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FORMALDEHYDE

Marian C. Marbury, Sc.D.
Robert A. Krieger, Ph.D.

Few indoor air pollutants have provoked more public, regulatory, or scientific controversy in the past ten years than formaldehyde (Graham, Green, and Roberts 1988). In the late 1970s, numerous reports described the adverse health effects in residents of homes insulated with urea-formaldehyde foam insulation (UFFI). By 1979, two state agencies in Massachusetts had received more than 350 complaints of adverse health effects (Walker et al. 1987). These reports generated intense public concern and spurred awareness of the ubiquity of formaldehyde in consumer products and residences. This concern was fueled by a report in 1979 from the Chemical Industry Institute of Toxicology (CIIT) that formaldehyde exposure caused nasal cancer in rats (Kerns, Donofrio, and Pavkov 1983).

The regulatory response to the evidence of adverse effects of formaldehyde has varied in speed and intensity. Massachusetts banned further installation of UFFI as early as 1979 (Walker et al. 1987). The Consumer Products Safety Commission followed suit, issuing a ban on UFFI in 1982 (Ashford, Ryan, and Caldant 1983). Other federal agencies were slower to act. The U.S. Environmental Protection Agency (EPA) did not take definitive action until April 1987, when it officially classified formaldehyde as a probable human carcinogen and performed an assessment of the health risks of formaldehyde to garment workers and home residents (U.S. EPA 1987). In a similarly slow response, the Occupational Safety and Health Administration (OSHA) initially declined to change the workplace standard of 3 parts per million (ppm) in effect in 1980. This standard was not revised until 1988, when, under threat of a contempt of court citation from the U.S. Court of Appeals, OSHA issued a new standard of 1 ppm with a short-term exposure limit of 2 ppm.

The public controversy over formaldehyde has been mirrored by scientific controversy. Numerous toxicologic, clinical, and epidemiologic investigations

have been conducted over the past ten years and their results extensively reviewed and debated (National Research Council [NRC] 1981; Hart, Terturro, and Neimeth 1984; Nelson et al. 1986; U.S. EPA 1987; Council on Scientific Affairs 1989). Scientific consensus has not been reached on the human carcinogenicity of low-level exposure to formaldehyde or on the ability of formaldehyde to induce respiratory sensitization (Hart, Terturro, and Neimeth 1984). Nonetheless, with the virtual freeze in installation of UFFI and the development of product standards regulating the amount of formaldehyde that can be emitted by consumer products, much of the public concern about formaldehyde seems to have abated (Mage and Gammage 1985).

This chapter provides an overview of what is known about formaldehyde, indicates where the controversies lie, and discusses some of the important studies in more detail. Of necessity, literature citation has been selective rather than comprehensive. Every effort has been made, however, to provide a balanced view of the issues.

EXPOSURE TO FORMALDEHYDE

Formaldehyde, the simplest chemical in the aldehyde family, is a one-carbon compound with the formula HCHO. Existing in both gaseous and liquid states, it readily polymerizes at normal room temperatures. Gaseous formaldehyde is colorless with a characteristic pungent odor. Formalin, which contains about 37 percent (by weight) dissolved formaldehyde in water, is a clear colorless liquid. It usually contains 6–15 percent methanol to prevent polymerization (U.S. EPA 1987).

Formaldehyde has been in widespread industrial use since World War II, with annual production increasing from one billion to more than five billion pounds during this period (Mage and Gammage 1985). Numerous sources of formaldehyde are present in the indoor environment. Formaldehyde is most commonly found in the form of urea- and phenol-formaldehyde resins. Urea-formaldehyde (UF) resins are used to treat many consumer products; facial tissues, paper towels, grocery bags, and other paper products are treated with these resins to increase their wet strength. UF resins are also used as stiffeners, water repellants, and wrinkle resisters, and thus formaldehyde may be emitted from permanent-press clothing, carpet backings, floor coverings, and adhesive binders. Formaldehyde is also emitted by gas stoves, is present in tobacco smoke, and is a constituent of numerous other consumer products, such as cosmetics and detergents (Mage and Gammage 1985).

Formaldehyde is also used in building materials and as a component of UFFI. Formaldehyde resins exhibit good bonding properties, and thus UF resins, in particular, have been used as a glue for plywood, which is made by gluing thin sheets of wood together; they are also used as a component of particleboard, which is manufactured by cooking small particles of wood with the resin and then pressing the particles into sheets. Both plywood and particleboard are used extensively in the manufacture of new furniture and cabinets and are also important building materials in mobile homes.

UFFI, a major source of residential formaldehyde exposure in the past, was used widely in the 1970s because it provided one of the few methods for insulating existing homes effectively. To make UFFI, partially polymerized UF resin was mixed with a foaming agent and an acid catalyst under pressure. The foam was then injected into wall cavities through small holes. After installation, formaldehyde was normally emitted for a few days as the foam hardened (or cured). However, if UFFI was not properly formulated or mixed—for example, if too much formaldehyde was used in the resin-concentrate solution—then the release of formaldehyde could be sustained over a longer period of time. The adverse publicity about UFFI and a large number of lawsuits against insulators have virtually ended the use of UFFI as an insulation material.

As would be anticipated from the sources of formaldehyde described previously, the highest indoor concentrations of formaldehyde have been found in homes insulated with UFFI; in new homes with new furnishings, particularly homes that are tightly sealed; and in manufactured and mobile homes, which combine extensive use of plywood, a high surface area to air ratio, and a low ventilation rate. Within these and other types of structures, however, formaldehyde concentrations vary extensively. In a particular dwelling, determinants of the formaldehyde concentration are the age of the residence, the specific formaldehyde sources, and the ambient temperature and humidity. Formaldehyde emissions result from the release of unreacted formaldehyde in formaldehyde-containing resins and the decomposition of the resins. The first half-life of formaldehyde in mobile homes and new homes with particleboard and plywood is generally four to five years; the half-life in homes with UFFI is one year (Hart, Terturro, and Neimeth 1984). High heat and humidity also contribute to formaldehyde release, and as a consequence, the highest indoor formaldehyde concentrations occur in the summer.

Numerous potential sources of formaldehyde also exist in office buildings and include insulation, new furniture and furnishings, carpets, carbonless copy paper, and tobacco smoke. Measurements of formaldehyde concentrations have not been performed systematically in office buildings but have been taken to evaluate building-related illness. Breysse (1985) reported that concentrations ranged from 0.01 to 0.30 ppm in twenty health hazard evaluations conducted in problem buildings. Although formaldehyde has been implicated as the causative agent in 4 percent of episodes of building-related illness investigated by the National Institute of Occupational Safety and Health (Melius et al. 1984), the true contribution of formaldehyde to the problem of building-related illness is not known.

Surveys of residential formaldehyde concentrations have been conducted in the past ten years by federal, state, and university investigators (Table 10.1). The results of these surveys cannot be readily compared because of differences in methods of selecting the study population (random sample versus volunteers) and

Table 10.1 Surveys of Formaldehyde in Residential Settings

Study Design	Number and Type of Dwellings	HCHO Results (ppm) Mean (Median)	Range
Investigated by Minnesota Department of Health at resident physician's request (Ritchie and Lehnen 1985)	397 mobile homes	0.4	0.02–3.69
	489 conventional homes (34% w/UFFI; no difference)	0.14	0.01–5.62
Convenience sample of Houston, Tex. homes (Stock and Mendez 1985)	78 residences: conventional and energy-efficient homes, apartments, condos	0.07	0.008–0.29
65 volunteers from random sample of 208 Wisconsin homes (Hanrahan 1984)	65 mobile homes	0.16	<0.10–0.80
Investigated by Wisconsin Division of Health at resident request (Dally et al. 1981)	65 mobile homes	0.35	<0.10–3.68
	14 UFFI homes	0.10	0.10–0.28
	13 UF wood products	0.10	0.10–0.92
Random sample of California homes (Sexton, Liu, and Petreas 1986)	663 mobile homes, summer	0.072	<0.10–0.46
	523 mobile homes, winter	0.078	0.17–0.31

in the measurement techniques. (Proper sampling technique is another entire issue; see, for example, Godish [1985].) The EPA has recently summarized the results of studies conducted since 1982 on random population samples. This review showed that the average concentrations of formaldehyde in mobile homes range between 0.2 and 0.5 ppm, and in conventional homes between 0.03 and 0.09. Higher levels may be found in conventional homes with plywood paneling or with new furnishings (U.S. EPA 1987).

TOXICOLOGY

Formaldehyde can enter the body through inhalation, ingestion, and dermal absorption. Data from animal studies suggest that the absorption rate from inhalation exposures is high. Because of formaldehyde's water solubility, more than 95 percent is retained in the upper respiratory tract of dogs (Egle 1972) and 98 percent in the nasal passages of rats (Dallas et al. 1985). Oral absorption in animals also occurs rapidly and efficiently (Malorny, Rietbrock, and Scheider 1965). In contrast, dermal absorption appears to be an inefficient exposure pathway. Depending on the animal species and the test conditions, dermal absorption ranges from 6 to 10 percent in experiments (Robbins et al. 1984).

Once absorbed, formaldehyde either oxidizes rapidly to formate and carbon dioxide (CO_2) or combines with tissue constituents. The major oxidative process is dependent upon the enzyme formaldehyde dehydrogenase, which oxidizes formaldehyde-glutathione adduct with NAD^+ to form NADH and *S*-formylglutathione. Hydrolase then reacts further with *S*-formylglutathione to produce formate and glutathione (Strittmatter and Ball 1955; Ulsamer et al. 1984). Formaldehyde is also oxidized by either a nonspecific dehydrogenase, a catalase, or other less important pathways (Palese and Tephley 1975). Formaldehyde is metabolized quite rapidly. Studies in primates demonstrate a half-life of formaldehyde in plasma of 1.5 minutes following infusion. Experimental studies of humans have also indicated that formaldehyde blood concentrations do not increase following inhalation of 2 ppm for forty minutes (Heck et al. 1985). Because formaldehyde is principally absorbed in the respiratory tract and metabolism of absorbed formaldehyde is rapid, several expert panels have concluded that the respiratory tract is the primary target following inhalation of formaldehyde and that formaldehyde itself is unlikely to cause adverse effects at sites that are distant from exposure (Hart, Terturro, and Neimeth 1984; U.S. EPA 1987).

In addition to being oxidized, absorbed formaldehyde can also bind electrophilically with macromolecules, including proteins, DNA, and RNA. This binding may result in formation of reversible adducts or irreversible cross-links with the macromolecules. *In vitro* studies of the effect of formaldehyde on human bronchial cells have demonstrated that formaldehyde can also induce single-strand breaks in DNA and inhibit the repair of breaks induced by ionizing radiation (Grafstrom et al. 1983).

The specific mechanisms by which formaldehyde exerts its toxic effects have not yet been identified. At the cellular level, the toxic effects of formaldehyde may be due to the action of monomethylol-amino acid intermediates formed by reactions with amino acids. These intermediates are known to have toxic effects and can cause DNA strand breaks (Poverenny et al. 1975). The sensory irritation caused by formaldehyde is thought to result from stimulation of the afferent trigeminal nerve, which induces a burning sensation and other reflexive responses (Barrow, Steinhagen, and Chang 1983). Formaldehyde also damages the mucociliary clearance system and the epithelial cell layer of the respiratory tract (Starr et al. 1984). The cytotoxic effect of formaldehyde exposure produces abnormal cell replication (metaplasia and hyperplasia) in the upper respiratory tract of some test animals. In *in vitro* experiments, formaldehyde causes genetic damage in a wide variety of test systems, including gene mutations, sister chromatid exchanges (SCE), and chromosome aberrations, as well as the single-strand breaks in DNA and DNA-protein cross-links mentioned previously (Hart, Terturro, and Neimeth 1984).

In 1979, the CIIT reported that rats exposed to formaldehyde developed nasal cancer, a tumor rarely found in control animals. In this bioassay, Kerns and coworkers (1983) exposed groups of 240 mice and 240 rats to four different concentrations of formaldehyde gas for six hours a day, five days a week, for two years. Squamous cell carcinomas developed in the nasal cavities of two mice and 103 rats exposed to 14.3 ppm and of two rats exposed to 5.6 ppm. Small numbers

of polypoid adenomas, which are benign tumors, were also observed at each dose level. These results have been confirmed in subsequent studies (Albert et al. 1982; Tobe et al. 1985).

Data regarding the effect of formaldehyde on the reproductive system have been much less consistent. The consensus panel, an expert panel gathered by the federal government to review all the available data on formaldehyde, noted that animal studies had not shown a teratogenic response to formaldehyde (Hart, Terturro, and Neimeth 1984). One study in which mice were intubated demonstrated no treatment-related difference in malformations, even at doses sufficiently high to kill 50 percent of the dams. In another study, pregnant beagles were fed hexamethylenetetramine, a substance that is metabolized to formaldehyde; again, no malformations were found. Studies of germ cell effects in animals have not provided consistent data. Other studies have demonstrated effects, such as embryo resorption, that are difficult to relate to humans (Overman 1985).

HUMAN HEALTH EFFECTS OF FORMALDEHYDE

Numerous adverse health consequences have been ascribed to formaldehyde, ranging from well-documented effects such as eye and nose irritation, to more controversial claims including menstrual irregularity, chronic respiratory disease, and neuropsychological deficit. The evidence for these effects is variable in quality and consistency. Although no biologic mechanism is currently known by which formaldehyde might exert an effect at sites distant to the point of absorption (Hart, Terturro, and Neimeth 1984), a toxic metabolite of formaldehyde could be responsible. Data on human health effects derive largely from surveys of residents of mobile homes or homes insulated with UFFI (Table 10.2) and from epidemiologic and clinical investigations of occupationally exposed workers.

CARCINOGENICITY

Although the evidence regarding the carcinogenicity of formaldehyde in rodents is unequivocal, the extrapolation of these results to humans has been controversial (Starr and Gibson 1985; Nelson et al. 1986; Bolt 1987). Unfortunately, human epidemiologic studies do not fully resolve this controversy.

Numerous studies of formaldehyde-exposed populations to assess carcinogenicity have now been performed. With the exception of a single study of mobile home residents, these investigations have focused on formaldehyde-exposed professional and occupational groups, and cancer of the respiratory tract has been the health outcome of primary concern.

Cohort studies, in which the mortality pattern of a group of formaldehyde-exposed workers is monitored over time, have not shown an excess of nasal cancer (Table 10.3). Since the baseline incidence of this cancer is quite low in human populations, however, these studies have been too small to detect anything less than a tenfold increase. Even the largest of the studies had only an 80 percent chance, as calculated by the authors, of detecting a fourfold increase (Blair et al.

Table 10.2 Surveys of Occupants Living or Working in Mobile Homes or Homes with UFFI

Study Population	Findings[a] Symptom	%	Comments
424 adults and 99 children living in 334 mobile homes; complaint investigations, Washington State (Breysse 1980)	Eye irritation Throat irritation Chronic headache Chronic cough Memory lapse/drowsiness	58A, 41C 66A, 62C 40A, 16C 9A, 33C 24A, 7C	Formaldehyde levels, 0.03–1.77 ppm; no control group; exposure response not examined
256 adults and children living in 65 mobile homes or 35 other structures; complaint investigations, Wisconsin (Dally et al. 1981)	Eye irritation Throat irritation Headache Cough Difficulty sleeping Wheezing	68 57 53 51 38 20	Formaldehyde levels, 0.0–3.68 ppm; no control group; exposure response not examined
162 residents of 68 homes with UFFI; complaint investigations, Connecticut (Sardinas et al. 1979)	Eye irritation Nose/throat/lung irritation Headache No apparent relationship between symptoms and crude formaldehyde level	39 48 17	Formaldehyde levels, 0.0–10 μg/liter with detectable and nondetectable levels
Unknown number of residents in 443 families living in mobile homes; complaint investigations, Texas (Norsted, Kozinetz, and Annegers 1985)	No difference in symptom prevalence in families living in homes with and without detectable levels		Formaldehyde levels, 0.0–8 ppm; comparison of homes with detectable and nondetectable levels
1,396 residents of UFFI homes and 1,395 residents of non-UFFI homes; retrospective cohort, New Jersey (Thun, Lakat, and Altman 1982)	Exposed more likely to report wheezing than nonexposed Wheezing Exposed Nonexposed Burning skin Exposed Nonexposed Subgroup, in whose homes odor persisted >7 days after foam installed, had higher symptom incidence	 0.6 0.1 0.7 0.1	Population-based study; formaldehyde concentrations not measured
70 exposed employees of 7 mobile home care centers and 34 nonexposed employees of 3 permanent structures, Denmark (Olsen and Dossing 1982)	Exposed reported significantly more symptoms than nonexposed Menstrual irregularities Exposed Nonexposed Excessive thirst Exposed Nonexposed Eye irritation Exposed Nonexposed Headache Exposed Nonexposed	 35 0 60 5 55 15 80 50	Formaldehyde levels in mobile day care centers, 0.24–0.55 ppm; permanent structures, 0.05–0.11 ppm

(*continued*)

Table 10.3 (*continued*)

Study Population	Findings[a] Symptom	%	Comments
21 exposed workers in mobile home office and 18 nonexposed workers in another office, Illinois (Main and Hogan 1983)	Exposed reported significantly more symptoms		Formaldehyde levels in offices, 0.12–1.6 ppm
	Eye irritation		
	Exposed	81	
	Nonexposed	17	
	Throat irritation		
	Exposed	57	
	Nonexposed	22	
	Fatigue		
	Exposed	81	
	Nonexposed	22	
	Headache		
	Exposed	76	
	Nonexposed	11	
	No difference in pulmonary function		

[a]A, adults; C, children.

1986). In addition, any elevated risk would not have been detected if the period between exposure and development of nasal cancer, the latent period, exceeded the follow-up interval in these studies.

Case-control studies, in which the exposure histories of people with a particular disease are compared with the exposure histories of people without the disease, provide a more sensitive method for investigating the etiology of a rare cancer. Several case-control studies have been conducted to examine the association between formaldehyde exposure and sinonasal cancer, nasopharyngeal cancer, or both. In five of these studies, formaldehyde exposure was not assessed directly; instead, the likelihood of exposure was based on an industrial hygienist's evaluation of the subjects' occupational history. Both Hayes and colleagues (1986) and Olsen et al. (1984) reported a statistically significant association between imputed formaldehyde exposure and sinonasal cancer. Nasopharyngeal cancer was not considered in the former study and was not found to be associated with formaldehyde exposure in the latter. The findings of an association between formaldehyde exposure and sinonasal cancer were not confirmed in studies by Hernberg et al. (1983), Vaughan and colleagues (1986a), or Roush and co-workers (1987), although the latter two studies did find nonsignificant associations between formaldehyde exposure and nasopharyngeal cancer after a latency period of at least twenty years. In another case-control study of sinonasal cancer, Brinton and colleagues (1985) reported an association between nasal cancer and previous employment in textile manufacturing, an industry in which the use of formaldehyde is widespread. In the study by Brinton and co-workers, formaldehyde exposure was directly asked about, however, and cases reported a history of exposure less frequently than controls.

Table 10.3 Studies of Formaldehyde-Exposed Cohorts and Cancer

Study	Findings	Comments
Cohort study of pathologists, Great Britain (Harrington and Shannon 1975)	SMR elevated for lymphoma and hematopoietic neoplasms (211) but not for leukemia	Less than 10% of cohort deceased; less than 20 years of follow-up
Proportional mortality study of embalmers, New York (Walrath and Fraumeni 1983)	PMR[a] significantly elevated for cancers of skin (221) and colon (143); nonsignificantly for cancers of brain (156) and kidney (150), and leukemia (140)	Limitations of PMR methodology
Proportional mortality study of embalmers, California (Walrath and Fraumeni 1983)	PMR significantly elevated for cancers of colon (188), brain (191), and prostate (176), and leukemia (174); nonsignificantly for bladder cancer (138)	Limitations of PMR methodology
Cohort study of pathologists, Great Britain (Harrington and Oakes 1984)	SMR significantly elevated for brain cancer (300) but not lymphoma	Less than 5% of cohort deceased; 6 years of follow-up
Cohort study of anatomists, U.S. (Stroup, Blair, and Erickson 1986)	SMR elevated for brain cancer (271, 95% CI[b] = 130–499) and leukemia (148, 95% CI = 71–272)	Excess brain cancer persisted when psychiatrists used as a reference group
Cohort study of undertakers, Canada (Levine, Andjelkovich, and Shaw 1984; Levine et al. 1984)	SMR nonsignificantly elevated for brain cancer (115) and leukemia (160)	20 years of follow-up
Proportional mortality study of chemical plant employees, Massachusetts (Marsh 1982)	PMR nonsignificantly elevated for cancers of digestive organs (152) among formaldehyde-exposed workers; no data reported on brain cancer and leukemia	No evidence of trend of mortality in relation to exposure
Cohort study of chemical plant employees, United States (Marsh 1983)	SMR significantly elevated for cancers of genitourinary tract (169); SMR for leukemia not elevated; no data for brain cancer	Case-control study within cohort showed no association between genitourinary cancer and a general plant exposure
Cohort study of chemical plant employees, Great Britain (Acheson et al. 1984)	SMR for lung cancer significantly elevated (124) in one of six plants with highest levels	Retrospective assessment made of level of exposure
Cohort study of industrial workers with formaldehyde exposure, U.S. (Blair et al. 1986)	SMR significantly elevated for nasopharyngeal cancer (318); SMR nonsignificantly elevated for lung cancer (111) and Hodgkin's disease (142); lung cancer significantly elevated in men with 20+ years latency (132)	Largest study reported to date; retrospective assessment of exposure level

(*continued*)

Table 10.3 (*continued*)

Study	Findings	Comments
Cohort study of garment workers, U.S. (Brinton, Blot, and Fraumeni 1985)	SMR significantly elevated for buccal cavity (343) and connective tissue cancer (364)	Retrospective assessment of exposure level
Cohort study of workers in a resin manufacturing plant (Bertazzi et al. 1986)	SMR for lung cancer significantly elevated (236)	Incomplete ascertainment of exposure history makes interpretation difficult

[illegible] mortality ratio.
[illegible]Confidence interval.

Although the studies described above considered only occupational sources of formaldehyde exposure, Vaughn and co-workers (1986b) also inquired about residential exposure to formaldehyde, including whether subjects had ever lived in a mobile home. Associations were not found between residence in a mobile home and cancer of the oropharynx or hypopharynx, or cancer of the sinus and nasal cavity. However, an increased risk of nasopharyngeal cancer was associated with living in a mobile home. Residence in a mobile home for one to nine years was associated with a relative risk of 2.1 (95 percent confidence interval = 0.7, 6.6), increasing to 5.5 (95 percent confidence interval = 1.6, 19.4) for residence exceeding nine years. Although these results were based on only eight exposed cases of nasopharyngeal cancer, the association persisted after control for effects of other factors, including cigarette smoking, alcohol consumption, and race.

Although an increase of nasal cancer has not been demonstrated in cohort studies of formaldehyde-exposed populations, two recent studies provide evidence of a possible relationship between formaldehyde and buccal-pharyngeal cancer. Unlike rats, humans are not obligate nose breathers, and consequently the buccal cavity is a biologically plausible site for formaldehyde-induced cancer. Blair and co-workers (1986, 1987) studied more than 26,000 workers employed in ten different plants in which formaldehyde was either used or produced. Initially, they reported a statistically significant excess of nasopharyngeal cancers with a standardized mortality ratio (SMR) of 318 (an SMR of 318 indicates that the mortality rate of nasopharyngeal cancer was 3.18 times higher in the formaldehyde-exposed group than in a nonexposed comparison group) and a nonsignificant excess of oropharyngeal cancer (SMR = 192). Further analysis (Blair et al. 1987) demonstrated that among workers who were simultaneously exposed to particulates, the SMR increased from 192 in the low-exposure category to 403 in the middle- and 746 in the high-exposure category. A similar trend was not present in workers who were not exposed to particulates or in cases of oropharyngeal cancer. However, four of the seven cases of nasopharyngeal cancer were among workers from one plant, a pattern suggesting that the exposure environment may have been unique in that plant.

Stayner and co-workers (1988) reported an increased risk of buccal cavity cancer (SMR = 343) but not pharyngeal cancer among a cohort of formaldehyde-exposed garment workers. The risk was highest among workers with a long duration of employment and follow-up. Although a significant excess of cancer of the tonsils was also reported, the small number of deaths restricted the ability to examine exposure trends.

The occurrence of lung cancer has also been examined in the formaldehyde-exposed cohorts, and an excess of lung cancer has been found in three. Acheson and co-workers (1984) studied seven thousand men employed in six different chemical and plastics factories. They found a 24 percent increase in lung cancer in one of the factories when national mortality rates were used as the standard of comparison. The investigators discounted the significance of these results because the elevation was confined to one of the factories and was not significant when local rates were used for comparison. However, the local rates were for the period 1968–78 whereas the study period included earlier years, when rates were lower. Consequently, use of these local rates might have overestimated the number of expected deaths. In addition, the lung cancer risk was greatest among men who started employment between 1935 and 1946, when exposures were highest, and the risk was elevated only among men in the high-exposure category.

Blair and colleagues (1986), in their study of formaldehyde-exposed workers, reported a small and not statistically significant excess of lung cancer. There was a statistically significant 32 percent increase among workers with more than twenty years since their first exposure. The investigators minimized the significance of this finding, noting that the excess did not increase either with estimates of intensity or duration of exposure or with cumulative exposure. Bertazzi and co-workers (1986), in a study of 1,332 men employed in a resins manufacturing plant, reported a statistically significant increase in lung cancer (SMR = 236) which persisted with comparison with local rates (SMR = 186). The excess could not definitely be attributed to formaldehyde as the risk was highest in the group whose exposure to formaldehyde was unknown, and the excess risk was not clearly related to either length of employment or latency.

These three studies show an excess risk of lung cancer in formaldehyde-exposed workers, but the evidence is not sufficient to establish a causal relationship between formaldehyde and lung cancer. The lack of a trend in the relationships between increasing exposure and excess risk may be due to misclassification of exposure or to the instability of comparisons based on the stratification of a small number of deaths. Alternatively, other exposures, either at the workplace or from personal habits such as smoking, may be responsible for the excess risk of lung cancer. Studies of formaldehyde-exposed professional groups, such as embalmers (Walrath 1983; Walrath and Fraumeni 1983; Levine, Andjelkovich, and Shaw 1984; Levine et al. 1984), anatomists (Stroup, Blair, and Erickson 1986), and pathologists (Harrington and Shannon 1975; Harrington and Oakes 1984) have not shown an excess of lung cancer.

Cancers of other sites have also been examined. Studies of the aforementioned professional groups, but not of formaldehyde-exposed industrial workers (Marsh

1982; Fayerweather, Pell, and Bender 1983; Acheson et al. 1984; Blair et al. 1986), have demonstrated significant excesses of brain cancer (Walrath 1983; Walrath and Fraumeni 1983; Harrington and Oakes 1984; Stroup, Blair, and Erickson 1986); excess leukemia has also been found in embalmers (Walrath 1983; Walrath and Fraumeni 1983; Levine, Andjelkovich, and Shaw 1984), anatomists (Stroup, Blair, and Erickson 1986), garment workers (Stayner et al. 1988), and one cohort of chemical workers (Bertazzi et al. 1986). Small excesses of Hodgkin's disease (Blair et al. 1986) and prostate (Walrath 1983), skin (Walrath and Fraumeni 1983), kidney (Walrath and Fraumeni 1983), connective tissue (Stayner et al. 1988), and digestive system cancers have been reported from individual studies (Marsh 1982; Walrath 1983; Walrath and Fraumeni 1983; Bertazzi et al. 1986) but have not been confirmed by other studies. As formaldehyde is rapidly metabolized and cleared from the plasma, the hypothesis that it causes cancer at sites distant from the point of absorption would not seem to have strong biologic plausibility (Hart, Terturro, and Neimeth 1984).

CARCINOGENIC RISK ASSESSMENT

Several scientific groups have described the evidence linking formaldehyde exposure to cancer in humans as "limited" (Hart, Terturro, and Neimeth 1984; Nelson et al. 1986; U.S. EPA 1987) and have concluded that the original study of nasal cancer in rats provides the most suitable data for quantitative risk estimation (Hart, Terturro, and Neimeth 1984; U.S. EPA 1987). Risk estimation requires both the selection of a model to extrapolate from observed effects at high doses to the lower doses anticipated from human exposures, and an understanding of the toxic mechanisms by which formaldehyde causes cancer.

The CIIT has argued that use of a simple linear extrapolation model overestimates the carcinogenic risk posed by formaldehyde (Starr and Gibson 1985; Swenberg et al. 1985). Based on an understanding of the toxic mechanisms of formaldehyde and the relationship between the administered dose (exposure) and dose to the target tissue, the CIIT proposes that the carcinogenic effect of formaldehyde demonstrable at high concentrations is unlikely to occur at low concentrations.

Based on experiments conducted at the CIIT, the CIIT asserts that the cell proliferation and hyperplasia following formaldehyde cytotoxicity are essential steps in the carcinogenic process, as formaldehyde binds only to single-stranded DNA. Since DNA in this form is more common during DNA replication with cellular proliferation, formaldehyde has a greater chance of binding to DNA during cell proliferation. It follows that errant DNA synthesis and expansion of initiated cell populations to neoplasia are also related to cell proliferation (Starr and Gibson 1985). Further, cytotoxicity and the resultant cell proliferation are related more closely to intensity of exposure than to duration, which implies that exposure to a high concentration for a short period is more carcinogenic than the same total dose delivered over a longer period of time.

The CIIT has also argued that the relationship between the administered dose and the dose to the target tissue is not linear over a range of concentrations. They contend that several respiratory defense mechanisms, which are overwhelmed by high concentrations, effectively minimize the amount of formaldehyde reaching target tissue at low concentrations. The defense of primary importance is the mucociliary apparatus, specifically the layer of mucus which flows continuously over the nasal epithelium. Formaldehyde readily reacts with the albumin component of mucus. At low concentrations, the binding reaction coupled with mucus clearance effectively prevents formaldehyde from reaching the epithelium. At higher concentrations, mucociliary function is inhibited, and large areas of the mucous blanket are immobilized, effectively removing this defense mechanism (Swenberg et al. 1985).

The CIIT concludes that these findings collectively suggest that the administered dose is a poor measure of delivered dose, which is of greater biologic relevance. The CIIT argues that a better measure of delivered dose is the amount of formaldehyde covalently bound to respiratory mucosal DNA, which also exhibits a nonlinear relationship with the administered dose. The use of bound formaldehyde as the measure of exposure lowers the estimates of risk from formaldehyde exposure by a factor of fifty-three at concentrations of 1 ppm or less, regardless of the specific mathematical dose-response model employed (Swenberg et al. 1985).

The appropriateness of this approach for quantitative risk assessment has been disputed, however, and the EPA chose not to consider it in assessing risks of formaldehyde to garment workers and to the general population (U.S. EPA 1987). The EPA stated that some evidence from mutagenicity studies suggests a linear relationship between formaldehyde exposure and point mutations, chromosome aberrations, and DNA damage. The EPA also asserted that the relationship between cellular proliferation and carcinogenesis had not been demonstrated unequivocally. Furthermore, the agency regarded the data on DNA adducts as an inappropriate basis for use in risk assessment.

As a result, the EPA concluded that the data provided by the CIIT were not sufficiently compelling to warrant deviation from the standard risk assessment procedure, which includes use of the linearized multistage model. Using this model, the EPA estimated that the upper bound estimate for the lifetime excess risk of developing cancer is three per ten thousand for garment workers exposed to formaldehyde concentrations of 0.17 ppm, two per ten thousand for mobile home residents exposed to 0.10 ppm for ten years, and one per ten thousand for residents of conventional homes exposed to 0.07 ppm for ten years. These estimates are upper bounds; the maximum likelihood, or point, estimate is substantially lower, particularly at low concentrations. The EPA stated that the lower bound estimate, as always, could be zero, but they noted the excess cancer incidences reported in various epidemiologic studies were consistent with these upper bound estimates (U.S. EPA 1987).

GENOTOXICITY

As a phenomenon closely related to carcinogenicity, the genotoxicity of formaldehyde has also received attention. Data concerning the *in vivo* genotoxicity of

formaldehyde in human studies are not consistent (Table 10.4) (Hart, Terturro, and Neimeth 1984). Yager and colleagues (1986) measured sister chromatid exchange (SCE) in the peripheral lymphocytes of eight anatomy students, before and after a ten-week anatomy class, during which they were exposed to formaldehyde embalming solution. The investigators reported a statistically significant overall increase in SCE which exceeded 20 percent in three students. Breathing zone samples of formaldehyde taken during the class were 1.2 ppm. Mierauskiene and Lekevicius (1985) found a statistically significant increase in chromosome aberrations (2.8 versus 1.3 percent) in fifty workers exposed to phenol, styrene, and formaldehyde, compared with twenty-five workers without such exposure. Bauchinger and Schmid (1985) studied the lymphocytes of twenty exposed and unexposed male paperworkers. The exposed paperworkers had a significantly elevated prevalence of dicentrics or of dicentrics and ring chromosomes. This excess was concentrated among the eleven most highly exposed workers. Other chromosomal aberrations and SCE values did not differ between the exposed and control groups.

Other studies of genetic effects have not been confirmatory. Fleig and coworkers (1982) found no statistically significant differences in chromosomal aberrations between fifteen workers with twenty-three to thirty-five years of exposure

Table 10.4 Studies of Genotoxicity in Formaldehyde-Exposed Populations

Study Population	End Point(s)	Findings
15 workers engaged in HCHO manufacture and 15 matched controls (Fleig et al. 1982)	Chromosomal aberrations	No difference in number of aberrations between groups
6 pathology workers and 5 nonexposed controls (Thomson, Shackleton, and Harrington 1984)	Chromosomal aberrations, SCE	Exposed group had nonsignificant increase in aberrations, no differences in SCE frequency
11 hospital autopsy service workers and 11 matched controls (Ward et al. 1984)	Sperm count and morphology, fluorescent body frequency	Exposed group had decreased sperm count, more abnormal morphology; differences not significant
50 workers exposed to HCHO, phenol, styrene and 25 nonexposed controls (Mierauskiene and Lekevicius 1985)	Chromosomal aberrations	Exposed had twice the frequency of aberrations, independent of age and smoking
20 papermakers exposed to HCHO and 20 nonexposed workers as controls (Bauchinger and Schmid 1985)	Chromosomal aberrations, SCE	Frequency of dicentrics or dicentrics and ring chromosomes significantly increased for most heavily exposed group
19 HCHO-exposed hospital autopsy service workers and 20 matched controls (Connor, Ward, and Legator 1985)	Urine mutagenicity	No difference in mutagenicity between the two groups
8 students, studied before and after a 10-week anatomy class (Yager et al. 1986)	SCE	Small but significant increase in SCEs after exposure

to formaldehyde manufacture and processing and a matched unexposed control group from the same workplace. Exposures had not exceeded 1 ppm in this workplace for eleven years prior to this study. Thomson and colleagues (1984) studied members of a pathology staff, six recently exposed to formaldehyde at peak concentrations exceeding 6 ppm. In these six, the frequency of chromosomal aberrations was increased, but not significantly in comparison with five nonexposed workers. SCE values did not differ between the two groups. Ward and coworkers (1984) evaluated sperm count, sperm morphology, and fluorescent body frequency in eleven autopsy service workers and eleven nonexposed controls. Formaldehyde concentrations were between 0.61 and 1.32 ppm as a time-weighted average, with peaks up to 5.8 ppm. The mean sperm count of exposed workers was lower (62.9 versus 87.4 $\times$ 10^6/ml), and the percentage of abnormal sperm morphology was higher among nonexposed workers (53.3 versus 44.5 percent), but these differences were not statistically significant. Finally, Connor and colleagues (1985) did not find an increase in the urine mutagenicity of nineteen workers exposed to formaldehyde on an autopsy service when compared with twenty nonexposed workers.

Inconsistency among these results may be due to differences in the outcomes measured, in study techniques, or in study populations. More importantly, because formaldehyde is oxidized so rapidly, neither peripheral lymphocytes nor germ cells should be targets for formaldehyde. The positive studies, therefore, must be confirmed before much weight can be given to them.

IRRITATION OF THE EYES AND UPPER RESPIRATORY TRACT

Formaldehyde is indisputably a mucous membrane irritant that causes discomfort of the eyes, nose, and throat. Symptoms of irritation have been reported by residents of mobile homes and homes insulated with UFFI (Table 10.2), by subjects exposed to formaldehyde in environmental chambers (Sauder et al. 1986; Schachter et al. 1986; Kulle et al. 1987), and by employees exposed in the workplace (Schoenberg and Mitchell 1975; Alexandersson, Hedenstierna, and Kolmodin-Hedman 1982; Alexandersson and Hedenstierna 1989; Horvath et al. 1988). Formaldehyde induces sensory irritation through stimulation of the afferent trigeminal nerve as well as other reflexive responses. Questions remain, however, about the concentrations of formaldehyde necessary to elicit these responses.

Questionnaire surveys of symptoms have been performed on residential populations, usually selected because of health complaints attributed to formaldehyde exposure from UFFI or to offgasing from building materials. These surveys show seemingly high prevalences of both respiratory and nonrespiratory symptoms. However, the investigations of complaints in Washington (Breysse 1980), Wisconsin (Dally et al. 1981), Connecticut (Sardinas et al. 1979), and Texas (Norsted, Kozinetz, and Annegers 1985) cannot be readily interpreted because of methodologic problems. Comparison populations were not evaluated in two studies (Breysse 1980; Dally et al. 1981), bias may have resulted from the selection of complaining subjects, and formaldehyde measurements were obtained only once,

although formaldehyde concentrations vary with ambient heat and humidity. A Canadian study involving comparison of symptoms in two formaldehyde-exposed groups illustrates the potential for reporting bias (Morgan 1984). In this study, subjects from homes insulated with UFFI were compared with pathology laboratory employees, who are presumably exposed to higher concentrations of formaldehyde than were the persons from the UFFI-insulated homes. The prevalences of symptoms related to upper respiratory irritation were similar in the two groups, but vague symptoms characteristic of anxiety, such as headache, loss of libido, anorexia, and malaise, were substantially higher in the subjects from homes with UFFI. The questionnaire surveys of symptom prevalence provide documentation, however, that formaldehyde exposure occurs in the domestic environment and that individual response to exposure is variable.

Thun and colleagues (1982) used a more informative and less biased design in a study of 1,396 residents of homes insulated with UFFI and 1,395 residents of homes without UFFI. Subjects were selected from a roster of homes that had been insulated with UFFI rather than on the basis of symptom status. By telephone interview, the investigators ascertained symptom prevalence over the previous year and the timing of symptom onset in relation to installation of UFFI. The reported incidence of all symptoms was low, and only wheezing and burning skin were significantly more frequent in residents of homes with UFFI. Subjects who reported that odor had persisted for more than seven days after UFFI installation had the highest incidence of symptoms.

To assess the persistence of symptoms among residents of older homes with particleboard, Daugbjerg (1989) sent questionnaires to the parents of three groups of children living in homes that had varying amounts of particleboard: 254 children from homes with large amounts, 144 from homes with small amounts, and 574 from homes free of particleboard. Living in a home with a large amount of particleboard was found to be a risk factor for coughing, eye and nose irritation, and wheezy bronchitis among children zero to five years of age but not among older children. A large amount of particleboard was also a risk factor for headache, throat irritation, and a need for daily asthma medication for all children. Living in a home with a small amount of particleboard was not a risk factor for any respiratory symptoms. Environmental measurements were not obtained.

In the most comprehensive study performed to date of the health effects of UFFI Broder and colleagues (1988a, 1988b, 1988c) studied 1,726 subjects from 571 homes insulated with UFFI and 720 controls from 231 homes not insulated with UFFI at two intervals a year apart. In addition to the administration of health questionnaires, study methods included the measurement of nasal airway resistance, pulmonary function, and sense of smell; patch tests for sensitivity to formaldehyde and to UFFI; and nasal surface cytology. Most of the subjects were reevaluated one year later. At the one-year follow-up, two-thirds of the subjects originally living in homes insulated with UFFI had either removed the UFFI or had taken some other remedial action (Broder et al. 1988c). The average formaldehyde concentration was 0.043 ppm in UFFI houses and 0.035 ppm in control houses; the average age of the UFFI was 4.6 years (Broder et al. 1988b). At the initial survey, subjects from the UFFI homes had more nasal symptoms than controls, but nasal resistance and the distribution of smell threshold were similar in the two groups (Broder et al. 1988b). Throat and eye complaints were also more frequent in the UFFI-exposed subjects, and the subjects from UFFI homes also reported an increased prevalence of skin irritation, cough, sputum, wheeze, headache, dizziness, tiring easily, troubled hearing, increased thirst, nausea, diarrhea, constipation, menstrual trouble, and arthritis. The excess symptom prevalence occurred primarily among those who intended to have the UFFI removed from their homes.

Positive dose-response relationships between formaldehyde concentration and many of these symptoms were found among the subjects from UFFI homes but not among the control subjects. When 135 subjects whose mean formaldehyde concentration exceeded 0.08 ppm were eliminated, the exposure-response relationship persisted only for cough and sputum. The authors interpreted the presence of a dose response only among subjects from UFFI homes as evidence that the excess symptom prevalence was due to a combination of formaldehyde and some unidentified UFFI-associated factor rather than formaldehyde alone.

At follow-up one year later, the prevalence of nasal symptoms dropped in the groups removing the UFFI or taking some other action (Broder et al. 1988c). The prevalence of nasal and other symptoms declined to the level in the UFFI-exposed group who took no action, but a small excess persisted relative to the controls. The reduction of symptom rates was not associated with changes in formaldehyde levels. Overall, the investigators concluded that their study supported a causal relationship between impaired health and living in a house with UFFI, but they considered the demonstrated health effects to be relatively minor and reversible.

These studies demonstrate the difficulty of quantitating the irritative potential of formaldehyde. The EPA concluded that existing population studies did not provide an adequate basis for risk assessment because of their limitations; evidence from clinical studies was also judged insufficient because study subjects were volunteers, and study sizes were small (U.S. EPA 1987). Instead, the EPA affirmed the more qualitative conclusion that 95 percent of people respond to concentrations of 0.1–3.0 ppm and that fewer responses are expected to be associated with lower concentrations.

LOWER RESPIRATORY TRACT EFFECTS

Based on studies of occupationally and domestically exposed populations, formaldehyde has been reported to cause respiratory symptoms, acute and chronic reduction of lung function, and asthma. Questionnaire symptom surveys performed on populations selected because of their complaints about formaldehyde exposure have shown seemingly high prevalences of respiratory and nonrespiratory symptoms. These findings have been interpreted as evidence that formaldehyde might be a lower respiratory tract irritant and also be capable of inducing a

specific sensitization reaction. These potential effects of formaldehyde have been more adequately investigated in clinical and epidemiologic studies of both acute and chronic effects.

Effects of acute formaldehyde exposure on the lung function level of asthmatics and healthy nonsmoking volunteers have been evaluated in chamber studies (Table 10.5). Three studies of asthmatics showed no changes in pulmonary function following exposures of up to 3 ppm formaldehyde, either at rest (Harving et al. 1986) or during moderate exercise (Sheppard, Eschenbacker, and Epstein 1984; Green et al. 1987). Studies of healthy nonsmokers exposed to up to 3 ppm formaldehyde either at rest or during moderate exercise have similarly found no effect of exposure (Schachter et al. 1986; Kulle et al. 1987). Some evidence suggests, however, that exposure during more intense exercise may produce a small and transient bronchoconstriction. Sauder and colleagues (1986) exposed nine volunteers to 3 ppm formaldehyde for three hours during intermittent exercise and found a 2 percent decrease in FEV_1 and a seven percent decrease in FEF_{25-75}. The reductions were no longer apparent at 60 and 180 minutes. These findings were replicated by Green and co-workers (1987), who exposed twenty-two healthy volunteers to 3 ppm formaldehyde for one hour during intermittent heavy exercise. By increasing respiratory rate and depth, heavy exercise may plausibly increase the dose and the deposition of formaldehyde in the lower respiratory tract. Increases in upper respiratory symptoms of irritation were also reported uniformly in these studies.

The acute effects of UFFI offgas on pulmonary function in nonasthmatics has been examined in a clinical study by Day and colleagues (1984). They studied nine residents of UFFI-insulated homes, who attributed their nonrespiratory symptoms to UFFI, and nine subjects who were either asymptomatic or living in homes without UFFI. Lung function, as assessed by spirometry, did not change after exposure either to 1 ppm formaldehyde or to UFFI offgas that contained 1.2 ppm formaldehyde. Although these clinical investigations have evaluated only small numbers of subjects, the findings suggest that in most cases, symptoms of lower respiratory irritation experienced by residents of mobile homes or houses insulated with UFFI are unlikely to result solely from formaldehyde.

Epidemiologic approaches have also been used to examine the relationship between pulmonary function and residential formaldehyde exposure. Norman and co-workers (1986), using data gathered during a previous study in Canada, identified children who had been living in homes insulated with UFFI. Two children from homes with conventional insulation were matched to each exposed child ($n = 29$) on the basis of nine variables that had been shown to predict pulmonary function. No association was found between residence in a home insulated with UFFI and respiratory function or symptoms. Measurements of formaldehyde were not made.

In the study of UFFI exposure reported by Broder et al. (1988a, 1988b, 1988c) differences in ventilatory function between the UFFI-exposed and nonexposed subjects were not present at either the initial or follow-up surveys. Cross-sectional

Table 10.5 Clinical Studies of Acute Formaldehyde Exposure and Pulmonary Function

Study Design and Population	Findings
7 mild asthmatics, exposed to 1 and 3 ppm HCHO at rest and during moderate exercise for 10 min (Sheppard, Eschenbacker, and Epstein 1984)	No increase in specific airways resistance before and after exposure
15 healthy volunteers, exposed to 9 and 2 ppm HCHO at rest and during moderate exercise for 40 min (Schachter et al. 1986)	No changes in $FEV_{1.0}$, FVC, MEF_{50}, MEF_{40}, airway resistance; follow-up of 3 subjects showed no late responses; irritative symptoms increased
9 healthy volunteers, exposed to 3 ppm HCHO for 3 h during intermittent heavy exercise (Sauder et al. 1986)	2% decrease in $FEV_{1.0}$ and 7% decrease in MEF_{25-75} at 30 min, no longer present at 60 and 180 min
15 subjects with bronchial hyperreactivity exposed to 0.85, 0.12, and 0 mg/m³ for 90 min at three different times (Harving et al. 1986)	No changes in $FEV_{1.0}$, airways resistance, or functional residual capacity or symptoms of asthma
22 healthy volunteers, exposed to 0 and 3 ppm HCHO during intermittent heavy exercise; 16 asthmatics exposed at rest and moderate exercise for 1 h (Green et al. 1987)	Healthy volunteers had small but statistically significant decreases in $FEV_{1.0}$, FVC, and $FEV_{3.0}$; asthmatics showed no changes; 13% of study group showed changes >10%
19 healthy volunteers exposed to 0–3 ppm HCHO at rest, 2.0 ppm during exercise (Kulle et al. 1987)	Dose response for irritation symptoms; nasal flow resistance increased at 3.0 ppm; no changes in pulmonary function or bronchial hyperreactivity
9 subjects with previous complaints from UFFI and 9 controls, exposed to 1 ppm HCHO and UFFI offgas for 90 and 30 min, respectively (Day et al. 1984)	No changes in $FEV_{1.0}$, FVC, or MMEF either immediately or 8 h after exposure

studies conducted in occupational settings, where exposures are usually higher and more readily quantified than in the residential setting, also supply information on formaldehyde and lung function. Levine and co-workers (Levine et al. 1984) surveyed ninety embalmers attending a continuing education course and found that levels of spirometric parameters were not reduced in comparison with standard reference populations. The pulmonary function of subjects with higher exposures, as estimated by the number of embalmings performed, was similar to that of subjects with lower exposures. The pulmonary function of fourteen policemen, who worked in mobile trailers with formaldehyde concentrations ranging from 0.12 to 1.6 ppm, was evaluated by Main and Hogan (1983). Decrements in function were not found when the values were compared either with a standard reference population or with a nonexposed control population. Pre- and postexposure pulmonary function were not evaluated in either study.

At least four studies have surveyed the pulmonary function of workers in industrial environments in which formaldehyde exposure was accompanied by exposure to particulates. Each demonstrated transient decreases in pulmonary function as measured by pre- and postshift spirometric evaluation (Schoenberg and Mitchell

1975; Gamble et al. 1976; Alexandersson, Hedenstierna, and Kolmodin-Hedman 1982; Horvath et al. 1988). Only one of these four studies reported lower baseline spirometric values for exposed workers, which the investigators interpreted as providing evidence of a persistent effect of exposure (Schoenberg and Mitchell 1975). Another study did not find changes in pulmonary function across shift among exposed workers but did report that the baseline spirometric values were lower (Alexandersson and Hedenstierna 1988).

The most informative of these investigations was conducted in Wisconsin by Horvath and colleagues (Horvath et al. 1988). These investigators evaluated pre- and postshift pulmonary function of 109 workers employed in a particleboard or molded products operation and of 254 workers employed in two other plants not using formaldehyde. Formaldehyde exposures were estimated for each participant from active and passive monitoring. Formaldehyde concentrations ranged from 0.17 to 2.93 ppm, with a median of 0.62 ppm. Across the work shift, both the FEV_1 and the FEV_1/FVC ratio dropped significantly in the exposed group. A reduction in FEV_1 and FVC of similar magnitude was also found in the control group. The investigators attributed this unexpected finding in both groups to diurnal variation in lung function. The exposed workers also demonstrated statistically significant decreases in FEF_{25-75}, FEF_{50}, and FEF_{75}. These parameters, as well as the FEV/FVC ratio, were positively correlated with measured formaldehyde concentrations. In addition, the investigators reported a significant association between formaldehyde exposure and symptoms of cough, chest complaints, phlegm, burning nose, stuffy nose, itchy nose, sore throat, burning eyes, and itchy eyes.

The investigators attempted to assess the bias that may have resulted from selective withdrawal from the work force of formaldehyde-sensitive individuals. To evaluate this bias, Horvath and co-workers determined the reasons for the departure of fifty-four former employees from the company; only two employees had left for reasons related to respiratory health, both because of exacerbations of preexisting respiratory conditions.

In summary, the available evidence suggests that exposure to formaldehyde at levels up to 3 ppm does not result in permanent pulmonary impairment. In certain working conditions, transient reductions in lung function of uncertain clinical significance have been demonstrated. These deficits have been detected in industrial settings in which formaldehyde exposure occurred along with exposure to particulates. Adsorption of formaldehyde onto particulates may result in deposition of the formaldehyde in the lower respiratory tract rather than absorption onto the mucosa of the upper respiratory tract. Alternatively, physical exertion in an industrial setting may increase minute ventilation and thereby increase both the dose and deposition of formaldehyde in the lower respiratory tract.

Formaldehyde has been shown to cause occupational asthma (Popa et al. 1969; Hendrick and Lane 1977; Hendrick et al. 1982) although the mechanism of effect is uncertain. Formaldehyde might induce asthma through specific immunologic sensitization or exacerbate preexisting asthma by causing bronchoconstriction through nonspecific irritation (Imbus 1985). Medical and nonmedical publications (anonymous *Lancet* editorial 1981; Breysse 1981) have raised concern that residential formaldehyde exposure could also be associated with asthma. These concerns are supported by surveys of formaldehyde-exposed populations that have reported high prevalences of wheezing, chest tightness, and other symptoms compatible with asthma. However, cases of asthma resulting from domestic exposure to formaldehyde have not been published. In a unique documented case of a woman who developed asthma after installation of UFFI, the offending agent was found to be UFFI dust rather than formaldehyde (Frigas, Filley, and Reed 1981).

Several case series provide evidence on the role of formaldehyde as a cause of asthma. In each series, subjects referred to a clinical facility for investigation of suspected formaldehyde-induced asthma were evaluated with bronchial provocation tests. Nordman and colleagues (1985) reported that 12 of 230 workers referred to the Finnish Institute of Occupational Health had a positive bronchial provocation test when exposed to formaldehyde at 2 ppm. In England, Burge and co-workers (Burge et al. 1985) described fifteen workers evaluated for occupational asthma. The authors concluded that three subjects showed specific hypersensitivity to formaldehyde, two were affected through irritant mechanisms, and the remaining ten subjects were probably affected by other agents.

Frigas and co-workers (1984) evaluated thirteen subjects who believed they had developed asthma secondary to formaldehyde exposure in their work or home environments. As none of the subjects responded to formaldehyde challenge, the investigators questioned the importance of formaldehyde as a cause of asthma at levels below 3 ppm, the range generally encountered in the domestic environment. However, because this series comprised only thirteen subjects, firm conclusions on the role of formaldehyde cannot be drawn from its results.

Studies of immunologic function have not helped to resolve whether formaldehyde causes disease through immunologic mechanisms. Although IgE antibody has been produced against other chemicals known to be allergens, specific IgE antibodies to gaseous formaldehyde have not been demonstrated (Hart, Terturro, and Neimeth 1984; Imbus 1985). Two investigative groups have demonstrated the presence of antibodies against formaldehyde-human serum albumin conjugates in some formaldehyde-exposed persons (Patterson et al. 1986; Thrasher et al. 1987). The clinical significance of these antibodies has not been established.

Pross and colleagues (1987) conducted a comprehensive immunologic investigation of twenty-three subjects with asthmalike symptoms attributed to the subjects' living in UFFI-insulated homes and four asthmatics who served as controls, who lived in conventionally insulated homes. The subjects were exposed in an environmental chamber to placebo, dust, formaldehyde, and UFFI offgas at levels usually found in UFFI-insulated homes. A broad range of immunologic parameters was evaluated. At the base line, the data for the UFFI-exposed subjects and the controls were similar. Minor changes were noted in some tests after UFFI exposure; only transient increases in eosinophil and basophil count, a slight increase in the T8 (suppressor) cell population, and a decrease in the NK (natural killer) cell

response to low concentrations of interferon were detected. Although this study provides some evidence that formaldehyde is not a potent immunotoxin, interpretation of the data is limited by the small size of the study and the investigators' failure to characterize the study subjects adequately. It is unclear whether the subjects had documented asthma, and if so, whether their symptoms had any objective relationship to UFFI exposure.

Collectively, these studies suggest that asthma may be attributed mistakenly to formaldehyde exposure and that the incidence of true formaldehyde-induced asthma may be low. Although not widely available, specific bronchial provocation testing with formaldehyde is essential for diagnosis. A careful clinical history is important for raising initial concern about formaldehyde-related asthma but by itself may be misleading.

OTHER EFFECTS

Questionnaire surveys of symptoms in subjects concerned about formaldehyde exposure have suggested that formaldehyde may have an adverse effect on both the central nervous system and the female reproductive system (Table 10.2). More formal studies of these effects have been preliminary in nature, and current understanding of the metabolism of formaldehyde suggests that formaldehyde per se is unlikely to have a significant impact on either system. Consequently, studies of the relationship between formaldehyde exposure and these two organ systems will be discussed only briefly.

Olsen and Dossing (1982) reported that day-care workers in mobile homes, compared with day-care workers in permanent structures, experienced significantly more symptoms of headache and unnatural fatigue, but memory and concentration did not differ in the two groups. Kilburn and co-workers (1985) compared the frequency of neurobehavioral, mucous membrane, and respiratory symptoms among seventy-six histology technicians exposed to formaldehyde and fifty-six secretaries and clerks. The histology technicians were more likely to have experienced disturbances of memory, sleep, balance, mood, concentration, and appetite. Each technician estimated the average number of hours per day of exposure to formaldehyde. The prevalence of most symptoms increased with lengthening exposure. Of forty-four technicians who completed a twenty-item depression scale, four had scores suggesting depression. Limitations in the study design preclude attaching much significance to these results until they have been replicated independently.

In order to measure neuropsychological symptoms objectively, Schencker and co-workers (1982) used standardized neuropsychological tests in a study of twenty-four residents of six homes insulated with UFFI. Nine of twenty-three subjects reported neuropsychological symptoms, including memory difficulty, headaches, difficulty concentrating, and emotional lability. Complaints of memory loss were not validated by formal tests. However, eleven of the fourteen tested subjects demonstrated a deficit in their attention, and nine of those eleven also had elevated depression scores. Although the use of objective tests of neuropsychological function represents an improvement over questionnaire assessment of symptoms alone, the results of this study are nonetheless limited by the lack of a comparison population and the small number of study subjects.

These cross-sectional epidemiologic studies involved small numbers of subjects, and their results are not definitive. Further laboratory investigation is needed to establish biologic mechanisms that may underlie the neuropsychological effects of formaldehyde. Formaldehyde might exert a direct toxic effect on the central nervous system. Alternatively, its odor could make individuals more aware of symptoms and more likely to attribute significance to them (Hart, Terturro, and Neimeth 1984).

Although the data base concerning relationships between formaldehyde exposure and adverse reproductive outcomes is not complete, available evidence suggests that formaldehyde does not pose a teratogenic risk to humans (Hart, Terturro, and Neimeth 1984; U.S. EPA 1987). Only a few studies of the relationship between formaldehyde exposure and reproductive outcomes in humans have been published. As described in the report of the consensus panel (Hart, Terturro, and Neimeth 1984), Shumilina studied female workers who were and were not exposed to UF resins. The author concluded that exposed women had three times the prevalence of menstrual disorders and a higher proportion of babies weighing between 2,500 and 3,000 grams, but the translation of the article did not provide sufficient information for the consensus panel to assess the methodologic adequacy of the study.

An increase in menstrual disorders among women exposed to formaldehyde was noted by Olsen and Dossing (1982) in a prevalence survey of women working in mobile homes. In this study, 35 percent of exposed women reported menstrual irregularities as compared with 0 percent of the control group. Finally, Hemminki and co-workers (1982) did not find an increased rate of spontaneous abortions among hospital staff who sterilized hospital instruments with formaldehyde.

The biologic significance of the reported association between formaldehyde exposure and menstrual irregularity remains to be elucidated. Menstrual irregularity cannot be investigated readily, and little is known about its etiology. At present, biologic mechanisms by which formaldehyde could affect menstrual regularity have not been identified.

SUMMARY

Since formaldehyde was first identified as an animal carcinogen, substantial research effort and money have been expended to investigate the human health consequences of exposure to this pollutant. Much has been learned about sources of formaldehyde in the domestic environment, and control technology has been developed to reduce concentrations from these sources. Significant progress has also been made in understanding acute human responses to formaldehyde exposure.

As for many environmental pollutants, the chronic effects of formaldehyde

exposure have not been readily identified. Epidemiologic studies are unlikely to resolve fully the issue of formaldehyde's human carcinogenicity, and establishing a "safe" dose will depend on further refining our risk assessment models. Progress has been made, however, in elucidating the underlying mechanisms of formaldehyde carcinogenicity and in understanding the relationship between the administered and delivered doses. This progress represents a major step in understanding the toxicology of inhaled pollutants in general.

The most important lesson of formaldehyde is that prudent public health measures need not wait for the full resolution of scientific issues. Complete understanding of the human health effects of this pollutant will probably never be achieved. Nonetheless, exposure to formaldehyde in the residential setting has been mitigated to the extent that the urgency of further research has also diminished.

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