72 Formaldehyde

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Formaldehyde (HCOH) is a highly reactive chemical that is ubiquitous in the natural environment and widely used in occupational and environmental settings. It is an essential component of many consumer products, although little or none is present in final products. It is also an endogenous chemical found in living cells, where small quantities derive from the metabolism of amino acids, and its metabolites are in equilibrium with the labile methyl group pool.

The health effects of formaldehyde have been the subject of a large amount of research (1–3). Formaldehyde causes mucous membrane and upper respiratory tract irritation at relatively low exposure. Inhalation at high concentrations can cause reversible bronchoconstriction; however, allergic sensitization does not appear to play a substantial role in formaldehyde-associated pulmonary effects (4,5). Residential formaldehyde exposure during childhood may increase the risk of asthma (6). Formaldehyde is an acute skin irritant and an important cause of occupational allergic contact dermatitis (3,5).

Formaldehyde is a proven animal carcinogen (1–3, 7,8), but the findings of epidemiologic studies have been inconsistent, so its carcinogenicity in humans has been controversial. The strongest evidence of human cancer risk is for cancer of the nasopharynx, with weaker evidence for leukemia and sinonasal cancer (7,8). However, some investigators have expressed doubts about carcinogenicity in humans, especially for leukemia (9–11). Based on a 2004 evaluation of published research that included updates of three major occupational cohort studies and meta-analyses of case–control studies, the International Agency for Research on Cancer (IARC) concluded that formaldehyde is carcinogenic to humans based on *sufficient evidence* in humans and *sufficient evidence* in experimental animals (7,8). Formaldehyde is considered a probable human carcinogen by most United States governmental agencies (12–14), although these agencies are currently revising their risk assessments in light of recent research and the IARC determination that formaldehyde is a human carcinogen.

CHEMICAL AND PHYSICAL PROPERTIES

Formaldehyde is a flammable, colorless gas with a pungent odor at room temperature and atmospheric pressure. It is the simplest of the aldehydes, consisting of a single carbonyl group flanked by two hydrogen atoms. Formaldehyde has a relative molecular mass of 30.03, a boiling point of −21°C, and a melting point of −92°C (1). For conversion of units, 1 ppm = 1.23 mg per m^3 at normal temperature and pressure.

Formaldehyde is soluble in water, ethanol, and diethyl ether. Formaldehyde-alcohol solutions are stable, as is the gaseous form of the compound in the absence of water. It is incompatible with acids, alkalis, oxidizers, phenols, and urea (2,3). Formaldehyde reacts explosively with peroxide, nitrogen oxide, and performic acid. It can also react with hydrogen chloride and other inorganic chlorides to form bis-(chloromethyl) ether, a potent carcinogen.

PRODUCTION AND USE

Formaldehyde is produced by the oxidation of methanol, most commonly using the metal oxide catalyst and silver catalyst processes. Approximately 21 million metric tons were manufactured worldwide in 2003 (8). The United States is the leading manufacturer, with a reported annual production of more than five million metric tons (15). Other leading producers include Japan, Germany,

China, and Sweden. Formaldehyde is most commonly available as formalin, a 30% to 50% by weight aqueous solution.

Formaldehyde is used mainly in the production of urea, phenol, melamine, and acetal resins, which account for approximately 70% of the formaldehyde produced (3,16). These resins are used as adhesives and impregnating resins in the manufacture of wood-based products, such as particleboard, plywood fiberboard, and furniture. They are also used as raw materials in the production of surface coatings and controlled-release nitrogen fertilizers. Other applications include paper treating and coating, molding, and foams for insulating materials. Resins also act as binders for foundry sand, abrasive paper, and brake linings. Approximately 20% of formaldehyde is used in the production of chemical intermediates, including acetylenic chemicals and methylene diisocyanate.

Formaldehyde is used in aqueous solution (formalin) for disinfection of room surfaces and acts as an antimicrobial agent in a variety of cosmetic products, such as makeup, nail products, lotions, hair products, deodorants, and soaps. It is used as a tissue preservative and disinfectant in embalming fluids.

EXPOSURE

Occupational Exposures

Several million people are occupationally exposed to formaldehyde in industrialized countries alone. The Occupational Safety and Health Administration (OSHA) estimated that 2.1 million workers in the United States were exposed to formaldehyde in 1995 (16). Formaldehyde was produced at 40 plants in 20 states in 2005 (15) and used in more than 112,000 facilities (16). More than 50,000 workers in each of the following industries had some formaldehyde exposure: manufacture of chemicals and allied products, furniture and fixtures, paper and allied products, printing and publishing, apparel and allied products, health services, machinery, transport equipment, personal services, and business services.

The main pathway of exposure in occupational settings is inhalation of formaldehyde gas, which arises as a vapor from formalin or from decomposition of polymer resins. When powdered resins are used, inhalation of formaldehyde-containing particulates may occur. Formaldehyde-based resins may also become airborne when attached to wood dust or other carrier agents. Dermal exposure may occur if liquid resins or formalin solutions come into contact with the skin.

The highest continuous exposures have been measured in particleboard mills, during the varnishing of furniture and wooden floors, in foundries, and during finishing of textiles. Lower exposures occur in plywood mills and in embalming areas of mortuaries. Short-term high exposures can occur during disinfection in hospitals and food processing plants, as well as in some agriculture operations and during firefighting. Occupational exposures have decreased over time because of the development of resins that release less formaldehyde (3). Many occupations with formaldehyde exposure have concurrent exposures to other substances (Table 72.1) (17).

Environmental Exposures

Ambient Air

Although formaldehyde occurs naturally in ambient air, levels in remote areas are generally <1 μg per m^3 [0.8 parts per billion (ppb)]. Hence, most of the

Table 72.1
Formaldehyde Exposures by Occupational Group

	Formaldehyde Source		
Group	**Vapor/Gas**	**Particle**	**Other Exposures**
Anatomists and pathologists	Formalin		Other preservatives, xylene, toluene, chloroform, methyl methacrylate
Embalmers	Formalin	Paraformaldehyde dust	Solvents in disinfectant sprays, methanol, phenolic solutions
Wood and paper industries	Polymer decomposition	Polymer dust	Wood dust, pesticides, other preservatives
Textiles	Polymer decomposition	Polymer dust	Cotton dust, oil mists
Plastics production	Formalin, polymer decomposition	Polymer dust	Other raw materials
Chemical production	Formalin, polymer decomposition	Polymer dust	Other raw materials

Adapted from Higginson J, Jenson OM, Kinley L, et al. Epidemiology of chronic occupational exposure to formaldehyde: report of the ad hoc panel on health aspects of formaldehyde. *Toxicol Ind Health*. 1988;4:77–90 with permission.

formaldehyde found in populated regions may be attributed to anthropogenic sources. Urban environments have variable outdoor air concentrations of formaldehyde, which are highly dependent on local conditions and range between 1 and 40 μg per m^3 (0.8 to 32 ppb) with a median of about 3 μg per m^3 (2.5 ppb) (3). Ambient urban air levels up to 100 μg per m^3 (81 ppb) have been found during periods of heavy traffic or severe inversions.

Combustion processes account directly or indirectly for most of the formaldehyde entering the environment (3). Stationary sources, such as incinerators and home fires, as well as mobile sources, including internal combustion, diesel, and jet engines, release formaldehyde into the environment. Vehicular emissions are a major source of formaldehyde in outdoor urban air. Emissions were reduced with the introduction of the catalytic converter in 1975, but they have increased again with the introduction of oxygenated fuels (3). Emitted hydrocarbons from these sources can also produce formaldehyde through secondary photochemical reactions.

Residential Indoor Air

Formaldehyde concentrations found indoors are usually higher than those found outdoors. Indoor air levels are determined by the formaldehyde sources present, age of the source materials, ventilation, humidity, and temperature. Common sources include release from structural materials, furnishings, insulation, clothing, and cosmetics (3,8). Tobacco smoking and wood burning also generate formaldehyde. Environmental tobacco smoke can contribute 10% to 25% of the total indoor exposure (3). Formaldehyde in mobile homes, due to off-gassing of particleboard, has been studied since the 1970s. As a result of standards established in the 1980s for mobile home building materials, mean formaldehyde levels in mobile homes have dropped from 0.5 ppm in the 1980s to 0.1 ppm or less today (3,8).

Consumer Products

Cigarette smoke from one cigarette may contain from a few micrograms to several milligrams of formaldehyde. Consumers may be exposed to formaldehyde, formalin, and paraformaldehyde through the use of cosmetic products. Ingredient labels of cosmetics and toiletries rarely list formaldehyde itself as a component of the product. However, formaldehyde may be released from several preservatives or be present as an impurity. Typically, the concentration of a preservative in a commercial product is 0.1% to 0.2%. Concentrations of formaldehyde are thus even lower. However, even minute concentrations may induce allergic contact dermatitis among sensitized individuals.

Foods naturally contain small amounts of formaldehyde, but they may also be contaminated through fumigation, cooking, or release from formaldehyde resin-based cooking utensils. Formaldehyde has also been used as a bacteriostatic in cheeses and other foods (18).

INDICATORS OF EXPOSURE

Formaldehyde exposure is usually monitored by measuring the concentration of formaldehyde gas in the air. Active area air or personal samples may be taken. Passive monitors have been developed to monitor workplace and residential exposures (19,20). Methodologies for compliance monitoring of formaldehyde, specified by OSHA, state that passive samplers are acceptable for monitoring (12). Other countries have also accepted the use of passive monitors for exposure monitoring (21).

Biologic monitoring of formaldehyde exposure is not considered to be reliable (3). Because formaldehyde is rapidly metabolized, no increase in blood concentration is detectable even moments after exposure (3,22). Urinary excretion of formic acid was suggested as a possible biologic monitoring method, but it was shown not to correlate reliably with formaldehyde exposure (23).

Formaldehyde that is not rapidly metabolized can react with cellular components including nucleotides, proteins, and glutathione, forming adducts and DNA-protein crosslinks (3,24). Several of these formaldehyde-induced adducts and DNA-protein crosslinks (DPC) have been evaluated as potential biomarkers of exposure or effects for repeated formaldehyde exposure (3). For example, Shaham et al. (25) examined DPC and p53 protein expression in peripheral blood lymphocytes of formaldehyde-exposed workers and unexposed workers. They found that the formaldehyde-exposed workers had significantly higher levels of DPC, which also correlated with a higher risk of having pantropic p53 >150 pg per mL. Similar findings were obtained in a study that measured sister-chromatid exchange (SCE) in peripheral lymphocytes (26). They concluded that these biomarkers could be used to assess formaldehyde exposure and genotoxic effects (25). However, DPC and SCE formation are not unique to formaldehyde exposure, so they cannot be considered specific biomarkers (27). Recent advances in the chromatographic analysis of formaldehyde-modified DNA from nasal epithelial cells suggests that measurement of formaldehyde-induced DNA adducts in samples taken by nasal lavage or brush biopsy may be feasible biomarkers (27).

ABSORPTION AND BIOTRANSFORMATION

Because formaldehyde has a high aqueous solubility, the upper respiratory tract is its principal site of deposition with inhalation exposure. Essentially all inhaled formaldehyde will deposit in the nasal and

nasopharyngeal mucosa during nasal breathing. Experimental studies in animals indicate that any formaldehyde that penetrates the nasal cavity or upper airways will be deposited in the lower airways.

There are two major protective mechanisms in the nasal passages—mucous clearance and glutathione (GSH)-dependent detoxification (24,28). Formaldehyde reacts with the proteins and polysaccharides of the mucous layer, reducing the concentration of formaldehyde to which epithelial cells are exposed. There is also constant mucus removal by ciliary motion, which tends to limit the extent and severity of formaldehyde cytotoxicity. However, when the inhaled dose of formaldehyde reaches a sufficient level, formaldehyde produces inhibition of mucociliary function and a decrease in mucus flow.

Once in the cell, formaldehyde may react with nucleic acids or proteins, or be metabolized to formic acid. It is metabolized by incorporation into the labile methyl group pool via tetrahydrofolate-dependent pathways. In addition, formaldehyde reacts with GSH, and further biotransformation is mediated by formaldehyde dehydrogenase to produce the thiol ester of formic acid, S-formylglutathione, which yields free GSH and formic acid. The latter is subsequently degraded to carbon dioxide and exhaled, incorporated into the labile methyl group, or excreted in the urine.

The metabolic pathway involving GSH and formaldehyde dehydrogenase is an important defense mechanism because this pathway tends to inhibit the covalent reaction of formaldehyde with nucleic acids (24). Depletion of GSH diminishes the capacity of the respiratory mucosa to protect itself from the formation of DPC after administration of formaldehyde. At concentrations that exceed the endogenous protective mechanisms, formaldehyde can produce higher concentrations of DPC per unit of time, as well as greater cellular toxicity and enhanced cell proliferation. Formaldehyde also can penetrate human skin (3).

HEALTH EFFECTS

Because inhaled formaldehyde is completely absorbed and metabolized in the respiratory tract except, with very high exposure, it is unlikely to produce systemic toxicity in organs distant from the site of absorption. Thus, most health effects associated with formaldehyde occur in the mucosa of the eyes and upper respiratory tract, and the skin. Gastrointestinal and systematic toxicity have been reported in cases of ingested formalin.

Mucosa and Respiratory Tract

Irritation

Formaldehyde is a known irritant of the eyes and upper respiratory tract. The threshold for eye, nose, and throat irritation in most people is 0.3 to 1.0 ppm (2,3,29,30), although eye and respiratory irritation have been reported by some persons with exposure to formaldehyde concentrations as low as 0.1 ppm (1). The proportion of persons reporting eye irritation and the severity of the irritation increases with increasing concentrations of formaldehyde (29). Discomfort will occur almost immediately with exposure at 4 to 5 ppm, and intense lacrimation and difficulty in breathing may occur at 10 to 20 ppm (29). A short-term tolerance usually develops to low doses but is lost if exposure is resumed after a 1- to 2-hour interruption.

Nasal Epithelial Damage

Histopathologic effects and cytogenic changes in the nasal mucosa have been reported among persons with occupational or residential exposure to formaldehyde. Exposure to formaldehyde was associated with loss of cilia, goblet cell hyperplasia, and squamous metaplasia, based on cell smears or biopsy samples, among persons living in urea-formaldehyde foam-insulated homes and workers with occupational exposure (1,3). Higher frequencies of micronucleated nasal respiratory cells and squamous metaplasia were seen among exposed workers compared with control workers in a warehouse area of a plywood factory (31). Increased micronuclei were seen in buccal cells, but not nasal cells in mortuary science students exposed to embalming fluid containing formaldehyde following a 90-day embalming class (32).

Acute and intermediate animal studies have confirmed that formaldehyde causes epithelial damage (1,3,24). Inhalation exposure to formaldehyde produced purulent rhinitis, epithelial dysplasia, and squamous metaplasia and hyperplasia in rats, mice, and monkeys (24). Epithelial dysplasia preceded the appearance of squamous metaplasia. The frequency and severity of squamous metaplasia increased in a time- and dose-dependent manner during repeated exposures. After daily exposure to formaldehyde was discontinued, the prevalence of squamous metaplasia and rhinitis decreased, indicating reversibility of cellular damage.

Pulmonary Effects

Acute changes in pulmonary function with formaldehyde exposure have been studied using controlled human exposure studies and cross-sectional occupational studies. The findings are not completely consistent, but the studies generally indicate that formaldehyde does not cause significant bronchoconstriction or airway hyperresponsiveness at exposure levels below about 3 ppm (3,29,30). Reversible bronchoconstriction can occur following exposure to formaldehyde above 5 ppm (2). There have been case reports of asthma in individuals exposed to formaldehyde (3,33,34), although it does not appear that the mechanism usually involves allergic sensitization.

In several controlled human exposure studies, exposures up to 3 ppm formaldehyde caused upper respiratory tract irritation, but no significant bronchoconstriction (3). For example, pulmonary function was not significantly altered in healthy nonsmokers and asthmatic subjects exposed to 2 ppm for 40 minutes (35), in hospital laboratory workers exposed to 2 ppm for 40 minutes (36), in nonsmokers exposed to 2 ppm while exercising (37), or in formaldehyde-exposed textile or shoe manufacturing workers with reported bronchial asthma exposed to 0.4 ppm for 2 hours (38).

Similar to findings in controlled exposure studies, numerous assessments of pulmonary function in formaldehyde-exposed workers have found either no effects or only small effects from formaldehyde exposure during a work shift (3). Some studies of workers with exposures in the range of 0.02 to 5.0 ppm formaldehyde have found symptoms of bronchoconstriction and reversible reductions in pulmonary function measures (e.g., forced expiratory volume in 1 second) including particleboard and plywood workers, urea-formaldehyde resin producers, embalmers, and anatomy and histology workers (3). A study of students exposed to 1.1 ppm formaldehyde while dissecting cadavers 2.5 hours per week found increased irritant symptoms to the eyes, nose, and throat and reduced peak expiratory flow associated with formaldehyde exposure during the previous 2.5 hours (−1.0% per ppm) and additionally by average exposure during the preceding weeks (−0.5% per ppm) (39). The short-term exposure effect diminished during the first 4 weeks of the course, suggesting partial acclimatization. However, other occupational studies did not find effects on pulmonary function associated with lower exposures to formaldehyde (3,30).

One explanation for the inconsistency is that some occupational groups may be exposed intermittently to high concentrations of formaldehyde, which is not reflected in time-weighted exposure measurements. Another explanation is that in some workplaces, formaldehyde may be adsorbed to fine particles and then transported to the lower respiratory tract, causing the airways effect (40). Also, several occupational groups are exposed to other irritating substances that may contribute to the pulmonary effects.

Environmental epidemiology studies suggest that children may be more sensitive than adults to formaldehyde exposures (41). Kryzanowski et al. (42) studied adults and children in 202 households using passive samplers for indoor formaldehyde concentrations, while collecting information on symptoms, doctor diagnosis of asthma, and peak expiratory flow rates. The study found significantly greater prevalence rates of asthma and chronic bronchitis among children, but not among adults, in homes with 0.06 to 0.12 ppm compared with homes with lower formaldehyde concentrations. Exposure to 0.06 ppm formaldehyde reduced peak expiratory flow rates by 22% compared with unexposed children. The effects in adults were less evident. Other studies, which included only children, also reported increased asthma and atopic sensitization among children exposed to formaldehyde in the range 0.02 to 0.06 ppm in primary schools (42) and homes (6,43).

Lower respiratory tract effects have been reported in particular circumstances. For example, chemical pneumonitis and pulmonary edema have been reported after very high levels of exposures. Inhalation of paraformaldehyde particles may penetrate more deeply into the lungs than inhalation of formaldehyde vapors, resulting in pulmonary irritation.

Role of Allergic Sensitization

There has been substantial discussion about whether formaldehyde can cause immunologically mediated respiratory disease (3–5). Formaldehyde exposure is capable of causing antibody-mediated hypersensitivity. Immunoglobulin E (IgE), IgG, and IgM antibodies to formaldehyde-hemolytic red blood cell membrane protein and formaldehyde-human serum albumin conjugates have been identified in persons who received intravenous formaldehyde during dialysis (3). Nevertheless, studies that have measured formaldehyde-specific antibodies in the sera of occupationally and environmentally exposed persons have found that only a small proportion of exposed individuals develop specific IgE or IgG, and among these groups, specific antibodies did not correlate with symptoms. Dykewicz et al. (44) performed environmental assessments, respiratory challenges, and immunologic testing on 55 volunteers, 34 with reported occupational exposure to formaldehyde. Although antibodies to formaldehyde-human serum albumin (F-HSA) were found in some subjects, there was no relation between the presence of IgE or IgG to F-HSA and a history of formaldehyde exposure.

Wantke et al. (45) reported that the presence of formaldehyde-specific IgE correlated with measured formaldehyde in schoolchildren; however, elevated IgE levels to formaldehyde did not correlate with symptoms. In animal studies, formaldehyde displayed no significant potential to influence serum IgE levels in the mouse IgE test (5). On the other hand, it has been suggested that low-level formaldehyde exposure may increase the risk of allergic sensitization to common aeroallergens (41,43). Experimental research in guinea pigs also showed that repeated exposure to formaldehyde increased bronchoconstriction through enhancing antigen sensitization (46). Although the general conclusion has been that formaldehyde exposure rarely causes immunologically mediated respiratory disease (4,5,47), exposure may enhance sensitization to other aeroallergens (41).

Chronic Pulmonary Effects

Findings of studies on the long-term effects of formaldehyde exposure on pulmonary function have been inconsistent (40). Studies using pulmonary function tests performed on a variety of groups with occupational exposure have generally found that formaldehyde does not induce chronic decrement in lung function (3). Several mortality studies in industries with formaldehyde exposure have not generally shown increased risk for noncancerous respiratory causes (1,3,48,49). However, a major cohort study of British chemical workers exposed to formaldehyde did find an increased risk of respiratory disease mortality [standardized mortality ratio (SMR) = 1.19; 95% confidence interval (CI), 1.02 to 1.38], with the primary cause being chronic obstructive lung disease (50). There was not a strong exposure-response association and the study did not have information on smoking habits, so this apparent association could be due to confounding.

Dermatitis

Formaldehyde is an acute skin irritant and an important cause of occupational allergic contact dermatitis (3,5). Formaldehyde induces cell-mediated hypersensitivity, which results in allergic contact dermatitis. Experimental studies using the guinea pig test methods and the local lymph node assay demonstrated the contact-sensitizing potential of formaldehyde (5). In a study of persons with positive patch tests to formaldehyde, only two of 15 persons demonstrated formaldehyde-specific serum IgE and these two persons had no clinical signs of atopy, indicating that specific IgE antibodies are not involved in the pathogenesis of contact sensitivity to formaldehyde in either non-atopic or atopic persons (51).

Other than occupational exposures, the most common sources of exposure include cosmetics, skin and hair products, and permanent press textiles. In the past, contact dermatitis caused by formaldehyde-based textile resins was common. Introduction of formaldehyde resins that release little or no formaldehyde has brought about a substantial reduction in the incidence of dermatitis from permanent press clothing. People who are sensitive to formaldehyde-based textile resins in permanent press clothing may react to the resin, to formaldehyde, or to the monomers themselves. Individuals who are hypersensitive to formaldehyde resins are often not allergic to formaldehyde itself. Therefore, formaldehyde alone cannot be reliably used for patch test screening persons with sensitivity to clothing. Resins should be tested as well.

Systematic Effects

Effects of Ingestion

Toxic effects following ingestion of formaldehyde have been confirmed by reports of a number of deaths attributed to this type of exposure. Ingestion of large amounts of formaldehyde has been known to cause severe corrosive damage to the esophagus and stomach. Ingestion of formalin can cause corrosive gastritis with associated nausea, vomiting, pain, and bleeding. Ingestion of concentrated formaldehyde solutions can result in necrosis and ulceration of the stomach and intestine (3). Metabolic acidosis can develop following ingestion as a result of metabolism of formaldehyde to formic acid.

Reproductive and Developmental Toxicity

The reproductive and developmental toxicity of formaldehyde has been reviewed (1,3,52). In animal experimental systems, formaldehyde did not exert adverse effects on reproduction or fetal development whether administered by inhalation, ingestion, or skin exposure to various rodent species (52). Some epidemiologic studies have shown adverse reproductive outcomes among women with occupational formaldehyde exposure (53,54). For example, an increase in spontaneous abortion was observed in a study of women working in Finnish laboratories [odds ratio (OR) = 3.5; 95% CI, 1.1 to 11], but most of the cases and controls that had been exposed to formalin were also exposed to xylene (53). A case–control study of cosmetologists also observed an increase in spontaneous abortions (OR = 2.1; 95% CI, 1.0 to 4.3) associated with self-reported formaldehyde exposure (54). However, other occupational studies did not observe adverse reproductive effects. Collins et al. (52) (N20) conducted a meta-analysis of nine occupational studies of adverse pregnancy outcomes and calculated a meta-relative risk for spontaneous abortion of 1.4 (95% CI, 0.9 to 2.1) associated with formaldehyde exposure, but they suggested that this apparent association resulted from recall bias from self-report of exposures and publication bias. They also noted that the small number of studies on birth defects, low birth weight, and infertility among formaldehyde workers, and inconsistent finding across these studies, makes it difficult to evaluate the effects of formaldehyde exposure on these outcomes.

Neurologic Effects

Neurobehavioral effects, including impaired memory, equilibrium, and dexterity, have been reported among histology technicians (55), fiberglass batt makers, and dental office personnel (3,56). However, because of rapid metabolism in the respiratory tract it is unlikely that formaldehyde would reach the brain to cause direct central nervous system effects. Williams and Lees-Haley (56) reviewed prior studies on the neuropsychological effects of low-level occupational formaldehyde exposure and concluded that most of the studies relied on self-reported exposures, had possible confounding from exposures to other neurotoxicants, and were subject to

selection bias. In comparison with research on other neurotoxicants, the research on neurobehavioral effects of formaldehyde exposure is sparse.

Carcinogenicity

The question of whether formaldehyde causes cancer in humans has been the subject of considerable research and controversy since it was reported that exposure to high concentrations of formaldehyde gas produced squamous cell carcinomas in the nasal cavities of rats (57,58). Animal and *in vitro* experimental research have demonstrated that formaldehyde is an animal carcinogen and directly genotoxic in a variety of experimental systems (1). It was found that formaldehyde exhibits a sublinear dose-response for animal carcinogenicity with little or no effect at low exposure levels (1,24). Tumors appear to occur only in tissues with direct contact to high concentrations of formaldehyde. These experimental research findings motivated a large number of epidemiologic studies.

Epidemiologic Studies

The relationship between formaldehyde exposure and cancer has been investigated in more than 25 cohort studies of professional groups and industrial workers with potential formaldehyde exposure. More than 20 case–control studies have investigated formaldehyde exposure related to various tumor types, including nasal cavities, nasopharynx, lung, and leukemia. Reviews have summarized the epidemiologic data (1–3,7,8). Six meta-analyses of the data have been published (59–64). IARC convened expert panels to review the research in 1981, 1987, 1994, and 2004. Based on the published research through 2004, IARC concluded that formaldehyde is a human carcinogen based on "sufficient evidence" in humans studies (7,8).

Professional Workers Cohort Studies

Professional groups such as pathologists, anatomists, embalmers, and funeral directors have been studied because they are exposed to formalin as a tissue preservative. The cohorts were identified from occupational associations or lists of professional licensees. These studies include a cohort mortality study of pathologists and medical laboratory technicians in the United Kingdom (65), cohort mortality studies of pathologists (66) and anatomists in the United States (67), proportionate mortality studies of embalmers in the United States (68,69), and a cohort mortality study of embalmers in Ontario (70).

The findings were pooled in a meta-analysis by Blair et al. (59). Among professionals, significant excess mortality occurred for leukemia [cumulative relative risk (CRR) = 1.6], brain cancer (CRR = 1.5), and colon cancer (CRR = 1.3). There were fewer deaths than expected from lung cancer. Similar findings were reported in the meta-analysis by Partanen (60). A meta-analysis by Collins et al. (61) reported a deficit in lung cancer mortality among pathologists and a null association among embalmers. Another meta-analysis by Collins and Lineker (63) found a small increase in leukemia mortality among embalmers [meta relative risk (mRR) = 1.6; 95% CI, 1.2 to 6.0] and pathologists (mRR = 1.4; 95% CI, 1.0 to 1.9). There were too few expected deaths from sinonasal or nasopharyngeal cancer to draw meaningful inferences in these studies.

Concerns have been raised about the studies of professionals. First, data on formaldehyde exposures were not consistently available. Second, data were not generally available to adjust for tobacco use or potentially confounding occupational exposures, such as chemicals used by embalmers and in anatomy laboratories. Third, many of the studies used external population comparisons, which introduced the possibility of diagnostic bias or confounding as a result of differences in socioeconomic status between the professional groups and referent populations.

Industrial Workers Cohort Studies

The cohort studies of industrial workers are important because some of them were large and had quantitative estimates of formaldehyde exposure. Three studies reported follow-ups of occupational cohorts since 2003: a National Cancer Institute study of U.S. industrial workers (48,71), a study of British industrial workers (50), and a study of U.S. garment workers (49) (Table 72.2). These studies were considered to be of significant value by the IARC expert panel (7,8) because of their long follow-up period and quality.

The National Cancer Institute study included 25,619 workers (865,708 person-years) employed before 1996 in 10 facilities producing a variety of products such as formaldehyde, formaldehyde resins and molding compounds, laminates, photographic film, and plywood (48,72). Formaldehyde exposures were estimated based on the combination of job, department, plant, and calendar-year linked with results of plant visits, job descriptions, process descriptions, work processes, and current and historical monitoring data. Peak exposures were estimated by an industrial hygienist from knowledge of the job tasks. The cohort was followed for mortality through 1994. Compared with the U.S. population, mortality from solid cancers overall was lower than expected (48). Nasopharyngeal cancer mortality was elevated compared with that in the general population (SMR = 1.56 for the nonexposed and 2.10 for the exposed). In an internal comparison, the relative risk for nasopharyngeal cancer significantly increased with cumulative exposure, highest peak exposure, and duration of exposure. Relative risk for leukemia, particularly for myeloid leukemia, increased with peak and average

Table 72.2
Summary of Updated Industrial Workers Cohort Mortality Studies

Cohort	Study Population	Total Deaths	Nasopharyngeal Cancer	Sinonasal Cancer	Lung Cancer	Leukemia
10 U.S. formaldehyde-producing or using facilities (48,71)	25,619 workers (865,708 p-y)	1,921	9 deaths; SMR = 2.10 (1.05–4.21) in exposed. Increased RR with duration, average intensity, cumulative, and peak exposure	3 deaths; SMR = 1.19 (0.38–3.68) in exposed. Increased RR with average intensity and peak exposure.	744 deaths; SMR = 0.97 (0.90–1.05) in exposed.	69 deaths; SMR = 0.85 (0.67–1.09) in exposed. RR increased with average intensity and peak exposure.
3 U.S. garment manufacturing facilities (49)	11,098 workers (339,241 p-y)	2,206	0 deaths; 0.96 expected	0 deaths; 0.16 expected	152 deaths; SMR = 0.98 (0.82–1.15)	24 deaths; SMR = 1.09 (0.70–1.62). Increased SMR with exposure duration.
6 British chemical factories (50)	14,014 workers	5,185	1 death; 2.0 expected	2 deaths; 2.3 expected	594 deaths; SMR = 1.22 (1.12–1.32)	31 deaths; SMR = 0.91 (0.62–1.29)

p-y, person-years; RR, relative risk; SMR, standardized mortality ratio

intensity formaldehyde exposure (71). Compared with workers exposed to low peak levels of formaldehyde (0.1 to 1.9 ppm), the relative risk for myeloid leukemia was 3.46 (95% CI, 1.27 to 9.43) for workers exposed to peak levels ≥4.0 ppm. The investigators found no evidence that lung cancer was associated with formaldehyde exposure and there were too few cases of sinonasal cancer for a meaningful assessment.

Another major study of industrial workers was based on 14,014 workers employed after 1937 in six British facilities producing or using formaldehyde (50,73). Estimates of formaldehyde exposure were made for each job. Twenty-five percent of the cohort were unexposed, while 35% were in the highest exposure category (>2.0 ppm). However, the validity of this category is unclear because the investigators assigned the same exposure category to jobs for all time periods, although exposure levels decreased over time. Furthermore, the workers were categorized by the highest exposure job ever held, rather than based on measures of average or cumulative exposure (2). The cohort was followed for mortality from 1941 through 2000. Among 5,185 recorded deaths, two were from sinonasal cancer (2.3 expected) and one from nasopharyngeal cancer (2.0 expected). Relative to national population rates, mortality from lung cancer increased, especially in the highest exposure category (>2 ppm) (SMR = 1.58; 95% CI, 1.40 to 1.78). However, there were 10 deaths from mesothelioma, typically associated with asbestos exposure, and no information was available on cigarette smoking, so it is quite possible that the apparent increase in lung cancer mortality could have been due to confounding from other occupational exposures or cigarette smoking. There was no apparent increase in mortality from leukemia (SMR = 0.91; 95% CI, 0.62 to 1.29), but the risk for myeloid leukemia was not separately reported.

The third major study that was recently updated was a cohort mortality study of garment workers in the United States (49,74). A cohort of 11,039 workers (339,241 person-years) was assembled from three garment manufacturing facilities that produced shirts from fabrics that were treated with formaldehyde resins. Exposure to formaldehyde was assessed by area monitoring combined with work histories and personal monitoring of a subgroup of the cohort. The area monitoring indicated that exposures to formaldehyde were similar across departments and plants, and formaldehyde levels were essentially constant without substantial peaks. The overall geometric mean concentration of formaldehyde was 0.15 ppm. Mortality was followed from 1955 through 1998. Total mortality and cancer mortality rates in the cohort were lower than the U.S. reference rates. Mortality from trachea, bronchus, and lung cancer was similar to the U.S. reference rates. A small, nonsignificant excess was observed for leukemia (SMR = 1.09), which was stronger for myeloid leukemia (SMR = 1.44; 95% CI, 0.80 to 2.37). The excess was greater for workers with longer duration of exposure and earlier year of first exposure, when formaldehyde exposure levels were higher. Multiple-cause mortality from myeloid leukemia among workers with both 10 or more years of exposure and 20 years or more since first exposure was significantly increased (SMR = 2.55; 95% CI, 1.10 to 5.03). There were no reported deaths from sinonasal or nasopharyngeal cancer, but only 0.16 and 0.96 deaths, respectively, from these causes were expected.

Mortality was also studied among workers in a resin manufacturing plant in Italy (75), the abrasives industry in Sweden (76), and an iron foundry in the United States (77). These studies did not find increased lung cancer mortality risk associated with formaldehyde exposure, and the studies were too small to meaningfully evaluate risk for sinonasal or nasopharyngeal cancer.

Case–Control Studies

Several case–control studies have evaluated cancer risk associated with formaldehyde exposure. The most pertinent are those evaluated cancers of the upper respiratory tract because of findings in the animal studies and cohort studies. This study design is relevant for sinonasal and nasopharyngeal cancers because these cancers are too rare to be evaluated with sufficient statistical power in most cohort studies. The limitations of this study design are that exposures were estimated retrospectively based on reported work histories and occupational titles. Another complication for evaluation of sinonasal cancer is that some occupations may have concurrent exposure to wood dust, which is a recognized cause of sinonasal adenocarcinoma. Four studies during the 1980s accounted for most of the exposed cases and therefore contributed most to the subsequent meta-analyses and expert panel reviews.

Olsen et al. (78) studied cases with sinonasal and nasopharynx cancers reported to a cancer registry in Denmark, using controls with cancers of other sites. Exposure histories were assessed by industrial hygienists. A nonsignificant increased risk of squamous cell carcinoma was observed for persons who had been exposed to formaldehyde, adjusted for wood dust exposure (OR = 2.0; 95% CI, 0.7 to 5.9) (79).

Hayes et al. (80) conducted a case–control study of cancer of the nasal cavities and paranasal sinuses in the Netherlands using medical records from major medical institutions, with age-matched population controls. Work and exposure histories were obtained from the subjects or next-of-kin and evaluated by industrial hygienists. An excess risk was found for adenocarcinoma associated with wood dust exposure. Therefore, a separate analysis was done for squamous cell cancer, which found significantly increased risk associated with formaldehyde exposure alone.

Roush et al. (81) conducted a population-based case–control study of sinonasal or nasopharyngeal cancer mortality using a tumor registry in Connecticut. Controls were randomly selected from state death certificates. Occupations of subjects were identified from the death certificates and city directories, and coded by an industrial hygienist. Relative risks for sinonasal cancer and for nasopharyngeal cancer were increased among subjects who had probably been exposed to high levels of formaldehyde 20 or more years before death.

Vaughan et al. (82,83) examined both occupational and residential exposure to formaldehyde in a population-based case–control study in Washington State. Occupational exposure was assessed based on interviews with subjects or next-of-kin using a job-exposure linkage system. Increased relative risks for nasopharyngeal cancer were associated with occupational formaldehyde exposure and with a residential history of living in a mobile home or in a home with formaldehyde-containing insulation and plywood or particleboard. Sinonasal cancer was associated with a nonsignificantly decreased risk with occupational formaldehyde exposure; mixed associations were found for residential formaldehyde exposure.

Three studies of nasopharyngeal cancer have been reported since 2000. Vaughan et al. (84) conducted a multicenter, population-based case–control study using five cancer registries in the United States. Newly diagnosed cases between 1987 and 1993 (n = 196) and controls (n = 224) selected by random digit dialing were interviewed about personal risk factors and lifetime history of occupational and chemical exposures. Potential exposures to formaldehyde and wood dust were evaluated by industrial hygienists. After adjustment for personal risk factors, an increasing risk of squamous and unspecified epithelial carcinomas was significantly associated with increasing duration and cumulative exposure to formaldehyde. The OR for persons with cumulative exposure to >1.1 ppm-years was 3.0 (95% CI, 1.3 to 6.6) compared with unexposed persons. There was no association between formaldehyde exposure and undifferentiated and nonkeratinizing carcinomas.

Hildesheim et al. (85) conducted a study in Taiwan among 375 newly diagnosed cases of nasopharyngeal cancer and 325 community controls matched by age, sex, and geographical residence. An occupational history was obtained and evaluated by industrial hygienists. Individuals potentially exposed to formaldehyde had a modest increased risk of nasopharyngeal cancer (OR = 1.4; 95% CI, 0.93 to 2.2). However, it was noted that more than 90% of the cases in this study were diagnosed with nonkeratinizing and undifferentiated carcinomas, while only 10% were diagnosed with squamous cell carcinomas. The latter cancer has been more strongly associated with nasopharyngeal cancer in other studies.

Armstrong et al. (86) conducted a study of 282 Chinese residents of Malaysia who had prevalent or incident cases of squamous cell nasopharyngeal carcinoma during 1990 to 1992. Age- and sex-matched community controls were selected by multistage geographic sampling. A lifetime history was obtained by interview and evaluated for inhalational exposures and occupational title. After adjustment for personal risk factors, wood dust and industrial heat but not formaldehyde were associated with increased risk of nasopharyngeal cancer. However, it was noted that the prevalence of exposure to formaldehyde was very low with only 51 of 564 (9%) of participants having potential occupational formaldehyde exposure, of whom only eight persons had ≥10 years of exposure outside of a 10-year latency period. Therefore, the apparent lack of an association with formaldehyde may be to the result of the low prevalence of exposure in this population.

Meta-analyses

Meta-analyses by Blair et al. (59) and Partanen (60) published during the early 1990s reported a small excess aggregate relative risk across all of the studies for sinonasal and nasopharyngeal cancers. Relative risks for both types of cancer increased with increasing exposure. Both Blair et al. and Partanen concluded that occupational formaldehyde exposure was causally associated with sinonasal and nasopharyngeal cancers. As noted above, they also observed increased risks for leukemia, brain cancer, and colon cancer in the professional cohorts.

A meta-analysis by Collins et al. (61) published in 1997 analyzed many of the same studies. Their analyses indicated that workers with formaldehyde exposure had no apparent increased risk for lung cancer or sinonasal cancer. They reported an mRR for nasopharyngeal cancer across cohort studies of 1.6 (95% CI, 0.8 to 3.0), but made an adjustment for apparent underreporting of expected deaths and found that the mRR was then 1.0. They also reported a mRR for seven case–control studies of 1.3 (95% CI, 0.9 to 2.1), but stated that the formaldehyde exposure estimates were unreliable. Therefore, Collins et al. concluded that the studies did not provide evidence of a causal association between formaldehyde and nasopharyngeal cancer.

Collins and Lineker (63) also conducted a meta-analysis of formaldehyde exposure and leukemia based on a review of 18 studies that evaluated this association. They reported a small increase in the rate of leukemia overall among embalmers (mRR = 1.6; 95% CI, 1.2 to 6.0) and pathologists or anatomists (mRR = 1.4; 95% CI, 1.0 to 1.9), but no increase among industrial workers. Despite these moderately increased risks, the investigators concluded these data did not provide support for an association between formaldehyde exposure and leukemia risk because there was no consistent pattern across the studies of observed latencies between onset of exposure and mortality and because there was some suggestion of publication bias in which "positive"

studies were more likely to be published than "negative" studies.

Luce et al. (64) conducted a pooled analysis of 12 case–control studies in seven countries of sinonasal cancer and occupational exposures. The data set included 195 adenocarcinoma cases, 432 squamous cell carcinoma cases, and 3,136 controls. Occupational exposures to formaldehyde, silica dust, textile dust, coal dust, flour dust, asbestos, and man-made vitreous fibers were assessed with a job-exposure matrix. Exposures were categorized into nonexposed and three levels of cumulative exposure based on tertiles of the distribution among controls. The pooled ORs of formaldehyde exposures were calculated separately by histologic type and sex, and were adjusted for age and cumulative exposure to wood dust and leather dust. The findings are summarized in Table 72.3. A significantly increased risk of sinonasal adenocarcinoma was associated with exposure to formaldehyde. The ORs for the highest level of exposure were 3.0 (95% CI, 1.5 to 5.7) among males and 6.2 (95% CI, 2.0 to 19.7) among females. An elevated risk of squamous cell carcinoma was observed among males (OR = 1.6; 95% CI, 1.1 to 2.3) and females (OR = 2.5; 95% CI, 0.6 to 10.1) with a high probability of exposure to formaldehyde. They concluded that occupational exposure to formaldehyde increases the risk of sinonasal cancer.

Following two reports of associations between potential formaldehyde exposure and increased risk of pancreatic cancer (87,88), Collins et al. (62) reviewed more than 50 studies that evaluated formaldehyde exposure and cancer risk, and identified 14 with sufficient data on pancreatic cancer for a meta-analysis: eight cohort studies, four proportionate mortality studies, and two case–control studies. Across all of the studies, formaldehyde exposure was associated with a modest increase of pancreatic cancer risk (mRR = 1.1; 95% CI, 1.0 to 1.3). The increased risk was limited to embalmers and pathologists and anatomists. There was no increase in pancreatic cancer risk in the industrial worker cohorts. The updated cohort mortality study of U.S. industrial workers also found no association between formaldehyde and pancreatic cancer (48).

International Agency for Research on Cancer Expert Panel Review

The IARC convened a panel of experts in 1994 to review the published research on formaldehyde exposure and cancer. That panel concluded that formaldehyde is *probably carcinogenic to humans* (Group 2A) (1). In 2004, following the publications of updates to three major occupational cohort studies and several new case–control studies, IARC convened another expert panel to evaluate the risk of formaldehyde exposure. Based on the published research through 2004, IARC changed the earlier classification and concluded that formaldehyde is *carcinogenic to humans*, based on *sufficient evidence* in humans and in experimental animals (Group 1) (7,8). IARC concluded based on the epidemiologic studies that there was *sufficient evidence* that formaldehyde causes nasopharyngeal cancer, "strong but not sufficient" evidence of leukemia, and limited evidence of sinonasal cancer (8). The panel concluded that the overall findings from epidemiologic studies did not support a causal role for formaldehyde exposure in relation to cancers of the lung, pancreas, or brain.

The panel's conclusion about sufficient evidence regarding nasopharyngeal cancer was based on the statistically significant excess of deaths in the U.S. industrial cohort study (48), excess nasopharyngeal deaths in

Table 72.3
Odds Ratios of Sinonasal Cancer Risk for Cumulative Exposure to Formaldehyde; Pooled Analysis of 12 Case–control Studies

		Squamous Cell Carcinoma			Adenocarcinoma		
Exposure by Gender	No. of Controls	No.	OR[a]	95% CI	No.	OR[b]	95% CI
Males							
Low	265	43	1.2	0.8–1.8	6	0.7	0.3–1.9
Medium	266	40	1.1	0.8–1.6	31	2.4	1.3–4.5
High	211	30	1.2	0.8–1.8	91	3.0	1.5–5.7
Females							
Low	96	6	0.6	0.2–1.4	2	0.9	0.2–4.1
Medium	53	7	1.3	0.6–3.2	0	-	-
High	25	6	1.5	0.6–3.8	5	6.2	2.0–19.7

[a]ORs adjusted for age and study.
[b]ORs adjusted for age, study, cumulative exposure to wood dust and leather dust.
OR, odds ratio; CI, confidence interval
Adapted from Luce D, Leclerc A, Begin D, et al. Sinonasal cancer and occupational exposures: a pooled analysis of 12 case–control studies. *Cancer Causes Control*. 2002;13:147–157 with permission.

earlier proportionate mortality studies, and elevations of risk for formaldehyde exposure in five of seven case–control studies of nasopharyngeal cancer. The panel noted that other cohort studies did not report an excess of nasopharyngeal cancer deaths, but the studies had low statistical power to do so. The panel considered it "improbable that all of the positive findings for nasopharyngeal cancer . . . could be explained by bias or unrecognized confounding effects" (7).

The IARC panel concluded that the evidence was "strong, but not sufficient for a causal association between leukemia and occupational exposure to formaldehyde" because, in part, the epidemiologic evidence was consistent, but the panel could not identify clear mechanisms by which formaldehyde could cause leukemia. Excess mortality from leukemia, primarily myeloid leukemia, was observed in six of seven studies of the professional cohorts (1,7). In addition, two of the three major updated industrial cohort studies showed associations between leukemia mortality and formaldehyde peak exposure and average intensity of exposure (71) or with longer duration of exposure and follow-up (49). The British industrial workers cohort study did not find excess mortality from leukemia (50), but that study did not report on peak exposures or the risk of myeloid leukemia specifically.

The IARC panel concluded that the epidemiologic evidence for sinonasal cancer was "limited" in humans. The pooled analysis of 12 case–control studies showed an increased risk of sinonasal cancer (64), but the three major cohort studies of industrial workers showed no excesses of sinonasal cancer. The panel noted that most studies did not distinguish between cancers of the nose or sinus, which may have different associations, and some of the case–control studies could not completely control for potential confounding by wood dust exposure.

Conflicting with the conclusions of the IARC expert panel, several investigators have continued to question whether formaldehyde exposure causes cancer in humans by writing letters to journal editors (11,89), writing editorials or review papers regarding biologic plausibility of the associations (90,91), and doing re-analyses of published studies (10,92). The acknowledgments in these publications indicate that the work was completed by consultants to the Formaldehyde Epidemiology, Toxicology, and Environmental Group; former staff of the Chemical Industry Institute of Toxicology; or investigators with the support of the Formaldehyde Council, Inc., which are organizations affiliated with formaldehyde-producing or using industries. These organizations contribute substantially to the scientific debate concerning the carcinogenicity of formaldehyde.

Cancer Mechanisms

Possible mechanisms for formaldehyde carcinogenicity have been discussed (24,93). The current understanding is that formaldehyde is a direct-acting, genotoxic carcinogen that exhibits sublinear dose-responses for DNA reactivity, enhancement of cell proliferation, and carcinogenicity (24). Formaldehyde can cause DNA-protein crosslinks, DNA-DNA crosslinks, point mutations, and single- and double-strand DNA breaks, which result in cytogenetic damage (32). The primary genotoxic effect seems to be the formation of DPC, although it is not clear whether formaldehyde-induced DPC are directly involved in the formation of mutations and what kind of mutations might be responsible for formaldehyde-induced carcinogenesis (93). Conversion of the initial DNA damage into chromosome aberrations and micronuclei appears to be facilitated by increases in cell proliferation and inhibition of DNA repair (24,70,94). The sublinear—J-shaped or hockey stick-shaped—dose-response relationship presumably derives from the endogenous protective mechanisms in the nasal passages (24,95).

A focus of research on DNA reactivity has been on the ability of formaldehyde to form and repair DPC (24,96,97). DPCs induced by formaldehyde exposure were measured in the nasal mucosa of the upper respiratory tract of exposed animals. The formation of DPC was a sublinear function of formaldehyde concentration in inhaled air (98). The repair of DPC is not completely understood. Studies have found that both spontaneous loss and active repair processes contribute to the rate of disappearance of DPC (96). Quievryn and Zhitkovich (96) reported that DPC removal involves a repair pathway that appears to act through the proteolytic degradation of crosslinked proteins. Speit et al. (99) suggest that more than one repair pathway can be involved in the repair of crosslinks and that disturbed excision repair has more impact on the formation of chromosomal aberrations after formaldehyde treatment than does disturbed crosslink repair.

Although DPCs are considered to play a major role in formaldehyde carcinogenesis, other mechanisms may also be involved, as suggested by reports that formaldehyde exposure potentiated the tumor rate when administered in combination with known carcinogens such as *N*-nitrosodimethylamine (1,100).

Cell proliferation appears to play an important role in formaldehyde carcinogenesis (6). Tyihák et al. (101) demonstrated that low doses of formaldehyde (0.1 millimole) inhibited apoptotic and enhanced proliferative activity in both colon carcinoma and human endothelial cultured cell lines, while higher doses inhibited cell proliferation. Monticello et al. (102,103) studied the correlation of cell proliferation indices with sites of formaldehyde-induced squamous cell carcinoma in rats. They found a good spatial correlation between a cell population-weighted index of cell proliferation and regional tumor incidence. The dose-response curve for cell proliferation also correlated well with nasal epithelial

lesions and other biologic effects, such as inhibition of mucociliary function (104). The basis for disturbances in cell proliferation has not yet been determined but may involve direct reaction of formaldehyde with DNA or other macromolecules, growth factors, mutations in growth regulatory genes, or an imbalance between cell proliferation and cell loss (102).

REGULATIONS

In the United States, occupational exposure to formaldehyde is regulated under an OSHA standard that specifies exposure limits and monitoring, respiratory and hygiene protection, medical surveillance, medical removal, and worker training (12,16). The permissible sexposure limit is 0.75 ppm as an 8-hour time-weighted average (TWA), the action level is 0.5 ppm as an 8-hour TWA, and the short-term exposure limit is 2 ppm over 15 minutes.

Medical surveillance is mandated for all workers exposed at or above the action level or short-term exposure limit, as well as for workers who experience symptoms or signs consistent with formaldehyde overexposure. The examinations should be performed prior to exposure, annually in those who will use respirators, and at the discretion of the physician. The examination must include a questionnaire about occupational exposures, smoking, and medical history, focusing on evidence of eye, nose, or throat irritation; upper or lower respiratory problems; chronic airways problems or hyperreactive airway disease; or allergic skin conditions or dermatitis. Medical examinations are given if the physician feels the worker may be at increased risk from formaldehyde exposure and annually to those who use respirators. Workers who use respirators should have baseline and annual pulmonary function tests. The surveillance provisions of this regulation may be used as a guideline for the clinical evaluation of any person with potential formaldehyde exposure.

The U.S. Environmental Protection Agency (EPA) has declared formaldehyde a hazardous air pollutant, water pollutant, waste constituent, and inert ingredient of pesticide products. The EPA regulates formaldehyde under the Clean Air Act; Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA); Food, Drug, and Cosmetic Act; Resource Conservation and Recovery Act; Superfund Amendments and Reauthorization Act (SARA); and Toxic Substances Control Act (TSCA). Under the Clean Water Act, the EPA established a reportable quantity of 1,000 pounds; under CERCLA, the EPA lowered the reportable quantity to 100 pounds. The EPA also requires that safety and health studies be submitted by manufacturers in relation to exposure to urea-formaldehyde resins. Formaldehyde is regulated as an indirect food additive under TSCA. Under SARA, the EPA established general threshold amounts and a threshold planning quantity. The EPA formaldehyde carcinogen risk estimates are currently being revised.

Under the authority of the Federal Hazardous Substances Act, the Consumer Products Safety Commission (CPSC) requires household products containing 1% or more of formaldehyde to be labeled with a warning that formaldehyde is a strong sensitizer. After studying the bioavailability and dermal penetration of formaldehyde from textiles, the CPSC did not find that formaldehyde from this source penetrated intact skin; consequently, no action based on carcinogenic risk was taken regarding the use of formaldehyde in the textile industry. The Housing and Urban Development established a federal regulation (24 CFR 2380.309) that requires manufactured homes to have a prominent temporary health display notice concerning the irritant and upper respiratory effects of formaldehyde, although the notice does not mention a possible risk of cancer.

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