Formaldehyde

Formaldehyde

INTRODUCTION

Formaldehyde (CAS Registry Number 50-00-0; CH_2O; molecular weight = 30.0) (Figure 16), also known as methanal, is a colorless gas having a strong, irritating odor. It is ubiquitous in the environment as a result of natural processes. It is also a major industrial chemical and is used extensively as a chemical intermediate (e.g., in the production of resins and fertilizers) and as a disinfectant and preservative in many industrial and consumer applications. Formaldehyde is also produced in the body as part of normal metabolism.

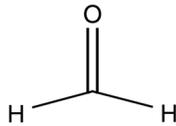At one atmosphere pressure and 25°C, 1 ppm formaldehyde is equivalent to 1.2 mg/m^3.

Figure 16. Structure of formaldehyde.

BENCHMARK LITERATURE

The following evaluation of research literature on formaldehyde is based on data and source tables listed in Appendices B–D (available on the HEI Web site) of this report. Additional information was obtained from HEI research reports by Kleinman and Mautz (1991), Leikauf (1991), Fennell (1994), and Grosjean and Grosjean (2002); the Agency for Toxic Substances and Disease Registry (ATSDR 1999a); WHO (2002); the Chemical Industry Institute of Toxicology (CIIT 1999); the EPA (1990, 2000e); the Organisation for Economic Co-operation and Development Screening Information Data Set (OECD 2002); the International Agency for Research on Cancer (IARC 1997a, 2006); and selected key articles.

EXPOSURE

SOURCES AND EMISSIONS

Formaldehyde is formed in all living cells. It is also formed from the photochemical oxidation of volatile organic compounds (VOCs) present in vehicle exhaust and from incomplete combustion of gasoline and diesel fuels. As formaldehyde is not present in appreciable quantities in fuels per se, it is not a component of evaporative emissions. Formaldehyde is also formed during other major combustion processes, such as the burning of forests, other wood, cigarettes, and coal in coal-fired power plants. Formaldehyde is a common component of resins in pressed-wood products and is emitted indoors in considerable quantities by building materials and furnishings. In the atmosphere, formaldehyde is subject to photolysis and reaction with hydroxyl radical. Photolysis is thought to be the most important atmospheric mechanism of formaldehyde removal. It is an important component in the production of atmospheric NO_2 and ozone. Formaldehyde has an atmospheric lifetime of approximately 4 hours (Seinfeld and Pandis 1998).

According to the National Air Toxics Assessment (NATA), on-road mobile sources account for 40% of emissions in urban counties and 13% of emissions in rural counties in the U.S. Non-road motor vehicles account for 27% of emissions in urban counties and 11% in rural counties (EPA 2006b). Using the Assessment System for Population Exposure Nationwide (ASPEN) model, Pratt and colleagues (2000) estimated that mobile sources contributed 58% of ambient concentrations in Minnesota.

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

Table 6 and Figure 17 show the range of mean and maximum concentrations of formaldehyde in μg/m^3 measured in outdoor (including in-vehicle) locations, in indoor environments, and by personal monitoring.

Ambient Concentrations

In the U.S., annual mean ambient concentrations of formaldehyde in air range from 0 to 49 μg/m^3, with an overall national mean concentration of 4.3 μg/m^3 (EPA 2006). The NATA reported higher modeled mean concentrations in urban counties (1.8 μg/m^3) than in rural counties

Table 6. Formaldehyde Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration ($\mu g/m^3$) Mean	Maximum	Citations	Comments
Outdoor Areas						
Urban						
	—	1 yr	1.8	—	EPA 2006b	Model
	437	24 hr	3.2	14.8	Manchester-Neesvig et al. 2003	
	> 1000	24 hr	2.4	15.0	Dann (Unpublished)	
	~ 600	24 hr	5.5		South Coast Air Quality Management District 2000	
	4–17	24 hr	1.3	2.0	Zielinska et al. 1998	
	4–17	24 hr	2.1	2.8	Zielinska et al. 1998	
	4–17	24 hr	0.8	1.1	Zielinska et al. 1998	
	~ 60	24 hr	4.4	24.5	Zielinska et al. 1998	
	~ 60	24 hr	1.4	4.2	Zielinska et al. 1998	
	395	Yearly	6.4	12.4*	Weisel et al. 2005	2 seasons
	36	48 hr	5.3		Kinney et al. 2002	
	36	48 hr	2.1		Kinney et al. 2002	Winter
Brazil						
	37	2 hr	15.1	56.9	Montero et al. 2001	
	13	3 hr	10.8	34.6	Grosjean and Grosjean 2002	Tunnel measurements excluded
Urban in-vehicle						
	50	~ 9 hr	20.7	65.3	Riediker et al. 2003	
	15	2 hr		23.6	Rodes et al. 1998	
	13	2 hr		18.5	Rodes et al. 1998	
Urban roadside						
	9	2 hr		8.3	Rodes et al. 1998	
	4–17	24 hr	5.1	7.8	Zielinska et al. 1998	
	10	2 hr		20.3	Rodes et al. 1998	
Urban roadside in Brazil						
	28	2 hr	16.8	66.8	Corrêa et al. 2003	1998–2001 (changing fuel composition)
	24	2 hr	80.2	122.8	Corrêa and Arbilla 2005	2001–2002 (changing fuel composition)
	101	1–2 hr	1.5–54.1	93.5	de Andrade et al. 1998	

Table continues on next page

[a] Data extracted from published studies.

* 99th percentile.

Table 6 (*Continued*). Formaldehyde Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging (Time)	Concentration ($\mu g/m^3$)		Citations	Comments
			Mean	Maximum		
Outdoor Areas (*Continued*)						
Suburban						
	~ 60	24 hr	1.1	5.3	Zielinska et al. 1998	Small community
Rural						
	—	1 yr	0.64	—	EPA 2006b	Model
	~ 840	4 hr	1.5	11.0	Dann (Unpublished)	
	~ 60	24 hr	1.3	5.6	Zielinska et al. 1998	
	~ 60	24 hr	1.3	6.2	Zielinska et al. 1998	
Urban–suburban–rural combined						
	> 1000	24 hr	4.3	182.0	EPA 2006b	
	> 1000	24 hr	3.2	49.2	EPA 2004d	
	> 1000	24 hr	1.7	21.0	Pratt et al. 2000	
Indoor Spaces						
Residences						
	75	1.5 hr	28.0	85.0	Feng and Zhu 2004	
	398	yearly	21.6	53.8*	Weisel et al. 2005	2 seasons
	36	48 hr	20.9		Kinney et al. 2002	Summer
	36	48 hr	12.1		Kinney et al. 2002	Winter
	26	24 hr	19.8	66.2	Reiss et al. 1995	
	36	3 hr	67.1	125.1	Zhang et al. 1994	
Schools						
	911	7–10 days	33.0	76.0	Whitmore et al. 2003b	
	199	6–8 hr	16.0	29.0	Whitmore et al. 2003a	
Personal Exposures						
	409	48 hr	21.7	45.4*	Weisel et al. 2005	Adults
	169	48 hr	20.8	47.4*	Weisel et al. 2005	Children
	42	48 hr	28.5		Kinney et al. 2002	Summer
	38	48 hr	11.5		Kinney et al. 2002	Winter

[a] Data extracted from published studies.

* 99th percentile.

(0.64 $\mu g/m^3$) (EPA 2006b). Pratt and colleagues (2000) also reported higher concentrations in urban than in rural areas in Minnesota. In contrast, Zielinska and colleagues (1998) did not find appreciably higher mean concentrations in urban (0.8 to 4.4 $\mu g/m^3$) than in rural locations (1.3 $\mu g/m^3$) or background (1.3 $\mu g/m^3$) in Arizona and suggested that atmospheric transport of formaldehyde could be affecting non-urban locations. Mean concentrations at an urban roadside site, however, were the highest in the study (5.1 $\mu g/m^3$). The California Children's Environmental Health Protection Program monitored six urban California locations for approximately 1 year and reported site averages ranging from 1.9 to 4.7 $\mu g/m^3$ (the highest site average was measured in Los Angeles), with an overall mean concentration of 3.2 $\mu g/m^3$ (Manchester-Neesvig et al. 2003). The Multiple Air Toxics Exposure Study (MATES-II) reported a mean concentration of 5.5 $\mu g/m^3$ from 10 monitoring sites over a 1-year period (South Coast Air Quality Management District 2000). In Minnesota, Pratt and colleagues (2000) reported mean concentrations from multiple monitoring sites
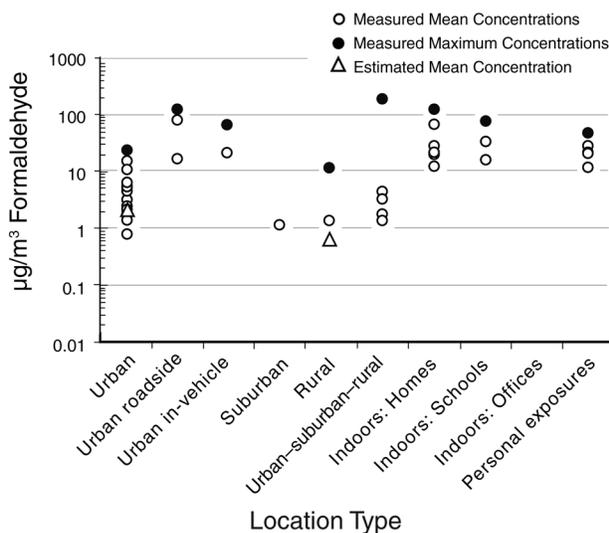
Figure 17. Concentrations of formaldehyde (μg/m³) at various locations. Data for figure are from Table 6.

ranging from 0.8 to 2.9 μg/m³, with an overall mean of 1.7 μg/m³. A study of outdoor and indoor concentrations for approximately 100 residences in Elizabeth, N.J., Houston, Tex., and Los Angeles, Calif., over two seasons reported an average of 6.4 μg/m³ with a 99th percentile concentration of 12.4 μg/m³ (Weisel et al. 2005). Measurements from the Canadian National Air Pollution Surveillance system show an overall mean concentration of 2.4 μg/m³ for nine urban sites and 1.5 μg/m³ for seven rural sites over the same period (2002 to 2004) (Environment Canada 2003a, 2004, 2005).

In Los Angeles, short-term measurements (2-hour samples) of formaldehyde showed a range of ambient (7 to 20 μg/m³) and urban roadside (11 to 15 μg/m³) concentrations. Short-term measurements in Sacramento showed a range of somewhat lower ambient (2 to 4 μg/m³) and roadside (4 to 6 μg/m³) concentrations. Although Grosjean and Grosjean (2002) measured 2-hour concentrations as high as 21 μg/m³ in a tunnel study, there is little evidence to suggest elevated in-vehicle exposures (discussed below). Measurements of formaldehyde from Brazil (discussed below) indicate short-term concentrations of up to 100 μg/m³ in urban areas.

Measurements from Brazil provide an interesting case study of the effect of fuel composition on ambient concentrations of aldehydes. In Brazil, ethanol was introduced in the late 1970s as part of a national program to decrease dependency on imported oil. By 1998, approximately 40% of the fuel used in vehicles was ethanol. Some vehicles ran on pure ethanol (at peak, approximately 26% of vehicles) and others on gasoline–ethanol mixtures (e.g., gasohol, which contains 76% gasoline and 24% ethanol, vol/vol) (Colón et al. 2001). At its peak, total ethanol-containing fuels accounted for over 83% of the fuel used by vehicles

(Colón et al. 2001; Corrêa et al. 2003; Corrêa and Arbilla 2005). Annual mean concentrations of 18 to 50 μg/m³ formaldehyde and short-term measurements (1- to 2-hour samples) as high as 100 μg/m³ were measured in Brazilian cities (de Andrade et al. 1998; Montero et al. 2001; Grosjean et al. 2002; Corrêa et al. 2003). Measurements made in Rio de Janeiro between 1998 and 2002 document an increase in annual mean formaldehyde concentrations from 20 μg/m³ in 2000 to 80 μg/m³ in 2002. At the same time, there was an 18-fold increase in vehicles fueled by compressed natural gas (6% in 2002) and a decrease in the percentages of vehicles fueled by 100% ethanol (to 14% from a peak of approximately 26%) and gasohol (Corrêa and Arbilla 2005).

In-Vehicle Exposures

Rodes and colleagues (1998) measured in-vehicle formaldehyde concentrations of 7 to 21 μg/m³ in Los Angeles and 5 to 12 μg/m³ in Sacramento over 2-hour driving periods. These concentrations were not higher than those measured in Los Angeles at an ambient monitoring site (7 to 20 μg/m³) or urban roadside sites (11 to 15 μg/m³). In Sacramento, where ambient concentrations were lower than in Los Angeles, in-vehicle concentrations were somewhat lower than roadside concentrations (4 to 6 μg/m³) but slightly higher than ambient concentrations (2 to 4 μg/m³). These results suggest that in-vehicle exposures to formaldehyde are only slightly higher than ambient exposures and that ambient background concentrations are a more significant source of exposure than are direct vehicle emissions.

However, Fitz and colleagues (2003) measured elevated in-vehicle concentrations of formaldehyde in a recent school-bus study on standard routes in Southern California. Compared with the mean concentration at an ambient monitoring site (0.4 μg/m³), the means ratio was 5.3 for windows-closed morning runs and 2.8 for windows-open afternoon runs. Comparison of sampling runs of 1 to 1.5 hours with closed or open windows suggested some indoor production or reentrainment of formaldehyde. Supporting the possibility of reentrainment was the finding that samples collected on a windows-closed compressed-natural-gas bus had concentrations of formaldehyde that were two to three times higher than those in windows-closed diesel buses. Overall, mean concentrations were higher when the bus windows were closed: On runs with windows closed, mean concentrations were 2.1 μg/m³ (ranging from 0.89 to 4.8 μg/m³). On runs with windows open, mean concentrations were 1.1 μg/m³ (ranging from 0.55 to 2.1 μg/m³). On rural and suburban runs with windows open, mean concentrations were 0.93 μg/m³ (ranging from 0.34 to 2.0 μg/m³). In a North Carolina state-trooper study (Riediker et al. 2003), in-vehicle concentrations (7- to

14-hour samples) of total aldehydes were higher than road-side or ambient concentrations. The overall in-vehicle mean concentration was 21 µg/m^3.

Indoor Exposures

In a study of New York City high school students, Kinney and colleagues (2002) reported personal formaldehyde exposures to be similar to indoor concentrations but higher than outdoor concentrations, reflecting the potential importance of indoor formaldehyde sources. At 21 µg/m^3, summer indoor concentrations (48-hour samples) were higher than winter indoor concentrations (12 µg/m^3). Personal exposures were also higher in summer (14 µg/m^3) than in winter (5 µg/m^3). Overall, indoor concentrations ranged from 5 to 22 µg/m^3 in winter (with a mean of 12 µg/m^3) and from 6 to 50 µg/m^3 in summer (with a mean of 18 µg/m^3). Similar measurements made in Los Angeles as part of the same study showed higher indoor concentrations in winter, ranging from 8 to 60 µg/m^3 (with a mean of 21 µg/m^3). In the study by Weisel and colleagues (2005) of Elizabeth, N.J., Houston, Tex., and Los Angeles, Calif., the average indoor residential concentration for all three cities was 21.6 µg/m^3 for both seasons, with a 99th percentile value of 53.8 µg/m^3.

Numerous other studies have reported indoor concentrations of formaldehyde that are higher than corresponding outdoor concentrations (Zhang et al. 1994; Gordon et al. 1999; Subramanian et al. 2000), with mean indoor concentrations in homes, office buildings, and schools typically three to five times higher than mean outdoor concentrations (Sawant et al. 2004). Typical median indoor concentrations (24-hour samples) ranged from 5 to 50 µg/m^3 in homes, slightly higher in schools (13 to 55 µg/m^3), and slightly lower in office buildings (Subramanian et al. 2000). Mean short-term concentrations (6-hour samples) in six residences in New Jersey were 67 µg/m^3, with a maximum concentration of 125 µg/m^3 (Zhang et al. 1994). Mean concentrations (100-minute samples) in 75 residences in Ottawa were somewhat lower, at 28 µg/m^3, and ranged from 6 to 85 µg/m^3. Substantially higher indoor concentrations (1.5- to 5-hour samples) have been found in association with certain activities in the kitchen, such as broiling fish (129 µg/m^3) and cleaning the oven (200 to 400 µg/m^3) (Fortmann et al. 2001).

Personal Exposures

Two recent studies (Kinney et al. 2002; Weisel et al. 2005) have investigated personal-exposure concentrations of formaldehyde. Both measured personal exposures over a 48-hour periods in summer and winter. In the study by Kinney and colleagues, 46 high school students in New York City were

monitored. Average concentrations were 28.5 µg/m^3 in summer and 11.5 µg/m^3 in winter. Personal-exposure concentrations in both seasons were approximately five times higher than outdoor concentrations and comparable to indoor residential concentrations. In the study by Weisel and colleagues, 312 adults and 118 children in Elizabeth, N.J., Houston, Tex., and Los Angeles, Calif., were monitored. Average concentrations were similar for both adults (21.7 µg/m^3) and children (20.8 µg/m^3). The 99th-percentile concentrations were similar as well (45.4 µg/m^3 for adults and 47.4 µg/m^3 for children). Personal-exposure concentrations were approximately three times higher than outdoor concentrations and similar to indoor residential concentrations. These studies suggest that in the U.S. indoor concentrations of formaldehyde are the predominant source of personal exposures.

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

Average urban concentrations of formaldehyde measured in several other countries are generally within the range of those reported for U.S. urban areas (see Table 6 and Figure 17). Ambient concentrations in China, Japan, Turkey, Australia, Denmark, Finland, France, Germany, Greece, Italy, Sweden, and Canada are in the range of those seen in the U.S. for urban, roadside, suburban, and rural measurements (Kalabokas et al. 1988; Shepson et al. 1991; National Environmental Protection Council 1993; Satsumabayashi et al. 1995; Possanzini et al. 1996, 2000, 2002; Slemr et al. 1996; Solberg et al. 1996; Granby et al. 1997; Khare et al. 1997; Ferrari et al. 1998; Christensen et al. 2000; Viskari et al. 2000; Mathew et al. 2001; Sin et al. 2001; Ho et al. 2002; Bakeas et al. 2003; Feng et al. 2004, 2005; Hellén et al. 2004; Chang et al. 2005; Chiu et al. 2005; Odabasi and Seyfioglu 2005; Tago et al. 2005; Japan Ministry of the Environment 2005b). Ambient concentrations in Taiwan and Africa were somewhat higher (ranging from 4.8 to 109 µg/m^3 in Taiwan, although the area included local industries that might have contributed). Ambient concentrations of 40 µg/m^3 were measured in Cairo, Egypt (Khoder et al. 2000; Chiu et al. 2005).

Measurements of formaldehyde concentrations in Mexico City (Baez et al. 1995, 2003; Grutter et al. 2005), however, were higher, ranging from 5 to 44 µg/m^3 in urban settings. In Brazil, measurements were somewhat higher (compared with the U.S.) in Rio de Janeiro (10.7 to 32 µg/m^3), but not in São Paulo (2.8 µg/m^3) (Nguyen et al. 2001; Grosjean et al. 2002). Average concentrations in roadway tunnels in several Brazilian cities were elevated, ranging from 17 to 80 µg/m^3 (Corrêa et al. 2003; Corrêa and Arbilla 2005; Vasconcellos et al. 2005) and up to 65 µg/m^3 near heavy traffic

(Corrêa et al. 2003). Brazil is of particular interest because of the widespread use of ethanol in fuels, as discussed earlier. Montero and colleagues (2001) recorded 2-hour mean and maximum formaldehyde concentrations in São Paulo that were as high as 22 μg/m^3 and 55 μg/m^3, respectively. Mean and maximum concentrations in Rio de Janeiro as high as 16 μg/m^3 and 65 μg/m^3, respectively, have been reported (Grosjean et al. 2002; Corrêa et al. 2003). In recent years, the use of compressed natural gas in vehicles has been increasing by 20% per year. Over the same time period, mean formaldehyde concentrations in Rio de Janeiro have risen fourfold, to 96 μg/m^3 (with peak 2-hour concentrations as high as 135 μg/m^3) (Corrêa and Arbilla 2005). In general, the highest mean formaldehyde concentrations in major Brazilian cities have proved to be nine or more times higher than the highest mean concentrations in U.S. urban areas; the differences in maximum concentrations are roughly similar.

SEASONAL CHANGES IN FORMALDEHYDE CONCENTRATIONS

Formaldehyde is both produced and degraded in ambient air by photochemistry. The highest seasonal ambient concentrations of formaldehyde are associated with the highest rates of photochemical activity. Zielinska and colleagues (1998), for example, reported a strong seasonal variation in formaldehyde concentrations. The highest concentrations were measured in June and July, when photochemical activity was highest. Measurements at roadside locations suggested that photochemical activity in summer contributes more formaldehyde to ambient concentrations than do direct vehicle emissions. (Random samples were taken every 6 days in summer and during periods of stagnant air in winter. Yet summer concentrations were still higher than winter concentrations.)

In New York City, Kinney and colleagues (2002) also reported higher ambient concentrations in summer (5.3 μg/m^3) than in winter (2.1 μg/m^3). Interestingly, they also reported that summer indoor concentrations (48-hour samples), at 21 μg/m^3, were higher than winter indoor concentrations, at 12 μg/m^3, possibly as a result of increased off-gassing from indoor sources and infiltration of ambient formaldehyde in summer (Kinney et al. 2002). Indoor formaldehyde concentrations that are higher in summer than in winter have also been reported elsewhere (Reiss et al. 1995). These are possibly related to higher concentrations of indoor ozone, which lead to increased formaldehyde formation indoors. Mean personal exposures were higher in summer (28.5 μg/m^3) than in winter (11.5 μg/m^3) (Kinney et al. 2002).

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

More than 90% of inhaled formaldehyde gas is absorbed and rapidly metabolized to formate in the upper respiratory tract (Figure 18). In primates, some absorption takes place in the nasal cavity as well as in the nasopharynx, trachea, and bronchi. It has been shown that when formaldehyde is mixed with particles, more of it is retained by the respiratory tract than when it is inhaled alone (Kleinman and Mautz 1991). This suggests that some particles can bind with gases and increase the retained dose of a gas. However, Rothenberg and colleagues (1989) estimated that the deposited dose of formaldehyde in the particle phase was substantially smaller than the dose from the vapor phase. Formate, the metabolic product of formaldehyde, is incorporated in normal metabolic pathways or further oxidized to carbon dioxide. Endogenous formaldehyde is present in all human cells. Exposure of humans, monkeys, or rats to formaldehyde by inhalation does not alter the concentration of formaldehyde in the blood (the concentration of endogenous formaldehyde in human blood is about 2 to 3 mg/L).

NONCANCER HEALTH EFFECTS

Acute Effects

In animals, after inhalation of formaldehyde, lesions are typically found in the upper respiratory tract; after oral administration, they are typically found in the stomach. The nature of the lesions depends on the ability of the tissues involved to respond to the exposure and on the local concentration of formaldehyde. Atrophy and necrosis as well as hyper- and metaplasia of epithelia can occur. The most sensitive no observed adverse effect levels (NOAELs) for morphologic lesions resulting from inhalation exposure to formaldehyde were concentrations ranging from 1.2 to 2.4 mg/m^3 (Greim 2002).

Reproductive and Developmental Effects

Because inhaled formaldehyde is rapidly metabolized and detoxified on contact with the respiratory tract, it is unlikely to reach the reproductive organs in concentrations sufficient to cause damage. In animal studies, the inhalation of formaldehyde had no effect on reproduction or fetal development (IARC 2006). Thrasher and Kilburn (2001) reviewed Russian and Japanese studies reporting birth defects and affects on enzyme function in the mitochondria, lysosomes, and endoplasmic reticulum of laboratory
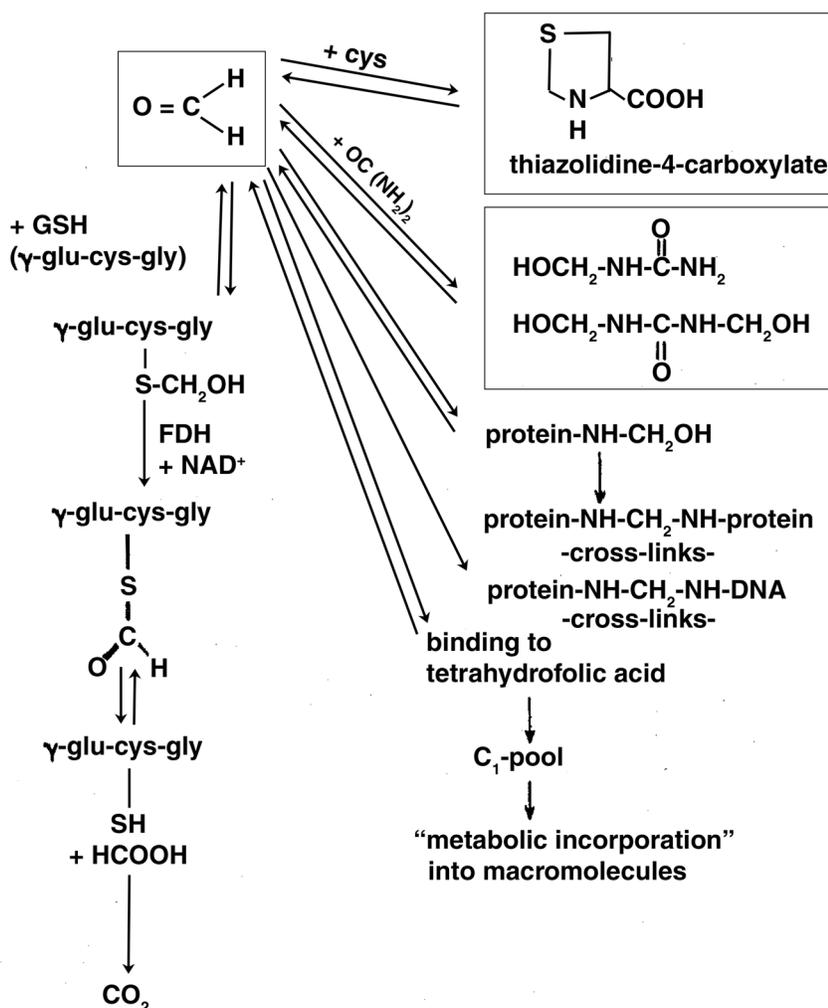
Figure 18. Metabolic pathway of formaldehyde. (Reprinted from Bolt 1987, with the permission of Springer Science and Business Media and the author.)

animals exposed to airborne formaldehyde. Because of severe limitations in these studies (e.g., simultaneous exposure to other chemicals and the lack of analytical concentration measures), they were not suitable for evaluating the reproductive and developmental toxicity of formaldehyde.

GENOTOXICITY

Upon absorption at the site of contact, formaldehyde forms intra- and intermolecular crosslinks with proteins and nucleic acids. Formaldehyde is genotoxic at high concentrations and can induce gene mutations and chromosomal aberrations in mammalian cells. However, the genotoxic effects are limited to cells in direct contact with formaldehyde; no effects are observed in vivo in distant-site tissues. DNA–protein crosslinks are a sensitive measure of DNA modification by formaldehyde. In conclusion, formaldehyde is a direct-acting, locally effective mutagen.

CANCER

In rats, inhalation exposure to formaldehyde induced squamous-cell carcinomas of the nasal cavity. The dose response was highly nonlinear, with sharp increases in tumor incidence occurring only at concentrations greater than 7.2 mg/m^3. No increased incidence of tumors was found in other organs. Nasal cancer was only found at concentrations that induced damage to nasal tissues, including epithelial degeneration and increased cell proliferation, leading to the conclusion that damage to nasal tissue plays a crucial role in the tumor-induction process for formaldehyde. No significant increase in tumors was seen in mice or Syrian hamsters (IARC 2006).

These species differences appear to be related to the local dosimetry and disposition of formaldehyde in nasal tissues. Species differences in nasal anatomy and respiratory physiology might have a profound effect on susceptibility to

formaldehyde-induced nasal tumors. Exposure of rats to formaldehyde in drinking water increased the incidence of forestomach papillomas, leukemias, and gastrointestinal tract tumors in one study (Sofritti et al. 1989) but not in others (IARC 2006). However, the study by Sofritti and colleagues has been questioned because of methodologic shortcomings (Feron et al. 1990).

HUMAN HEALTH

BIOMARKERS

Biomarkers of Exposure

Biomarkers of exposure have not been developed for use in epidemiologic research on the health effects of formaldehyde. Carraro and colleagues (1999) suggested that an immunologic assay that measures the humoral immune response to adducts of formaldehyde and human serum albumin could be used as a marker of environmental exposure to formaldehyde, but such a marker has not been developed.

CANCER

A relatively large number of cohort, nested case–control, and proportional-mortality studies have examined the relationship between occupational exposure to formaldehyde and cancer in two types of populations—people who work with formaldehyde in industrial settings and people in professions in which the use of formaldehyde is fairly common. The industrial settings included those in which formaldehyde is made and those that use formaldehyde in making other products. Workers in the garment industry have also been studied. The professional groups included embalmers, pathologists, laboratory technicians, and anatomists. Population-based case–control studies of selected cancers have also evaluated the association between these cancers and environmental exposure or occupational exposure to formaldehyde.

In 2004, the IARC reviewed formaldehyde and classified it as Group 1 ("an established human carcinogen") (IARC 2006). The IARC review indicated that there is sufficient epidemiologic evidence that formaldehyde causes nasopharyngeal cancer in humans, that there is strong but not sufficient evidence of a causal association between leukemia and occupational exposure to formaldehyde, and that there is only limited epidemiologic evidence that formaldehyde causes sinonasal cancer in humans. The review did not find that the epidemiologic evidence supported a causal role for formaldehyde in relation to cancer at other sites (oral cavity, oropharynx, hypopharynx,

larynx, lung, brain, or pancreas). At present, formaldehyde is classified by the National Institute for Occupational Safety and Health as a "potential human carcinogen," by the EPA as Group B1 ("a probable human carcinogen"), and by the National Toxicology Program as "reasonably anticipated to be a human carcinogen."

The conclusion that formaldehyde causes nasopharyngeal cancer in humans has been controversial (Marsh and Youk 2005; Tarone and McLaughlin 2005). In 1997, a meta-analysis of 47 epidemiologic studies of formaldehyde and upper-respiratory-tract cancer reported a weak positive association between exposure to formaldehyde and nasopharyngeal cancer in case–control studies (meta rate ratio [mRR] = 1.3; 95% CI, 0.90–2.10) (Collins et al. 1997). A weak positive association was also present in cohort studies (mRR = 1.6; 95% CI, 0.80–3.00), but no association remained in an analysis that took reporting problems into account (mRR = 1.0; 95% CI 0.50–1.80).

There are seven additional studies, not included in the meta-analysis by Collins and colleagues (1997), that have data on formaldehyde and nasopharyngeal cancer. Of these, two reported a positive association and five reported no association or a very weak association that was not statistically significant.

The additional studies include updates of the three largest studies of industrial workers exposed to formaldehyde. These evaluated mortality from cancer and other diseases among 11,039 workers employed at three U.S. garment factories (Pinkerton et al. 2004), among 25,619 workers at 10 U.S. factories that made or used formaldehyde (Hauptmann et al. 2003, 2004), and among 14,014 workers at six British factories that made or used formaldehyde (Coggon et al. 2003). Their results were inconsistent for nasopharyngeal cancer. No deaths from nasopharyngeal cancer (compared with an expected number of 0.96), occurred among the garment workers, who were estimated to have had exposure to constant low concentrations of formaldehyde (ranging from 0.11 to 0.24 mg/m^3) without intermittent exposure to much higher concentrations ("peaks") (Pinkerton et al. 2004). Among the British workers, 28% of whom were estimated to have been exposed to concentrations of formaldehyde at or above 2.4 mg/m^3, there was only one death from nasopharyngeal cancer (compared with 2.0 expected deaths). In contrast, among workers at the 10 U.S. factories, the ever-exposed group experienced a total of eight observed deaths (compared with 3.81 expected) from nasopharyngeal cancer (standardized mortality ratio [SMR] = 2.10; 95% CI, 1.05–4.21), and the nonexposed group experienced two observed deaths (compared with 1.28 expected) (SMR = 1.56; 95% CI, 0.39–6.23). Further analyses suggested a positive exposure–response relationship both for peak exposure

(seven naso-pharyngeal-cancer deaths were observed in workers in the highest-exposure category, i.e., at or above 4.8 mg/m^3 formaldehyde) and for cumulative exposure (three nasopharyngeal-cancer deaths were observed in workers in the highest-exposure category, i.e., 6.6 mg/m^3-years).

A fourth study of occupational exposure to formaldehyde compared the proportional cancer incidence among exposed men with the proportional incidence among unexposed men in Denmark from 1970 to 1984 (Hansen and Olsen 1995). Exposure was estimated on the basis of job titles (obtained from Danish pension data) and by linking job histories to records that identified all Danish companies that made or imported formaldehyde. The study found four cases of nasopharyngeal cancer among exposed men, compared with 3.2 expected cases (standardized proportionate incidence ratio [SPIR] = 1.3; 95% CI, 0.30–3.20).

In addition to these recent studies of industrial cohorts, there have been three population-based case–control studies of nasopharyngeal cancer. Armstrong and colleagues (2000) studied 282 cases of nasopharyngeal cancer in Chinese individuals and 282 Chinese control subjects living in two areas of Malaysia where people of southern Chinese ancestry have relatively high rates of this cancer. A semiquantitative measure of exposure to formaldehyde was estimated on the basis of self-reported occupational histories. The study found essentially no association with formaldehyde. Among 49 exposed pairs of cases and controls, the median difference in hours of exposure to formaldehyde was 0.6 (P = 0.25 after adjusting for diet and cigarette smoke). The adjusted odds ratio for any estimated exposure to formaldehyde was 0.71 (95% CI, 0.34–1.43), and the adjusted odds ratio for a tenfold exposure increase was 0.88 (95% CI, 0.70–1.12).

Vaughan and colleagues (2000) studied 194 cases of nasopharyngeal cancer identified between 1987 and 1993 in five U.S. cancer registries and 244 controls. Industrial hygienists used self-reported work histories to classify subjects' jobs according to the probability of exposure to formaldehyde (as "possible," "probable," or "definite") and according to estimated intensity of exposure ("none"; "low" as less than 0.12 mg/m^3; "moderate" as 0.12 to 0.60 mg/m^3; or "high" as greater than 0.60 mg/m^3). Odds ratios were 1.3 (95% CI, 0.80–2.10) for any possible, probable, or definite exposure, based on 79 exposed cases and 79 exposed controls; 1.6 (95% CI, 0.30–7.10) for the highest intensity of exposure (more than 0.60 mg/m^3), based on 5 exposed cases; and 2.1 (95% CI, 1.00–4.50) for the longest duration of exposure (more than 18 years), based on 29 exposed cases. Analyses restricted to cases with differentiated squamous-cell or epithelial nasopharyngeal cancers found a statistically significant positive association with duration of exposure and with cumulative exposure (average concentration-years), both when all possible, probable, or definite exposures to formaldehyde were included and when only definite exposures were included. The investigators concluded that their results supported a causal relationship between occupational exposure to formaldehyde and nasopharyngeal cancer.

Hildesheim and colleagues (2001) studied 375 cases of nasopharyngeal cancer and 325 community controls, all from Taipei, Taiwan. Exposure to formaldehyde was estimated on the basis of self-reported occupational data. The study found, at most, a weak association with formaldehyde. Odds ratios were 1.4 (95% CI, 0.93–2.20) for ever having been exposed, 1.6 (95% CI, 0.91–2.90) for greater than 10 years of exposure, 1.2 (95% CI, 0.67–2.20) for greater than 10 years of exposure after excluding the most recent 10 years before diagnosis, and 1.5 (95% CI, 0.88–2.70) for the highest cumulative exposure. Epstein-Barr virus is a well-established risk factor for nasopharyngeal cancer. Hildesheim and colleagues found that subjects who were seropositive for Epstein-Barr virus (360 cases and 94 controls) had an odds ratio of 2.7 (95% CI, 1.20–6.20) for ever having been exposed to formaldehyde, but there was no exposure–response trend in this group.

Marsh and Youk (2005) and Tarone and McLaughlin (2005) challenged the suggestion that the data from the study by Hauptmann and colleagues (2004) reflected a causal association between formaldehyde and nasopharyngeal cancer. Their arguments included the observation that all of the excess nasopharyngeal cancers among the exposed workers were confined to only 1 of the 10 plants in the study. This plant had 6 observed (compared with 0.66 expected) deaths; the other 9 plants, combined, had only 2 observed (compared with 3.15 expected) deaths. Also, the British study found no excess nasopharyngeal cancer, unlike the U.S. study, even though it included five times as many subjects with relatively high formaldehyde exposure (2.4 mg/m^3 or higher) (Tarone and McLaughlin 2005). At present, it is not known if differences in formaldehyde exposure, chance, or other factors explain the inconsistent results of these studies.

The IARC's conclusion in its 2004 review that there is "strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde" (IARC 2006) is also controversial. At the time of the IARC's 1995 review (IARC 1997a), there were three large studies of industrial workers (that were subsequently updated, see below), as well as a number of smaller studies, that reported data consistent with the absence of

an association between exposure to formaldehyde and leukemia. Seven of eight studies that evaluated professional groups and that were available in 1995 reported that leukemia was weakly associated with work as an embalmer or funeral director, as a pathologist or laboratory technician, or as an anatomist. For a number of reasons, however, the results of these studies did not constitute a satisfactory scientific basis for concluding that formaldehyde causes leukemia. The reported associations typically were weak (with rate or risk ratios of about 1.5), based on small numbers, and not statistically significant. The studies did not obtain direct, quantitative estimates of exposure to formaldehyde, did not evaluate exposure–response relationships, and did not assess possible confounding by other agents to which members of the professional groups might have been exposed. Thus, the research had not ruled out the possibility that the weak associations were caused by occupational exposures other than to formaldehyde, by nonoccupational exposure, or by chance or bias.

Among the updated studies of industrial workers, published after the 1995 IARC review (IARC 1997a), two reported a positive association between formaldehyde and myeloid leukemia. The first, by Pinkerton and colleagues (2004), found that the rate of death from all forms of leukemia, combined, among garment workers was similar to the rate in the general U.S. population (24 observed and 22 expected deaths), reflecting an SMR of 1.09, which was not statistically significant. The rate of death from lymphocytic leukemia was lower than expected (3 observed and 5 expected deaths, SMR = 0.60, not statistically significant). The rate of deaths from myeloid leukemia was higher than expected (15 observed and 10 expected deaths, SMR = 1.44, not statistically significant), particularly among workers who had 10 or more years of potential exposure to formaldehyde (8 observed and 3.7 expected deaths, SMR = 2.19, not statistically significant) and for workers with 20 or more years since first exposure (13 observed and 6.8 expected deaths, SMR = 1.91, statistically significant [$P < 0.05$]). Of the total of 15 myeloid leukemias observed among these workers, 9 were acute, 5 were chronic, and 1 was unspecified as acute or chronic. Quantitative estimates of individual subjects' exposure to formaldehyde were not available. The analysis controlled for sex, race, age, and calendar period but not for lifestyle exposures, such as smoking, which is suspected of being weakly associated with leukemia.

The second updated study, by Hauptmann and colleagues (2003), of U.S. plants that produced and used formaldehyde, reported that exposed workers had an overall leukemia-mortality rate that was 15% lower than in the general U.S. population (65 observed and 76 expected deaths,

SMR = 0.85, not statistically significant), after adjusting for gender, race, age, and calendar period. Other analyses did not compare the death rates of workers with those of the general U.S. population; instead, they compared the death rates of workers who had relatively high exposure with those of workers who had relatively low exposure. These analyses used several measures of exposure, including duration of exposure, estimated cumulative exposure, average intensity of exposure, and exposure to peaks. Leukemia in general was not strongly or consistently associated with duration of exposure or with cumulative exposure. But myeloid leukemia was positively associated both with exposure to peak levels of formaldehyde greater than 4.8 mg/m^3 (rate ratio [RR] = 3.46, statistically significant) and with an average intensity of exposure of greater than 1.2 mg/m^3 (RR = 2.49, statistically significant). The researchers did not report on acute and chronic forms of leukemia separately. They attempted to adjust their results for possible confounding by benzene and other agents and reported that such adjustments had little effect on the results for formaldehyde and leukemia.

The association between formaldehyde and leukemia seen in this study has been challenged for several reasons (Marsh and Youk 2004; Casanova et al. 2004; Cole and Axten 2004). The biologic mechanism by which formaldehyde might cause leukemia has not been established (Hauptmann et al. 2003, 2004; Collins 2004; Heck and Casanova 2004; Cogliano et al. 2005; Golden et al. 2006). No plausible biologic mechanism has been suggested to explain why there might be a true association between peak or average-intensity exposures and leukemia but no association between cumulative exposure and leukemia. The higher RRs for workers in the high peak and average-intensity exposure groups were caused by a rate of leukemia that was quite low in the low-exposure group compared with the general U.S. population (Marsh and Youk 2004). The explanation of this pattern is unknown, but the possibility that the positive results for myeloid leukemia are attributable wholly or in part to an unidentified confounder or bias cannot at present be excluded.

The British study found that the rate of death from leukemia was lower among formaldehyde-exposed workers than in the population at large, both for workers with any amount of exposure (31 observed and 34 expected deaths, SMR = 0.91) and for workers in high-exposure jobs (eight observed and 11 expected deaths, SMR = 0.71) (Coggon et al. 2003). The study did not present detailed results of analyses of leukemia according to alternative exposure indices, nor did it present results for specific forms of leukemia. The Danish study (Hansen and Olsen 1995) of proportional cancer incidence also did not find any evidence

of a positive association between potential exposure to formaldehyde and leukemia (39 observed and 47.0 expected cases; SMR = 0.8, 95% CI, 0.6–1.6).

Overall, the epidemiologic evidence of an association between formaldehyde and leukemia is inconsistent. A positive relationship between formaldehyde and myeloid leukemia was recently reported in studies of two groups of industrial workers. But these results are not supported by studies of several other groups of industrial workers. Studies of professional groups have reported that working as an embalmer, undertaker, pathologist, or anatomist is weakly associated with leukemia, but the association might be caused by other occupational exposures or unidentified sources of bias.

NONCANCER HEALTH EFFECTS

Formaldehyde is a skin sensitizer and one of the more common causes of contact dermatitis. High concentrations can cause asthmatic reactions by way of an irritant mechanism. Whether formaldehyde can cause bronchial asthma by way of immunologic mechanisms is unresolved at present. Studies in animals indicate that formaldehyde might enhance sensitization to inhaled allergens.

Short-term exposure to formaldehyde can lead to noncancer health effects in nonsensitized people, including irritation of the eyes, nose, and other upper-respiratory sites as well as small, reversible decrements in pulmonary function. (All of these are rare at concentrations below 0.36 mg/m^3.) Lachrymation, sneezing, coughing, nausea, dyspnea, and concentration-dependent discomfort are the chief symptoms of formaldehyde exposure. Individual responses to formaldehyde vary substantially, although the eyes are generally most sensitive to exposure. About 5 to 20% of individuals report eye irritation at concentrations ranging from 0.6 to 1.2 mg/m^3, but some begin to feel irritation even at airborne concentrations below 0.12 mg/m^3. Moderate to severe irritation of the eyes, nose, and throat occurs at exposures ranging from 2.4 to 3.6 mg/m^3. In healthy nonsmokers and asthmatics, lung function was generally unaffected even after 3 hours of exposure to up to 3.6 mg/m^3 formaldehyde. Concentrations ranging from 60 to 125 mg/m^3 caused death. Based on a review of chamber, community, and occupational studies of human exposure to formaldehyde, however, it was not possible to identify a specific NOAEL or lowest observed adverse effect level (LOAEL) for formaldehyde (Bender 2002).

In addition to contact dermatitis, epidemiologic studies have reported several other possible effects, but the evidence for a causal relationship is insufficient. These effects include asthma, neurobehavioral effects, histologic changes in the nasal epithelium of workers with occupational exposure, and adverse reproductive effects among occupationally exposed women, including spontaneous abortion, low birth weight, and congenital malformations.

Repeated exposure to formaldehyde typically causes toxic effects at the site of first contact. These are characterized by local cytotoxicity and subsequent repair of the damage. A limited number of studies have investigated histopathological changes in the nasal epithelium of relatively small populations of workers who were repeatedly exposed to formaldehyde. Some histopathological changes in the nasal epithelium were reported at 0.3 mg/m^3 formaldehyde, but the available data do not allow adequate dose–response evaluations.

In a meta-analysis of epidemiologic studies (Collins et al. 2001), no evidence of an increased risk of spontaneous abortions among workers exposed to formaldehyde was found.

Some studies report an association between long-term, low-concentration exposure to formaldehyde and chronic neurobehavioral deficiencies (Williams and Lees-Haley 1998). But because of severe limitations, such as selection biases and unblinded research, no firm conclusions about the neurotoxicity of formaldehyde can be drawn from these studies.

In the past 15 years, investigators have reported associations between formaldehyde in indoor air and asthma or asthma-like symptoms (Krzyzanowski et al. 1990; Czap et al. 1993; Norback et al. 1995; Wantke et al. 1996; Smedje et al. 1997; Wieslander et al. 1997; Garrett et al. 1999; Franklin et al. 2000; Smedje and Norback 2001). Most recently, Rumchev and colleagues (2002) carried out a population-based case–control study in Perth, Australia, to determine whether formaldehyde in indoor air is related to the risk of serious asthma in children. The subjects were 88 children, six months to three years of age, having a primary hospital-discharge diagnosis of asthma between 1997 and 1999. The controls were 104 children who were identified from birth records and did not have a history of asthma. Formaldehyde concentrations in the subjects' bedrooms and living rooms were measured twice, once in winter and once in summer. Mean formaldehyde concentrations were 30.2 μg/m^3 in subjects' bedrooms and 27.5 μg/m^3 in living rooms. Exposure concentrations were higher for cases than for controls. After adjusting for a large number of potential confounders, a statistically significant positive association between formaldehyde and asthma was found, with an odds ratio of 1.39 for exposure at or above 60 μg/m^3 and an estimated 3% increase in the risk of serious asthma per increase of 10 μg/m^3 in indoor formaldehyde concentration. The study had a number of limitations, including its rather small size, the large number of potential confounders, and the possibility of residual confounding, selection bias, and diagnostic uncertainty.

Only one investigation, by Delfino and colleagues (2003), has evaluated the relationship between formaldehyde in ambient air and asthma. A panel study conducted from November 1999 to January 2000 included 22 Hispanic children, 10 to 16 years of age, with physician-diagnosed asthma, living in Los Angeles County in an area characterized by high traffic. Subjects were nonsmokers who lived in nonsmoking households. The investigators analyzed daily ambient concentrations of formaldehyde and 19 other pollutants in relation to asthma severity as self-reported in daily diaries. Formaldehyde concentrations (69 measurements) ranged from 5.12 to 16.82 $\mu g/m^3$, with a mean of 8.65 $\mu g/m^3$ (SD = 2.89 $\mu g/m^3$) and an interquartile range of 3.79 $\mu g/m^3$; they were strongly correlated with the concentrations of a number of other pollutants. The odds ratios for moderate asthma symptoms were 1.09 (95% CI, 0.70–1.60) for the interquartile-range increase in formaldehyde measured on the same day as the symptoms and 1.37 (95% CI, 1.04–1.80) for the interquartile-range increase measured on the previous day. The odds ratios for more severe asthma symptoms were 1.90 (95% CI, 1.13–3.19) for the interquartile-range increase in formaldehyde measured on the same day as the symptoms and 1.30 (95% CI, 0.76–2.22) for the interquartile-range increase measured on the previous day. The apparent effects of formaldehyde were attenuated after adjustment for 8-hour maximum SO_2 or 8-hour maximum NO_2. The study had a number of limitations, including small size and resulting imprecision, a high potential for inaccurate reporting of asthma symptoms, and the possibility of confounding by other pollutants and factors.

REGULATORY SUMMARY

Formaldehyde is classified by the IARC (2006) as Group 1 ("carcinogenic to humans") and by the EPA (1990) as Group B1 ("a probable human carcinogen"). These classifications are based on both human and animal evidence that indicates a risk of nasopharyngeal cancer. Various risk assessments have been carried out for the purpose of defining acceptable exposure concentrations in occupational settings and in ambient air. These have generally relied on evidence from animal studies (EPA 1990).

The EPA (1990) has estimated a lifetime cancer risk of 1.3×10^{-5} associated with an exposure of 1 $\mu g/m^3$ formaldehyde over a lifetime—a concentration in the same range as those measured in ambient air. The EPA's risk estimate is based largely on the occurrence of squamous-cell carcinoma in exposed male rats (Kerns et al. 1983). A new EPA Integrated Risk Information System (IRIS) cancer-risk assessment is underway in light of a CIIT analysis that supports a unit risk estimate (URE) of approximately 5.5×10^{-9} per

$\mu g/m^3$. This value is substantially lower than the current IRIS URE of 1.3×10^{-5} per $\mu g/m^3$ (EPA 1990, 2000e; CIIT 1999; Conolly et al. 2004).

The EPA (1990) has not set an inhalation reference concentration (RfC) for formaldehyde at this time. It has set an oral reference dose (RfD) at 200 $\mu g/kg$-day, based on reduced weight gain and histopathology changes in rats (EPA 1990). The California EPA (1999) has set an acute 1-hour reference exposure concentration of 94 $\mu g/m^3$, with an interim 8-hour reference exposure concentration of 33 $\mu g/m^3$. Health Canada (2006) has set a residential indoor air quality guideline of 123 $\mu g/m^3$ for a 1-hour exposure and 50 $\mu g/m^3$ for an 8-hour exposure, with an action concentration of 60 $\mu g/m^3$ and a 1-hour average episode concentration of 370 $\mu g/m^3$ in British Columbia (British Columbia Ministry of Environment [Canada] 2006). The World Health Organization (WHO 2002) has set an air-quality guideline of 100 $\mu g/m^3$ for a 30-minute period.

Other regulatory standards worldwide call for a maximum air concentration of 12 $\mu g/m^3$ formaldehyde in Cambodia (Kingdom of Cambodia 2000) and an annual average air concentration of 48 $\mu g/m^3$ (30-minute average) in the Philippines (Republic of Philippines Department of Health 1999).

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

In the U.S., long-term mean ambient concentrations of formaldehyde typically range from 0 to 49 $\mu g/m^3$, with an overall national mean concentration of 4.3 $\mu g/m^3$. These concentrations are generally higher in urban than in rural environments, although atmospheric transport of formaldehyde might be affecting non-urban locations. Ambient measurements tend to be highest at roadside sites; some studies, but not all, report higher concentrations in vehicles than at roadside sites. Seasonally, the highest formaldehyde concentrations are associated with the highest rate of photochemical activity, and it appears that photochemical activity in summer contributes more formaldehyde to ambient concentrations than do direct vehicle emissions.

While mobile sources are clearly important contributors to ambient concentrations of formaldehyde, indoor sources are the predominant source of exposure. Indoor concentrations are generally three to five times higher than outdoor concentrations. Indoor concentrations and personal exposures show seasonal trends, with higher concentrations in summer than winter. However, the role of seasonal variability in ambient concentrations in determining these seasonal trends in indoor concentrations is not clear.

In Brazil, studies have shown that the widespread use of vehicles powered by ethanol-based fuels and compressed natural gas is associated with an increase in ambient formaldehyde, which has reached concentrations up to 10 times higher than those measured in U.S. urban areas and in the same range as the highest indoor concentrations recently measured.

TOXICITY

Formaldehyde is highly reactive. Direct contact with tissues, such as those of the upper respiratory tract, can cause local irritation and acute and chronic toxic and genotoxic effects. In rats, after long-term inhalation, formaldehyde causes tumors in the nasal mucosa. After long-term oral administration, it causes hyperplasia and keratinization in the forestomach as well as inflammation and ulcers in the glandular stomach.

HUMAN HEALTH

Formaldehyde has been classified as a human carcinogen, causing nasopharyngeal cancer at concentrations historically encountered in industrial settings. The mechanism of carcinogenesis is not fully understood. Nasopharyngeal cancer is rare in the U.S. and other Western countries; it is more common among people of southern Chinese ancestry. Formaldehyde, at concentrations found in occupational settings, might be associated with myeloid leukemia, although the evidence for this is not sufficient to conclude that a causal relationship exists. Again, the mechanism is not understood. There is limited evidence that exposure to formaldehyde in indoor air increases the occurrence of asthma symptoms in children. Formaldehyde is a respiratory irritant. Studies with volunteers yielded threshold concentrations of less than 0.6 mg/m^3 for odor perception, 0.6 to 1.2 mg/m^3 for eye irritation, and 1.2 mg/m^3 for nose and throat irritation. In workers with long-term exposure to formaldehyde, lesions in the nasal mucosa were observed at concentrations lower than 1.2 mg/m^3. At 0.4 mg/m^3, irritation of the eyes, which are considered to be the most sensitive to formaldehyde, is generally not observed. Formaldehyde causes sensitization of the skin. At present, there is little evidence that exposure to formaldehyde concentrations found in ambient air is hazardous.

KEY CONCLUSIONS

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

While mobile sources are clearly important contributors to ambient concentrations of formaldehyde, indoor sources are the predominant source of exposure. Indoor concentrations are higher than corresponding ambient concentrations and approximately the same as urban roadside and urban in-vehicle concentrations. In Brazil, studies have documented an increase in formaldehyde concentrations associated with the use of ethanol-based fuels and compressed natural gas. Ambient concentrations in Brazil have increased to the same range as the highest indoor concentrations recently measured in many countries.

2. Does formaldehyde affect human health?

Formaldehyde causes irritation of the eyes and respiratory system, with substantial variation in individual responses. Formaldehyde has been classified as a human carcinogen by regulatory agencies, but the human evidence is weak and inconsistent.

3. Does formaldehyde affect human health at environmental concentrations?

Ambient concentrations of formaldehyde are generally lower than those that cause irritation of the eyes and respiratory system. However, concentrations in certain outdoor environments, such as near roadways, can approach those at which sensitive people experience irritation. There is no evidence that ambient concentrations of formaldehyde cause any form of cancer.

RESEARCH GAPS AND RECOMMENDATIONS

EXPOSURE

An increased use of alcohols, particularly ethanol, as alternative vehicle fuels and in fuel blends might increase ambient concentrations of formaldehyde because the combustion of alcohols produces more formaldehyde than that of conventional fuels. Whether these increased emissions will increase the risk of adverse effects on human health, including cancer, is unknown. Research recommendations for formaldehyde-exposure studies include the following:

- Continue to update and critically evaluate the NATA model and compare the model with actual measurements to improve its usefulness in predicting the effect on ambient formaldehyde concentrations of increased use of alcohols as alternative motor-vehicle fuels.
- Develop a monitoring network capable of tracking long-term aldehyde concentrations in ambient air because such an increase in the use of alcohols in fuel is likely.

- Identify formaldehyde-exposure pathways and patterns of personal exposures (including diurnal and seasonal variations) in cities and rural areas throughout the U.S.

TOXICITY

Research recommendations for formaldehyde-toxicity studies include the following:

- Elaborate the quantitative relationship in humans between DNA–protein crosslinks and mutations and the time course of crosslink removal. This would help in understanding the mechanism of tumor induction and in establishing biomarkers of formaldehyde exposure and effect.

HUMAN HEALTH

Research recommendations for human-health studies of formaldehyde include the following:

- Identify populations with increased susceptibility to the irritant effects of formaldehyde (such as children, the elderly, and people with compromised lung function).
- Undertake additional research on the effect of long-term exposures to low formaldehyde concentrations on cancer, asthma, and other endpoints.
- Explore the effects on health of exposure to mixtures of aldehydes (and mixtures of aldehydes with other pollutants). Simultaneous exposure to formaldehyde and other upper-respiratory-tract toxicants, such as acetaldehyde, acrolein, crotonaldehyde, furfural, glutaraldehyde, ozone, and particulate matter might lead to additive or synergistic effects, especially with respect to sensory irritation and possible cytotoxic effects on the nasal mucosa.

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