of acetaldehyde in rats was reported to be 24,200 mg/m³ (AIHA 2004).

The primary effect of exposure to acetaldehyde through the air is irritation of the eyes, skin, and respiratory tract. In controlled exposure studies, a 15-minute exposure to 91 mg/m³ caused eye irritation in most human subjects; some more sensitive subjects experienced irritation at 45 mg/m³. At 364 mg/m³, red eyes and transient conjunctivitis were observed. Concentrations greater than 364 mg/m³ caused irritation of the nose and throat in most subjects (AIHA 2004). In susceptible persons with asthma, acetaldehyde can cause bronchial constriction (AIHA 2004).

Data on skin irritation and sensitization (the process in which a person becomes, over time, increasingly allergic to a substance through repeated exposure to that substance) were reviewed by the European Commission (2004). Exposures to concentrations of acetaldehyde greater than 1% in solution were found likely to be irritating to the skin. There is no clear evidence that acetaldehyde sensitizes skin in humans, although animal studies have demonstrated such a response.

Repeated-Dose Toxicity

Repeated-dose toxicity studies were reviewed and summarized by the AIHA (2004), Health Canada (2000), European Commission (2004), and EPA (1991). Whether acetaldehyde was inhaled or ingested, its toxic effects were limited principally to the sites of initial contact.

The no observed adverse effect level (NOAEL) for respiratory effects was 270 mg/m³ in rats exposed by inhalation (6 hours/day, 5 days/week) for 4 weeks and 700 mg/m³ in hamsters exposed for 13 weeks. At the lowest observed adverse effect levels (LOAEL), degenerative changes were observed at concentrations of 437 mg/m³ in the olfactory epithelium in rats and 2400 mg/m³ in the trachea in hamsters. Degenerative changes in the respiratory epithelium and larynx were observed at higher concentrations.

In a 28-day study in which acetaldehyde was administered to rats in drinking water to achieve an exposure of 675 mg/kg body weight/day, effects were limited to slight localized thickening of cells of the forestomach (NOAEL of 125 mg/kg body weight/day). After acetaldehyde was administered to rats at a concentration of 0.05% in drinking water for 6 months (yielding exposure of approximately 40 mg/kg body weight/day) synthesis of liver collagen was detected, an observation that was supported by in vitro data.

Reproductive and Developmental Effects

No information was found in the literature about the reproductive or developmental effects of acetaldehyde in humans.

No developmental studies in which acetaldehyde exposure was by the inhalation route were found. Numerous intraperitoneal and intravenous studies have been conducted in animals, mainly as part of investigations of the effects of ethanol, and were reviewed and summarized by the AIHA (2004), Health Canada (2000), and the World Health Organization (WHO 1995). These data suggest that acetaldehyde should probably be considered a potential developmental toxicant at high exposure concentrations or high metabolic-production levels. In fetal rats and mice exposed to acetaldehyde by intravenous or intraperitoneal injections of 50 to 400 mg/kg body weight between days 6 and 15 of gestation, skeletal malformations, reduced birth weight, and increased postnatal mortality have been reported. In the majority of these studies, maternal toxicity was not evaluated.

GENOTOXICITY

The genotoxicity of acetaldehyde was reviewed by Del-larco (1988), Feron and associates (1991), the IARC (1999a), and the WHO (1995). Acetaldehyde was not mutagenic in standard bacterial test systems (Ames test) with or without an exogenous metabolic activation system; it was, however, mutagenic in human lymphocytes and mouse lymphoma cells in the absence of an exogenous metabolism system. Chromosomal aberrations, sister-chromatid exchanges, and micronuclei were induced in in vitro test systems in the absence of exogenous metabolic activation. After intraperitoneal injection, acetaldehyde induced sister-chromatid exchanges in the bone marrow of Chinese hamsters and mice. However, acetaldehyde did not increase the frequency of micronuclei in early mouse spermatids. Acetaldehyde also induced protein–DNA crosslinks but only at concentrations that resulted in cell death (Lambert et al. 1994; Costa et al. 1997; WHO 1995). No conclusions can be drawn from the study's finding of acetaldehyde–DNA adducts in the peripheral white blood cells of alcoholics (Fang and Vaca 1997) in view of the lack of control for the effects of smoking in the study group and the well-known metabolic abnormalities observed in alcoholics. No conclusions can be drawn from the available studies in *Drosophila* either.

CANCER

An increased incidence of nasal tumors in rats and laryngeal tumors in hamsters was observed after inhalation of

acetaldehyde. In experiments in which rats were exposed to 0, 1365 mg/m³, 2730 mg/m³, or 5460 mg/m³ acetaldehyde (reduced to 2730 mg/m³ at 11 months because of toxicity) for 6 hours/day, 5 days/week for up to 27 months, dose-related increases in nasal adenocarcinomas and squamous-cell carcinomas (significant at all doses) were observed. All concentrations of acetaldehyde administered in these studies induced chronic tissue damage in the respiratory tract; the nasal olfactory mucosa was more sensitive than respiratory mucosa (Feron et al. 1982; Woutersen and Feron 1987). Increases in total malignant tumors, malignant mammary tumors, and hemolymphoreticular neoplasias were observed in rats administered acetaldehyde at concentrations between 50 and 2500 mg/L in drinking water (Soffritti et al. 2002). The overall incidence of carcinomas of the Zymbal gland, external ear ducts, nasal sinuses, and oral cavity increased only in animals treated with the highest concentration. The lack of a dose-response and limitations in reporting (e.g., no details on the methodology were available) make it impossible to draw firm conclusions from these data.

Although acetaldehyde is genotoxic in both in vitro and in vivo test systems, tumors were observed only at inhaled concentrations that produced significant cytotoxicity. Thus, it is likely that both the genotoxicity and irritancy of acetaldehyde play a role in its carcinogenicity. Acetaldehyde would, therefore, be expected to have in vivo activity only at sites such as the olfactory epithelium, where it is not rapidly metabolized to acetic acid and where cytotoxicity occurs.

HUMAN HEALTH

CANCER

Two epidemiologic investigations have examined the possible relationship between occupational exposure to acetaldehyde and cancer (Bittersohl 1974; Ott et al. 1989a,b). Bittersohl (1974) reported a fivefold higher than expected incidence of cancer among 200 German factory workers exposed to 1 to 7 mg/m³ acetaldehyde as well as to other aldehydes. The workers had squamous-cell cancers of the bronchi ($N = 5$) and mouth ($N = 2$) and adenocarcinoma of the stomach ($N = 1$) and cecum ($N = 1$). All of the affected workers were smokers. No detailed information on the study design and population was reported. The interpretation of this study is also hampered by the fact that workers were exposed to other chemicals.

Ott and colleagues (1989a,b) conducted a nested case-control study of cancers of the lymphatic and hematopoietic tissues among chemical manufacturing workers. Subjects

were identified from a review of the death certificates of male employees who had died between 1940 and 1978. They included 52 with non-Hodgkin's lymphoma, 20 with multiple myeloma, 39 with nonlymphocytic leukemia, and 18 with lymphocytic leukemia (Ott et al. 1989b). Five control subjects for each case subject were selected from the same group of workers. The investigators used subjects' job histories to classify them as ever- or never-exposed to acetaldehyde and 20 other agents and according to duration of exposure (less than 5 years or 5 or more years) (Ott et al. 1989a). The odds ratios associated with ever having been exposed to acetaldehyde were 2.5 for non-Hodgkin's lymphoma (7 cases), 2.3 for multiple myeloma (3 cases), and 1.3 for nonlymphocytic leukemia (3 cases). No subject with lymphocytic leukemia was classified as having been exposed. None of these results was statistically significant. Analysis of non-Hodgkin's lymphoma by duration of exposure found that the increased risk associated with acetaldehyde was concentrated in the subgroup with less than 5 years of exposure to this compound.

The cancer studies of Bittersohl (1974) and Ott and colleagues (1989a,b) have severe limitations for assessing the possible carcinogenic effect of acetaldehyde in humans. These limitations include (1) lack of exposure estimates and of exposure-response data, (2) possible confounding and effect modification by exposures to other agents present in the work environment and by age and smoking in the Bittersohl study (1974), and (3) inadequate statistical precision. Epidemiologic findings about the possible carcinogenic effects of acetaldehyde (Bittersohl 1974; Ott et al. 1989a,b) were not used in the latest EPA risk assessment for acetaldehyde (EPA 1991). The EPA judged the findings as weakly suggesting a possible association between acetaldehyde and various types of cancer but as inadequate for evaluating carcinogenic potential (EPA 1991, 1999b).

NONCANCER HEALTH EFFECTS

Acute health effects of acetaldehyde include eye irritation at 91 mg/m³ (and occasionally at 45 mg/m³) as well as bloodshot eyes and reddened eyelids at 364 mg/m³ (Silverman et al. 1946). Irritation of the skin, mucous membranes, throat, and respiratory tract have also been reported (EPA 1993a).

Acetaldehyde exposure via ingestion and metabolism of alcohol has been reported to cause bronchoconstriction in Japanese adults with asthma (Shimoda et al. 1996; Takao et al. 1998). A polymorphism of the aldehyde dehydrogenase 1 gene, present in up to 50% of Asian populations and 40% of South American Indian populations, appears to contribute to racial variation in the susceptibility of individuals with asthma to bronchoconstriction after

ingestion of alcohol. After consuming alcoholic beverages, persons with a variant form of alcohol dehydrogenase 2 are also less able to metabolize acetaldehyde to acetic acid and are therefore susceptible to intolerance reactions, including bronchoconstriction and exacerbation of asthma. This alcohol-induced asthma is believed to be due to histamine release stimulated by abnormally high levels of metabolic acetaldehyde. These studies of exposure to acetaldehyde through ingestion of alcohol have limited relevance to the issue of the human health effects of exposure to acetaldehyde as an air pollutant.

Several studies have evaluated the effects of inhalation of aerosolized acetaldehyde on bronchoresponsiveness in individuals with asthma. A series of small, randomized, double-blind clinical studies in Japan, each including 9 to 18 subjects, found that inhalation of aerosolized acetaldehyde caused bronchoconstriction in adults with asthma (Myou et al. 1993, 1994a,b, 1995); no such effects were reported in nonasthmatic adults (Myou et al. 1993).

Only one investigation has evaluated the relationship between concentrations of acetaldehyde in outdoor air and the occurrence of asthma symptoms (Delfino et al. 2003). This panel study, conducted in California from November 1999 through January 2000, included 22 Hispanic children, ages 10 to 16 years, with physician-diagnosed asthma, living in an area of Los Angeles County characterized by high traffic density. The subjects were nonsmokers who lived in nonsmoking households. The investigators analyzed daily outdoor concentrations of acetaldehyde and 19 other pollutants in relation to the severity of asthma as self-reported daily in subjects' diaries. Acetaldehyde concentrations ranged from 1.9 to 10.5 $\mu\text{g}/\text{m}^3$, with a mean of 5.66 $\mu\text{g}/\text{m}^3$ (standard deviation [SD] = 1.82 $\mu\text{g}/\text{m}^3$) and an interquartile range of 2.38 $\mu\text{g}/\text{m}^3$. The concentrations strongly correlated with the concentrations of a number of other pollutants. The odds ratios for moderate asthma symptoms were 1.39 (95% confidence interval [CI], 0.80–2.41) for the interquartile range increase in acetaldehyde measured on the same day as the symptoms and 1.48 (95% CI, 1.16–1.87) for the interquartile range increase in acetaldehyde measured on the previous day. The odds ratios for more severe asthma symptoms were 1.57 (95% CI, 0.70–3.54) for the interquartile range increase in acetaldehyde measured on the same day as the symptoms and 1.36 (95% CI, 0.87–2.14) for the interquartile range increase in acetaldehyde measured on the previous day. Exposure to acetaldehyde was statistically correlated significantly and positively with exposure to other pollutants. For example, the Spearman correlation coefficient for exposure to acetaldehyde in addition to

exposure to another pollutant was 0.79 for formaldehyde, 0.50 for benzene, 0.63 for ethylbenzene, 0.68 for toluene, and 0.65 for xylene. The effects of acetaldehyde were attenuated after adjustment for 8-hour maximum SO_2 concentration or 8-hour maximum NO_2 concentration. The study had a number of limitations, including small sample size and the resulting imprecision, the potential for inaccurate reporting of asthma symptoms resulting from the use of diaries, and the possibility of confounding by other pollutants as well as by other factors.

A single-blind study in patients from a clinic in Spain investigated differences in airway responsiveness to inhaled acetaldehyde and methacholine in 61 nonsmoking adult clinic patients with mild asthma and 20 nonsmoking healthy volunteers (Prieto et al. 2000). The study found that 56 (92%) of the 61 asthmatic patients showed evidence of bronchoconstriction. In the 56 asthmatic patients, FEV_1 (forced expiratory volume in 1 second) declined by at least 20% after inhalation of acetaldehyde (the geometric mean concentration that resulted in more than a 20% decline in FEV_1 was 17.55 mg/mL). None of the healthy subjects had bronchoconstriction after exposure.

A second study in clinic patients in Spain evaluated the effect of inhaled acetaldehyde (at concentrations up to 40 mg/mL) and methacholine on airway responsiveness (Sanchez-Toril et al. 2000). The main purpose was to determine whether challenge with acetaldehyde is a more specific test than challenge with methacholine for differentiating chronic bronchitis from asthma. The subjects were 62 clinic patients with asthma and 59 smokers with chronic bronchitis either alone ($N = 32$) or in combination with chronic obstructive pulmonary disease ($N = 27$). In 57 (92%) of the 62 asthmatic patients—compared with only 3 (5%) of the patients with chronic bronchitis— FEV_1 declined at least 20% after inhalation of acetaldehyde.

A third study in Spain examined the effect of inhaled acetaldehyde on lung function in 16 patients with asthma, 43 nonasthmatic patients with allergic rhinitis, and 19 healthy volunteers (Prieto et al. 2002b). All subjects were nonsmokers, and the study was single-blind. The study found that in 13 (81%) of the 16 patients with asthma, 8 (19%) of the 43 patients with allergic rhinitis, and none of the 19 healthy subjects, FEV_1 declined at least 20% after inhalation of acetaldehyde (the geometric mean concentration that resulted in a greater than 20% decline in FEV_1 was 35.5 mg/mL for asthmatic patients and 67.7 mg/mL for those with allergic rhinitis). The difference in the prevalence of a positive airway response between patients with allergic rhinitis and the healthy subjects was not statistically significant ($P = 0.09$). Bronchoconstriction

in response to acetaldehyde exposure depended on the presence of airway hyperresponsiveness to methacholine.

A fourth study in Spain investigated the relationship between airway responsiveness to inhaled acetaldehyde (up to 80 mg/mL), methacholine, and adenosine 5'-monophosphate and determined the repeatability and side effects of acetaldehyde challenge (Prieto et al. 2002a). All subjects were clinic patients, nonsmokers with mild, intermittent asthma. The study was single-blind. The first study component included 16 subjects and found that 12 (75%) of them experienced bronchoconstriction after exposure to acetaldehyde, that the geometric mean concentration producing a greater than 20% decline in FEV₁ was 38.9 mg/mL, and that responsiveness to the three agents was correlated. The second component, which included 14 subjects, found that the response to inhaled acetaldehyde was moderately repeatable; that the side effects of exposure included cough, dyspnea, and throat irritation; and that acute bronchoconstriction due to acetaldehyde inhalation was reversed within 15 minutes after the administration of inhaled salbutamol.

The findings in these studies of lung-function changes in response to inhaled acetaldehyde are limited in their generalizability to the human health effects of exposure to acetaldehyde as an air pollutant because of the special exposure settings and the focus on acute effects. Also, the procedures used to select subjects from clinic populations were not described in detail, and thus selection bias in these studies was possible.

REGULATORY SUMMARY

Acetaldehyde is classified by the National Institute of Occupational Safety and Health as “a potential human carcinogen,” by the EPA (1991) as Group B2 (“a probable human carcinogen”), and by the U.S. NTP (2005) as “reasonably anticipated to be a human carcinogen via inhalation exposure,” based on sufficient evidence in laboratory animals and inadequate evidence in humans. It is classified by the IARC (1999a) as Group 2B (“possibly carcinogenic to humans”).

The reference concentration (RfC) for acetaldehyde is 9 µg/m³ (EPA 1991), based on a NOAEL (human equivalent concentration, HEC) of 8.7×10^3 µg/m³ for degeneration of olfactory epithelium in male rats after a 4-week inhalation exposure (Appelman et al. 1982, 1986) and an uncertainty factor of 1000.

A search of the literature and published regulations for North America, Asia, Australia, and Europe did not reveal any exposure standards for acetaldehyde.

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

Sources of acetaldehyde exist outdoors and indoors. Outdoor concentrations are the result of both direct emissions from mobile sources and photochemical reactions in the atmosphere. On-road mobile sources account for approximately 30% of total nationwide acetaldehyde emissions. Although potentially limited in numerous respects (sample collection and analysis methods, number and type of environments sampled, number of samples collected, methods of accounting for presence or absence of sources, extent of geographic and seasonal variability, representativeness of residences and populations sampled, extent of sampling for sensitive populations, and other factors), available data provide some general insights into acetaldehyde exposures. Concentrations tend to be lowest outdoors, ranging from 1 to 7 µg/m³, and from 2 to 10 times higher in indoor spaces and inside vehicles. Personal-exposure concentrations tend to be higher than concentrations in residences and to be similar for adults and children. Overall, average and peak concentrations, independent of sampling location, appear to be below 100 µg/m³. The highest average and peak ambient concentrations of acetaldehyde in São Paulo and Rio de Janeiro, Brazil, where over 83% of vehicles use either hydrated ethanol or a mixture of gasoline and 24% vol/vol ethanol, were higher by a factor of approximately 5 or more than those measured in U.S. urban areas.

TOXICOLOGY

In humans, acetaldehyde is an irritant of the eye, skin, and respiratory tract starting at concentrations of about 45 mg/m³. In subchronic inhalation studies in animals, the NOAEL for respiratory effects is about 455 mg/m³. Higher concentrations lead to degenerative changes in the olfactory and respiratory epithelia. These concentrations are generally several orders of magnitude higher than those typically observed in ambient, outdoor, or indoor air. In the body, acetaldehyde is formed from alcohol by alcohol dehydrogenase and is then metabolized to acetic acid. It is a clastogen both in vitro and in vivo. The nasal tumors observed in animals in inhalation experiments occurred at cytotoxic concentrations only, and it is likely that acetaldehyde's genotoxicity and irritating properties, with the consequent increased cell proliferation, both play a role in its carcinogenicity.

HUMAN HEALTH

The data on the possible carcinogenicity of acetaldehyde in humans are inadequate, and the data on respiratory effects are limited mainly to small clinical investigations using exposure challenges with aerosols of acetaldehyde in asthmatic patients. There has been only one epidemiologic study of environmental exposure to acetaldehyde. This was a study of children with asthma, and it was small and was unable to distinguish the effects of acetaldehyde from those of other pollutants. The effect of environmental exposure on other respiratory conditions has not been investigated. Indoor sources of acetaldehyde account for most environmental exposure, and both ambient and indoor air concentrations at present appear to be well below those that are known to produce adverse health effects. Thus, there is no conclusive evidence that acetaldehyde in ambient air, at current levels, adversely affects human health.

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of acetaldehyde?

Mobile sources are an important, but not the only important, source of acetaldehyde. Urban concentrations of acetaldehyde measured in Brazil, where ethanol is widely used in motor vehicles as an alternative to conventional fuels, suggest that acetaldehyde concentrations elsewhere might increase in the future if the use of alcohols in fuels increases.

2. Does acetaldehyde affect human health?

Acetaldehyde is an irritant in humans at concentrations greater than 10 mg/m³.

3. Does acetaldehyde affect human health at environmental concentrations?

There is no evidence to suggest that current ambient concentrations of acetaldehyde adversely affect human health.

RESEARCH GAPS AND RECOMMENDATIONS

EXPOSURE

Data from studies in Brazil suggest that increased use of alcohols as alternative fuels and in fuel blends might increase ambient concentrations of acetaldehyde. The effect of such emissions on ambient air quality is unknown, as is whether such emissions increase the risk

of adverse effects on human health. Research recommendations for acetaldehyde include the following:

- Continue to update, critically evaluate, and compare the NATA model to actual measurements to improve its usefulness in predicting the effects of increased use of alcohols in motor-vehicle fuels on ambient acetaldehyde concentrations.
- Average and peak concentrations of acetaldehyde are highest inside urban vehicles, in homes, schools, and personal exposures. Therefore studies are needed to better characterize the sources and factors associated with acetaldehyde concentrations in these settings.
- Establish a monitoring network capable of tracking long-term acetaldehyde concentrations because an increase in the use of alcohols as motor-vehicle fuels is likely.
- Assess acetaldehyde exposures of subpopulations that might be at especially high risk for adverse health effects (e.g., people with asthma).

TOXICOLOGY

The mechanisms of the induction of cancer by acetaldehyde are not yet understood. Data on the carcinogenic potency of acetaldehyde in animals have not been extrapolated to humans. Data on reproductive and developmental toxicity are inconclusive. Research recommendations for toxicology studies of acetaldehyde include the following:

- Extrapolate the data on acetaldehyde cancer potency across exposures and species.
- Clarify the mechanism of carcinogenicity in humans, including the quantitative relationship between DNA-protein crosslinks and mutations and the time course of the removal of these crosslinks.

HUMAN HEALTH

The simultaneous exposure of humans to acetaldehyde and other upper-respiratory-tract toxicants, such as acrolein, formaldehyde, crotonaldehyde, furfural, glutaraldehyde, and ozone, might lead to additive or synergistic effects, particularly sensory irritation and possibly cytotoxic effects on the nasal mucosa. Research recommendations for human-health studies of acetaldehyde include the following:

- Identify additive or synergistic effects on human health from simultaneous exposure to acetaldehyde and other upper-respiratory-tract toxicants, including other air toxics and particulate matter.

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