DRAFT
Report on Carcinogens
Substance Profile for

Formaldehyde

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This DRAFT substance profile contains the NTP's preliminary recommendation on the listing status of formaldehyde ~~glass wool fibers~~ in the Report on Carcinogens, summarizes the scientific information that supports the recommendation, and provides information on use, exposure, and production as well as any existing federal regulations.

This draft is distributed solely for the purpose of public comment and predissemination peer review and should not be construed to represent final NTP determination or policy.

Additional information about the NTP Report on Carcinogens review process for candidate substances is available at http://ntp.niehs.nih.gov/go/29353.

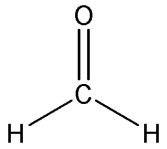
Revised June 22, 2010

Formaldehyde

CAS No. 50-00-0

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Formaldehyde is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans and supporting studies on mechanisms of carcinogenesis.

Cancer Studies in Humans

Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans. Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding.

Numerous epidemiological studies have evaluated the relationship between exposure to formaldehyde and cancer risk, including (1) cohort and nested case-control studies of industrial workers, (2) cohort and nested case-control studies of professional groups such as pathologists, funeral directors, or embalmers, and (3) population-based cohort and case-control studies. The most informative occupation-based studies are the National Cancer Institute (NCI) cohort of over 25,000 men and women who worked at companies that used or produced formaldehyde (Hauptmann *et al.* 2003, 2004, Beane Freeman *et al.* 2009) and the NCI nested case-control study of lymphohematopoietic cancer in embalmers (Hauptmann *et al.* 2009), because these are the only studies that evaluated quantitative exposure-response relationships. Occupational exposure to formaldehyde has also been evaluated in two other large cohort studies: (1) a National Institute for Occupational Safety and Health (NIOSH) cohort study of over 11,000 male and female garment workers, which evaluated risks of cancer at a few selected tissue sites by time since first exposure (latency), exposure duration, and year of first exposure (Pinkerton *et al.* 2004), and (2) a British cohort study of over 14,000 male chemical workers, which evaluated cancer risks by classification of workers as "ever exposed" or "highly exposed" (Coggon *et al.* 2003). In addition, occupational exposure has been evaluated in numerous smaller cohort studies.

For evaluating rare types of cancer, such as nasopharyngeal and sinonasal cancer, the collective body of population- and occupation-based case-control studies is more informative than the cohort studies. Particularly useful are the pooled analyses of 12 case-control studies of sinonasal cancer by Luce *et al.* (2002) and the population-based case-control study by Vaughan *et al*. (2000) evaluating different histological subtypes of nasopharyngeal cancer. In general, meta-analyses and smaller occupational cohort

studies have limited utility for cancer assessment, because they only reported risks for workers "ever exposed" and could not evaluate exposure-response relationships. However, the meta-analysis for lymphohematopoietic cancers by Zhang *et al*. (2009a) is more informative because it used data for individuals with the highest exposure to formaldehyde to calculate the summary relative risks.

Nasopharyngeal Cancer

Nasopharyngeal cancer is a rare cancer, with an annual incidence of less than 1 per 100,000 in most parts of the world. Therefore, case-control studies are most useful for evaluation of nasopharyngeal cancer risk. Histological subtypes of nasopharyngeal cancer include differentiated keratinizing squamous-cell carcinoma, differentiated non-keratinizing carcinoma, and undifferentiated non-keratinizing carcinoma. In southern China and some parts of Southeast Asia and Northern Africa, nasopharyngeal cancer is endemic, with a higher proportion of non-keratinizing and undifferentiated subtypes than in low-risk areas (Vaughan *et al.* 1996, Bray *et al.* 2008). Differentiated keratinizing squamous-cell carcinoma has been associated with chemical exposures, such as alcohol consumption and tobacco smoking, whereas non-keratinizing subtypes are more strongly associated with Epstein-Barr virus and familial history. Studies on nasopharyngeal cancer and formaldehyde exposure have been conducted in the United States, Europe, and Asia.

Evidence that formaldehyde causes nasopharyngeal cancer comes from (1) consistent findings of increased risk among individuals with the highest formaldehyde exposure in numerous case-control studies (Vaughan *et al.* 1986, 2000, Roush *et al.* 1987, West *et al.* 1993, Hildesheim *et al*. 2001), (2) excess cancer mortality associated with formaldehyde exposure in the NCI cohort of industrial workers (Hauptmann *et al.* 2004), and (3) findings of positive exposure-response relationships in a large multi-center case-control study (Vaughan *et al*. 2000) and in the NCI cohort (Hauptmann *et al*. 2004).

The multi-center case-control study by Vaughan *et al.* (2000) is especially informative, because it had the largest number of cancer cases in formaldehyde-exposed individuals, and the analysis was stratified by histological subtype and used several different measures of exposure to evaluate risk. In this study, formaldehyde exposure was associated with differentiated squamous-cell carcinoma and unspecified subtypes of nasopharyngeal cancer, but not with non-keratinizing and undifferentiated subtypes. The risk of nasopharyngeal cancer (differentiated squamous-cell carcinoma and unspecified subtypes) increased significantly with increasing cumulative exposure ($P_{trend} = 0.033$), duration of exposure ($P_{trend} = 0.014$), and probability of exposure (possible, probable, or definite). The odds ratio (OR) was 1.6 (95% confidence interval [CI] = 1.0 to 2.8, 61 exposed cases) for possible, probable, or definite exposure, increasing to 2.1 (95% CI = 1.1 to 4.2, 27 exposed cases) for probable or definite exposure, and 13.3 (95% CI = 2.5 to 70, 10 exposed cases) for definite exposure.

Other studies also found the highest risks of nasopharyngeal cancer for individuals with the highest formaldehyde exposure levels (assessed as cumulative exposure, exposure level, or exposure score) (Vaughan *et al.* 1986, Roush *et al.* 1987) and/or longest exposure durations (Vaughan *et al.* 1986, West *et al*. 1993 [after lagging exposures for 10 years]). Risks were also significantly elevated for individuals with longer latency (West *et al*. 1993) or who died at an older age (Roush *et al.* 1987); risk

was increased fourfold for individuals who died after the age of 68 and were probably exposed to high levels of formaldehyde for at least 20 years before death. The associations between formaldehyde exposure and nasopharyngeal cancer remained after adjustment for or consideration of potential confounding by tobacco smoking (Vaughan *et al.* 1986, 2000, West *et al.* 1993, Hildesheim *et al.* 2001) or by exposure to wood dust (West *et al.* 1993, Vaughan *et al*. 2000, Hildesheim *et al.* 2001). Not all of the estimates of increased risk were statistically significant, and some studies (Armstrong *et al.* 2000, Li *et al*. 2006, Hauptmann *et al.* 2009) did not find an association between formaldehyde exposure and nasopharyngeal cancer. However, most of these studies were limited by small numbers of individuals exposed to formaldehyde. The overall consistency of the findings argues against their being attributable to chance.

Excess mortality from nasopharyngeal cancer was found in the NCI cohort of industrial workers exposed to formaldehyde (standardized mortality ratio [SMR] = 2.10, 95% CI = 1.05 to 4.21). Relative risk increased with increasing cumulative exposure (P_{trend} = 0.025 across exposed subjects), peak exposure (P_{trend} < 0.001), and average exposure (P_{trend} = 0.066) (Hauptmann *et al*. 2004). Of the 7 exposed workers who died of nasopharyngeal cancer, all were in the highest peak-exposure category, and 6 were in the highest average-exposure category. Controlling for co-exposure to 11 potential occupational carcinogens and for plant did not alter the exposure-response relationships for nasopharyngeal cancer. Although the cohort included workers in 10 plants, most of the cases of nasopharyngeal cancer occurred in workers in the plant with the largest numbers of workers in the highest formaldehyde exposure category; 46% of workers at Plant 1 were in the highest peak-exposure category compared with 20.1% of worker in all other plants (Stewart *et al.* 1990, Marsh and Youk 2005). A nested case-control study of nasopharyngeal cancer among workers in Plant 1 found a statistically significant high risk for ever working in silver smithing jobs prior to or after employment at Plant 1; however, silver smithing was not correlated with formaldehyde exposure levels at this plant, and thus was not a confounder for formaldehyde exposure (Marsh *et al.* 2007).

No excesses of nasopharyngeal cancer mortality were found in the other large cohort studies (Coggon *et al.* 2003, Pinkerton *et al.* 2004); the statistical power of these studies was inadequate to evaluate the risks of rare cancers. For example, the power to detect a twofold or greater increase in mortality from nasopharyngeal cancer in the NIOSH cohort was 13%.

Sinonasal Cancer

Sinonasal cancer is a rare cancer, with an annual incidence of about 1 per 100,000, and case-control studies therefore are most useful to evaluate risk. Sinonasal cancer includes cancers of the paranasal sinus and the nasal cavity; the two major histological types are adenocarcinoma and squamous-cell carcinoma.

The evidence that formaldehyde exposure causes sinonasal cancer comes from consistent findings of increased risk in population-based case-control studies (Olsen *et al.* 1984, Olsen and Asnaes 1986, Hayes *et al.* 1986, Roush *et al.* 1987, Luce *et al.* 1993) and a pooled analysis of 12 case-control studies (Luce *et al.* 2002) that found an excess of sinonasal cancer. In most studies, estimates of increased risk were statistically significant for individuals ever exposed to formaldehyde, or with higher probabilities or levels of exposure (Olsen *et al.* 1984, Olsen and Asnaes 1986, Hayes *et al.* 1986, Luce *et al.* 1993, 2002).

Elevated risks were observed for both adenocarcinoma and squamous-cell carcinoma; however, some studies suggested that adenocarcinoma was more strongly associated with formaldehyde exposure than was squamous-cell carcinoma (Luce *et al*. 1993, 2002). The pooled analysis (which included studies by Hayes *et al.* 1986, Vaughan *et al*. 1986, and Luce *et al.* 1993) was especially informative for evaluating sinonasal cancer, because it had greater statistical power for evaluating risks of rare cancers than the individual studies, and it used an independent exposure analysis to assess cumulative exposure rather than relying on the exposure estimates from the original studies. In the pooled analysis, the relative risk of adenocarcinoma increased with increasing cumulative exposure; the odds ratios for individuals with high cumulative exposure were 3.0 (95% CI = 1.5 to 5.7, 91 exposed cases) for men and 6.2 (95% CI = 2.0 to 19.7, 5 exposed cases) for women. Support for a positive exposure-response relationship also comes from a case-control study in France that found higher risks of sinonasal cancer (adenocarcinoma) among individuals with higher average exposure levels and earlier dates of first exposure (Luce *et al*. 1993) and from a case-control study in the Netherlands that found a significantly ($P < 0.05$) higher relative risk of all sinonasal cancer or squamous-cell carcinoma among individuals with "high" exposure than those with "low" exposure (Hayes *et al.* 1986).

Although co-exposure to wood dust is a potential confounding factor for sinonasal cancer, and specifically for adenocarcinoma, increased risk of sinonasal cancer associated with formaldehyde exposure has been found among individuals with little or no exposure to wood dust or after adjustment for wood-dust exposure (Olsen *et al.* 1984, Hayes *et al.* 1986, Olsen and Asnaes 1986). Some studies suggested that co-exposure to formaldehyde and wood dust had an interactive (synergistic) carcinogenic effect (Luce *et al.* 1993, 2000). Two case-control studies did not find an association between formaldehyde exposure and sinonasal cancer; however, one study included only 12 cases of sinonasal cancer in exposed individuals (Vaughan *et al*. 1986), and the other had methodological limitations (Pesch *et al.* 2008). In the cohort studies of industrial workers (including studies of the large NCI, NIOSH, and British cohorts) and professional groups, the statistical power to detect an association between formaldehyde exposure and sinonasal cancer was limited. Nonetheless, a statistically significant excess of sinonasal cancer incidence was found among Danish male workers exposed to formaldehyde and who were unlikely to have been exposed to wood dust (Hansen and Olsen 1995, 1996), and a nonsignificant excess of mortality from sinonasal cancer was found in the NCI cohort. No excess mortality from sinonasal cancer was found in the other cohort studies. The power to detect a twofold or greater increase in mortality from nasal cancer in the NIOSH cohort was 16%.

Myeloid Leukemia

An association between excess mortality from leukemia or combined lymphohematopoietic cancer (cancer of the lymphatic and blood-forming systems) has been reported in numerous cohort studies, including all of the studies of professional groups and some of the studies of industrial cohorts (NTP 2010). Some of these studies reported positive exposure-response relationships for combined lymphohematopoietic cancer or specific subtypes (Beane Freeman *et al*. 2009, Hauptmann *et al*. 2009). Among studies that evaluated subtypes of lymphohematopoietic cancer, the strongest associations were observed for myeloid leukemia. The most informative studies for

evaluation of the risk of myeloid leukemia are the large cohort studies of industrial workers (the NCI, NIOSH, and British cohorts) and the NCI nested case-control study of lymphohematopoietic cancer in embalmers. Three of these four studies found elevated risks of myeloid leukemia among individuals with high exposure to formaldehyde, as well as positive exposure-response relationships. Confounding is unlikely to explain these increased risks, because there was no evidence of potential confounding in the individual studies, and the increased risks were observed for workers in different industries and occupations (workers at formaldehyde-producing companies, garment workers, and embalmers).

Both the NCI cohort study of industrial workers and the nested case-control study of myeloid leukemia in embalmers found positive exposure-response relationships between myeloid leukemia and peak formaldehyde exposure level. In the study of embalmers, relative risk also increased with increasing duration of employment in embalming (P_{trend} = 0.020) and with increasing average exposure level (P_{trend} = 0.058), in addition to increasing peak exposure level (P_{trend} = 0.036). In analyses using a comparison group of funeral directors with fewer than 500 lifetime embalmings, significantly elevated risks of myeloid leukemia (adjusted for smoking) were found among workers with longest duration of employment in embalming (OR = 3.9, 95% CI = 1.2 to 12.5, P = 0.024) and the highest cumulative exposure to formaldehyde (OR = 3.1, 95% CI = 1.0 to 9.6, P = 0.047). In addition, elevated risk estimates of borderline statistical significance were found for those who had performed the largest numbers of embalmings (OR = 3.0, 95% CI = 1.0 to 9.2, P = 0.057). In a 1994 update of the NCI cohort study (based on reanalyses that included additional deaths and recoding of deaths), risk was significantly higher for the highest category of peak exposure (relative risk [RR] = 2.79, 95% CI = 1.08 to 7.21) than for the lowest exposure category, and risk increased with increasing peak exposure (P_{trend} = 0.02) (Beane Freeman *et al*. 2009). In a 2004 follow-up study, elevated risk estimates were still observed, but the magnitude of the association between formaldehyde exposure and myeloid leukemia decreased as time since the last known exposure increased to at least 24 years. This pattern is consistent with a relatively short latency period, as has been observed for other leukemia-causing substances, such as benzene (Triebig 2010). Controlling for co-exposure to 11 potential occupational carcinogens did not alter the findings for myeloid leukemia.

In the NIOSH cohort study of garment workers, elevated risks of death from myeloid leukemia were found for all workers and for subgroups of workers with the highest exposure or longest latency. SMRs were highest among workers with longer exposure duration (≥ 10 years), longer latency (≥ 20 years), or earlier year of first exposure (before 1963, when exposure levels were higher). In an analysis that included all causes of death listed on the death certificate (rather than just the underlying cause), the risk of death from myeloid leukemia was significantly increased for workers who had been exposed for at least 10 years (SMR = 2.24, 95% CI = 1.02 to 4.25, 9 deaths) and was concentrated among workers with latency of at least 20 years who had been exposed for at least 10 years (SMR = 2.55, 95% CI = 1.10 to 5.03, 8 deaths) (Pinkerton *et al*. 2004). In the large cohort of British chemical workers, no increased risk of leukemia was found for formaldehyde exposure. However, this study did not evaluate myeloid leukemia specifically, and exposure-response analyses were limited; exposure was assessed as "high" or "ever," and the assessment was not calendar-year-specific (Coggon *et al*. 2003). Only one case-control study reported specific findings for myeloid

leukemia; an excess risk was found for chronic (but not acute) myeloid leukemia, based on small numbers of formaldehyde-exposed individuals with leukemia (Blair *et al.* 2001).

Although several meta-analyses have been published, none has included the nested case-control study of myeloid leukemia among embalmers by Hauptmann *et al.* (2009). The most informative meta-analysis (Zhang *et al.* 2009a) found a significantly elevated risk of myeloid leukemia (summary RR = 1.90, 95% CI = 1.31 to 2.76, $P = 0.001$) across studies using risk estimates, when available, for workers with the highest formaldehyde exposure. A meta-analysis by Bachand *et al*. (2009) did not find a significantly elevated risk of myeloid leukemia (summary RR = 1.09, 95% CI = 0.84 to 1.40). However, this analysis did not include the proportionate-mortality cohort studies (studies that compared the proportions of deaths between the study population and a reference population), which reported increased risks of myeloid leukemia. Bosetti *et al*. (2008) found an elevated risk of leukemia across studies of professional groups but not across studies of industrial workers. This finding is consistent with observations that embalmers have longer duration of exposure and higher cumulative exposure and are more likely to be exposed to peak exposure levels greater than 4 ppm than industrial workers, and that cancer risk is associated with peak levels of exposure to formaldehyde (Hauptmann *et al.* 2009).

Cancer at Other Tissue Sites

The association between formaldehyde exposure and cancer at other tissue sites is weaker than for nasal or lymphohematopoietic cancer (see NTP 2010 for a review of the studies). Increased risks of head and neck cancers (of the buccal cavity, pharynx, larynx, or combinations of these sites) were observed in many of the cohort and case-control studies, but most were not statistically significant, and there were no consistent findings of higher risk among the individuals with the highest exposure levels. An excess of brain cancer mortality was found in all studies of professional groups, but not in the cohort studies of industrial workers, and no positive exposure-response relationship was found in the NCI nested case-control study of brain cancer among embalmers. Findings for lung cancer were inconsistent and the data were inadequate to evaluate the association between formaldehyde exposure and cancer at other tissue sites.

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of formaldehyde from studies in experimental animals. Formaldehyde caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Long-term inhalation exposure to formaldehyde caused nasal tumors, both benign (polypoid adenoma) and malignant (predominantly squamous-cell carcinoma but also adenocarcinoma and carcinoma) in male and female F344 rats (Kerns *et al.* 1983, Monticello *et al.* 1996, Kamata *et al.* 1997), male Sprague-Dawley rats (Sellakumar *et al.* 1985), and male $B6C3F_1$ mice (Kerns *et al.* 1983a). Nasal tumors also were observed after short-term exposure (13 weeks) in male Wistar rats (Feron *et al.* 1988). Although the increased incidences of nasal tumors in mice and in the short-exposure study in rats were not statistically significant, they were considered to be biologically significant because of the rarity of this type of tumor. No tumors were observed in hamsters or monkeys

exposed to formaldehyde by inhalation (NTP 2010); the studies in monkeys were limited by small numbers of exposed animals and short exposure duration.

Long-term exposure of rats to formaldehyde in drinking water caused rare malignant tumors of the muscle of the stomach and intestine (leiomyoma and leiomyosarcoma) (Soffritti *et al.* 2002) in both sexes and benign tumors of the forestomach (squamous-cell papilloma) (Takahashi *et al.* 1986) and testes (interstitial-cell adenoma) (Soffritti *et al.* 2002, IARC 2006) in males. Mammary-gland tumors (combined types) in female rats and hemolymphoreticular tumors (combined types) in rats of both sexes also were significantly increased; however, it is unclear whether these tumors were treatment-related, because of limitations in the reporting of these tumors or the combined reporting of tumors with different cellular origins (Soffritti *et al.* 2002, IARC 2006). Increased incidences of intestinal tumors (primarily leiomyosarcoma but also adenocarcinoma) were observed in female rats exposed to formaldehyde *in utero* starting on gestational day 13 and throughout life via the drinking water (Soffritti *et al.* 1989). In tumor promotion and co-carcinogenicity studies, formaldehyde was shown to promote tumors of the stomach and lung in rats (NTP 2010).

Other Relevant Data

Formaldehyde exposure occurs from both endogenous and exogenous sources. It is rapidly absorbed after inhalation and oral exposure. The half-life of formaldehyde in the plasma of rats and monkeys is about 1 to 1.5 minutes (McMartin *et al*. 1979, IARC 2006). Differences in breathing patterns across species may affect differences in absorption and distribution. In rats, almost all inhaled formaldehyde is absorbed in the nasal passage, whereas in primates, some absorption occurs in the trachea and proximal regions of the major bronchi (Chang *et al.* 1983, Heck *et al.* 1983, Monticello *et al.* 1989, Casanova *et al.* 1991). The metabolism of formaldehyde is similar in all mammalian species studied (IARC 2006). Although formaldehyde is a gas at room temperature, it hydrates rapidly and is in equilibrium with its hydrated form, methanediol (Fox *et al.* 1985); at room and body temperatures, the dominant form is methanediol. Formaldehyde is rapidly metabolized by glutathione-dependent formaldehyde dehydrogenase (also known as alcohol dehydrogenase 5, ADH5) and *S*-formyl-glutathione hydrolase to formic acid, which enters the one-carbon pool and can be either excreted in the urine or oxidized to carbon dioxide and exhaled. ADH5 has been detected in all human tissues at all stages of development, from embryo through adult (Thompson *et al.* 2009). Although formaldehyde is rapidly metabolized, it is an electrophile that reacts with a variety of endogenous molecules, including glutathione, proteins, nucleic acids, and folic acid (NTP 2010).

Studies on Mechanisms of Carcinogenesis

Formaldehyde exposure is associated with multiple modes of action related to carcinogenicity, such as DNA reactivity, gene mutation, chromosomal breakage, aneuploidy, epigenetic effects (binding to lysine residues of histones), glutathione depletion, oxidative stress, and cytotoxicity-induced cellular proliferation (Lu *et al.* 2008, Guyton *et al.* 2009, NTP 2010). There is evidence for a genotoxic mode of action for formaldehyde-induced cancer; however, the mechanisms by which formaldehyde causes cancer are not completely understood and most likely involve several modes of action.

Formaldehyde is a direct-acting genotoxic compound and has given positive results for almost all genetic end points evaluated in bacteria, yeast, fungi, plants, insects, nematodes, and cultured mammalian cells. It caused base-pair gene mutations in bacteria (*Salmonella typimurium*) and DNA adducts, DNA-protein crosslinks, DNA-DNA crosslinks, DNA single-strand breaks, unscheduled DNA synthesis, inhibition of DNA repair, gene mutations, cell transformation, and cytogenetic effects (sister chromatid exchange, chromosomal aberrations, and micronucleus formation) in cultured mammalian cells (NTP 2010). It was also genotoxic in experimental animals and humans exposed *in vivo* (discussed below). There is some evidence to suggest that the Fanconi anemia complementation group (BRCA/FANC) response pathway may be important in the prevention of DNA damage from formaldehyde exposure (Zhang *et al.* 2009b). Cells deficient in FANC genes were hypersensitive to formaldehyde exposure and had increased frequencies of micronuclei (Speit *et al.* 2000, Ridpath *et al.* 2007).

Nasal Cancer

Mechanistic studies in humans and experimental animals support the findings that formaldehyde causes nasopharyngeal and sinonasal cancer in humans. Formaldehyde causes genetic damage to the nasal tissues of both experimental animals and humans exposed by inhalation. DNA-protein crosslinks were detected in the nasal mucosa of rats exposed to formaldehyde (Casnaova *et al.* 1989, 1994, NTP 2010) and in the nasal turbinates (Heck *et al.* 1989, Casanova *et al.* 1991) and the respiratory tract (larynx, trachea, carina, and bronchi) (Casanova *et al.* 1991) of rhesus monkeys exposed to formaldehyde, which correspond to the observed tumor sites in humans (nasal and nasopharygeal). In dose-response studies in rats, DNA crosslinks were correlated with tumor incidence (Liteplo and Meek 2003). DNA-protein crosslinks were also correlated with the severity and anatomical location of proliferative nasal lesions in rhesus monkeys (Casanova *et al.* 1991). N^2-hydroxmethyl-deoxyguanosine (dG) DNA monoadducts and dG-dG crosslinks were found in rat nasal mucosa (Lu *et al.* 2010). Mutations in the *p53* tumor-suppressor gene (at G:C base pairs) were found in formaldehyde-induced nasal squamous-cell carcinomas in rats, and all of the identified codon mutations have also been found in human cancers (Recio *et al.* 1992). In humans, formaldehyde exposure was associated with higher levels of serum p53 protein (wild-type and mutant p53 protein), and serum p53 protein level was positively correlated with mutant p53 protein level. Higher levels of DNA-protein crosslinks in lymphocytes were significantly associated with increased risk of higher serum p53 levels (Shaham *et al.* 2003). Numerous studies of industrial workers and professional groups exposed to formaldehyde have demonstrated that formaldehyde exposure causes increased micronuclei frequency in the nasal epithelium and buccal epithelium (Ballarin *et al.* 1992, Suruda *et al.* 1993, Titenko-Holland *et al.* 1996, Kitaeva *et al.* 1996, Ying *et al*. 1997, Burgaz *et al.* 2001, 2002, Ye *et al*. 2005).

Inhalation-exposure studies in experimental animals have shown that airway deposition and cytotoxicity-induced cellular proliferation also are important factors in the carcinogenicity of formaldehyde to nasal cells. In rats, regional formaldehyde flux (as estimated by computational fluid dynamic models) was correlated with the anatomical distribution of formaldehyde-induced lesions (squamous metaplasia) (Kimbell *et al.* 1997) and DNA-protein crosslinks (Hubal *et al*. 1997). Inhalation of formaldehyde by rodents causes cytotoxicity of the respiratory epithelium (rhinitis,

epithelial dysplasia, and squamous metaplasia) (Chang *et al.* 1983, Monticello *et al*. 1991, 1996), which can result in cellular proliferation and the promotion of chemically induced or spontaneous mutations. Cellular proliferation has been shown to be correlated with local nasal tumor incidence (Monticello *et al*. 1989, 1996). Formaldehyde exposure also causes cytotoxicity and cellular proliferation at anatomical sites that are not thought to be the origin of the squamous-cell carcinoma, suggesting that factors other than cellular proliferation play a role in formaldehyde-induced nasal cancers (Monticello *et al.* 1991).

Myeloid Leukemia

The mechanisms by which formaldehyde causes myeloid leukemia in humans are not known; nevertheless, the available evidence taken together does not indicate that such mechanisms are implausible.

Lymphohematopoietic diseases arise from damage to stem cells at different levels of hematopoietic and stem-cell development (Greaves 2004), and most agents known to cause leukemia are thought to do so by directly damaging stem cells in the bone marrow. In order for a stem cell to become malignant it must acquire genetic mutations and genomic instability (Zhang *et al.* 2009b). Formaldehyde is highly reactive and rapidly metabolized. The endogenous concentration in the blood of humans, monkeys, and rats is about 2 to 3 μg/g, and the concentration does not increase after inhalation of formaldehyde from exogenous sources (Heck *et al*. 1985, Casanova *et al*. 1988, Heck and Casanova *et al*. 2004). Moreover, N^2-hydroxymethyl-dG–DNA adducts have not been detected at distal sites in rats (such as the bone marrow, white blood cells, lung, spleen, liver, or thymus) (Lu *et al*. 2010). For these reasons, the plausibility of formaldehyde's causing cancer at distal sites, such as myeloid leukemia, has been questioned (Golden *et al*. 2006, Pyatt *et al*. 2008).

However, there is some evidence for systemic distribution of formaldehyde in humans. Serum levels of formaldehyde-albumin adducts were significantly higher in laboratory workers exposed to high levels of formaldehyde than in workers exposed at lower levels (Pala *et al*. 2008). In addition, levels of formaldehyde-DNA adducts in leukocytes were significantly higher in smokers than in nonsmokers; however, it is not known whether the source of the adducts was formaldehyde in tobacco smoke or from metabolism of a tobacco-specific compound (Wang *et al.* 2009). Numerous studies in humans and experimental animals have demonstrated that inhaled formaldehyde can cause toxicity, genotoxicity, and cancer at distal sites. In humans, formaldehyde exposure has been associated with (1) hematological toxicity (see below), (2) genotoxic damage in lymphocytes, including DNA-protein crosslinks, DNA strand breaks (Shaham *et al.* 2003, Costa *et al*. 2008), micronuclei (Suruda *et al*. 1993, He *et a*l. 1998, Orsiére *et al*. 2006, Costa *et al.* 2008), and chromosomal aberrations (albeit not in all studies) (NTP 2010, Jakab *et al*. 2010), and (3) myeloid leukemia (discussed above).

In experimental animals, inhaled formaldehyde was associated with toxicity to the liver in several species (Beall and Ulsamer 1984, Cikmaz *et al*. 2010) and the nervous system (neurobehavioral changes and cellular and biochemical changes in the hippocampus) in mice and rats (Aslan *et al*. 2006, Sarsilmaz *et al.* 2007, Lu *et al*. 2008, Songur *et al.* 2010). In rats, it was also associated with toxicity to the testes (morphometric changes in the seminiferous epithelium) (Özen *et al.* 2005, Golalipour *et al.* 2007), spleen (morphometric alterations in the white pulp) (Golalipour *et al.* 2008),

and thyroid (lower weight and changes in levels of thyroid hormones) (Patel *et al.* 2003). The mechanisms for systemic toxicity in experimental animals are not known, but oxidative stress has been suggested to play a role in testicular toxicity and neurotoxicity. In general, most studies did not present information on whether respiratory injury was observed with formaldehyde exposure.

Inhaled formaldehyde also caused DNA single-strand breaks in the liver and lymphocytes of male rats (Im *et al.* 2006), dominant lethal mutations in rats (Kitaeva *et al.* 1990), and heritable mutations in mice (Liu *et al.* 2009); however, most studies found no cytogenetic effects (NTP 2010). Findings for chromosomal aberrations in bone marrow of rats exposed to inhaled formaldehyde are conflicting; aberrations were found by Kitaeva *et al*. (1990), but not by Dallas *et al.* (1992). Prenatal exposure of rats to formaldehyde by intraperitoneal injection caused DNA-protein crosslinks and DNA strand breaks in the fetal liver (Wang and Liu 2006), and oral exposure to formaldehyde caused testicular tumors (Soffritti *et al.* 2002).

The mechanism by which formaldehyde causes toxicity at distal sites is unknown. The formation of methanediol (discussed above) helps to explain how a reactive chemical can be distributed and undergo metabolism throughout the body (Fox *et al.* 1985, Matubayasi *et al.* 2007). In addition, formaldehyde reacts reversibly with a variety of endogenous molecules, including glutathione, amino acids, and folic acid (Heck *et al.* 1982). These reversible products may be transported from the portal of entry to reach remote sites where free formaldehyde can then be released.

Zhang *et al.* (2009a) proposed that formaldehyde could also cause leukemia by other mechanisms that do not involve direct damage to the bone marrow: (1) formaldehyde could damage stem cells circulating in the blood, which travel to the bone and become initiated leukemia cells, or (2) it could damage stem cells that reside in the nasal turbinates or olfactory mucosa. Hematopoietic stem cells have been identified in the peripheral circulation and can circulate back to the bone marrow (Fritsch *et al.* 1996). The findings of cytotogenetic damage in circulating lymphocytes of formaldehyde-exposed workers (discussed above) support the first hypothesis, and the findings of cytogenetic damage (micronuclei) in nasal tissue support the second. High levels of chromosomal aberrations and micronuclei are associated with increased cancer risks in otherwise healthy individuals (Bonassi *et al.* 2008, Murgia *et al.* 2008). Moreover, Murrell *et al.* (2005) found that olfactory epithelial cells obtained from nasal passages contained hematopoietic stem/progenitor cells that were shown to repopulate the hematopoietic tissues of irradiated rats and to form progenitor cells of multiple lineages.

Regardless of the proposed mechanism, hematological toxicity of formaldehyde would be expected, and adverse hematological effects have been reported in some, but not all, studies in humans. However, no adverse hematological effects have been reported in subchronic or chronic studies in experimental animals (Dean *et al.* 1984, Appelman *et al.* 1988, Kamata *et al*. 1997). Zhang *et al.* (2010) found that formaldehyde-exposed workers had lower counts of white blood cells, granulocytes, platelets, red blood cells, and lymphocytes than nonexposed workers, and that a subset of workers showed an increased frequency of aneuploidy of chromosomes 7 (monosomy) and 8 (trisomy). Monosomy 7 and trisomy 8 are associated with myeloid leukemia (Johnson and Cotter 1997, Paulsson and Johansson 2007). In addition, formaldehyde exposure *in vitro* caused a decrease in colony-forming progenitor cells

(erythroid burst-forming units, erythroid colony-forming units, and granulocyte, erythrocyte, monocyte, and megakaryocyte colony-forming units). A review of the Chinese literature reported that decreased white blood cell counts were observed in most studies of formaldehyde-exposed workers; in the largest study, exposed workers had higher percentages of blood abnormalities (decreased white blood cell and platelet counts and abnormal hemoglobin levels) (Tang *et al.* 2009).

Properties

Formaldehyde is the simplest aldehyde. It exists at room temperature as a nearly colorless gas with a pungent, suffocating odor (ATSDR 1999, HSDB 2009). It is soluble in water, ether, acetone, and benzene. The primary form of formaldehyde in dilute aqueous solutions is its monomeric hydrate methylene glycol (methanediol), and the primary forms in concentrated solutions are oligomers and polymers of polyoxymethylene glycols (IARC 2006). Commercially, formaldehyde is most often available as 30% to 50% (by weight) aqueous solutions of the hydrated form, which is commonly referred to as formalin (IARC 2006). Formalin contains added stabilizers, generally up to 15% methanol or lower concentrations (usually several hundred milligrams per liter) of various amine derivatives. In the absence of stabilizers, formaldehyde in solution oxidizes slowly to form formic acid and polymerizes to form oligomers, including paraformaldehyde, a polymer with 8 to 100 units of formaldehyde (HSDB 2009). Formaldehyde can also exist in solid form as 1,3,5-trioxane, a cyclic trimer. Formaldehyde gas is generally stable in the absence of water, but it is flammable and can be ignited by heat, sparks, or flame. Vapors form explosive mixtures with air. Formaldehyde gas reacts violently with strong oxidizing agents and with bases and reacts explosively with nitrogen dioxide at around 180°C (356°F) (Akron 2009). Physical and chemical properties of formaldehyde are listed in the following table.

Property	Information
Molecular weight	30.0[a]
Specific gravity	0.815 at –20°C/4°C[b]
Melting point	–92°C[a]
Boiling point	–19.5°C[a]
Log K_{ow}	0.35[a]
Water solubility	400 g/L at 25°C[a]
Vapor pressure	3,890 mm Hg at 25°C[a]
Vapor density relative to air	1.067[a]
Dissociation constant (pK_a)	13.27 at 25°C[a]

[a]HSDB 2009; [b]O'Neil *et al.* 2006.

Use

Formaldehyde has numerous industrial and commercial uses; it is used in industrial processes primarily as a solution (formalin) or solid (paraformaldehyde or trioxane). The predominant use (~55% of total consumption) is in the production of industrial resins (mainly urea-formaldehyde, phenol-formaldehyde, polyacetal, and melamine-

formaldehyde resins) (Bizzari 2007). These resins are used to manufacture numerous commercial products, including adhesives and binders for composite wood products, pulp and paper products, plastics, and synthetic fibers, and in textile finishing. Another major use (~29%) is as a chemical intermediate to produce other chemicals. Various agricultural uses (~5%), paraformaldehyde production (~3%), and production of chelating agents (~3%) account for most of the remaining uses. The remaining 5% of formaldehyde goes toward other uses that may still be important for human exposure, including in disinfectants and pesticides, as a medical treatment for some skin conditions, as an antibacterial agent or disinfectant, as a tissue preservative for pathologists and embalmers, and as a biocide and preservative in food and cosmetic products (ATSDR 1999, IARC 2006). The main uses for paraformaldehyde are as foundry resins and in applications where the presence of water could interfere with a production process.

Production

Annual production of formaldehyde in the United States increased from about 0.9 million metric tons (1 million tons) in 1960 to 4.5 million metric tons (5 million tons) in 2006 (Bizzari 2007). Formaldehyde is produced by catalytic oxidation of methanol via a silver or metal-oxide catalyst process. In 2009, formaldehyde was produced at 39 U.S. manufacturing plants (SRI 2009a) by 12 companies and their subsidiaries (Bizzari 2007), and paraformaldehyde and trioxane each were produced at 1 U.S. manufacturing facility (SRI 2009b,c), and 36 U.S. suppliers of formaldehyde, 25 U.S. suppliers of paraformaldehyde, and 11 U.S. suppliers of trioxane were identified. Internationally, 152 formaldehyde suppliers in 25 countries, 59 paraformaldehyde suppliers in 15 countries, and 21 trioxane suppliers in 9 countries were identified in 2009 (ChemSources 2009a,b,c). Because of transportation and storage issues associated with formaldehyde, it usually is produced close to the point of consumption; therefore, international trade in formaldehyde is minimal (less than 2% of worldwide production) (Bizzari 2007). In 2006, U.S. imports of formaldehyde were about 10,000 metric tons, and U.S. exports were about 14,000 metric tons (15,400 tons).

Exposure

Humans are exposed to formaldehyde in the environment and in the workplace. Exposure levels are highest in the workplace, occurring in the range of parts per million. Formaldehyde concentrations in the environment generally are reported in parts per billion. Formaldehyde is also produced endogenously in humans and animals.

Environmental Exposure

Formaldehyde is ubiquitous in the environment and has been detected in indoor and outdoor air, soil, food, treated and bottled drinking water, surface water, and groundwater (NTP 2010). For the general public, the major sources of formaldehyde exposure include combustion sources, offgassing from numerous construction and home-furnishing products, and offgassing from consumer goods. Formaldehyde gas is produced from the oxidation or incomplete combustion of organic material. Combustion sources include automobiles and other internal combustion engines, power plants, incinerators, refineries, forest fires, wood stoves, and cigarettes. Formaldehyde is also

formed in the early stages of decomposition of plant residues in soil (IARC 2006). Formaldehyde can be produced secondarily in air via photochemical reactions involving virtually all classes of hydrocarbon pollutants; in some instances, secondary production may exceed direct air emissions. Formaldehyde concentrations in outdoor air generally range from 0 to 100 ppb (0 to 0.1 ppm) and usually are less than 10 ppb (0.01 ppm). Indoor air levels can be higher, and some of the highest levels have been reported for manufactured or mobile homes. Levels in the trailers provided by the Federal Emergency Management Agency as temporary shelter for residents of Louisiana and Mississippi displaced by Hurricanes Katrina and Rita ranged from 3 to 590 ppb (0.003 to 0.59 ppm), with a geometric mean of 77 ppb (0.077 ppm) (CDC 2008). Ingestion of food and water can also be a significant source of exposure to formaldehyde. Estimated daily formaldehyde exposure levels are highest for food (up to 14 mg), workplace air with occupational exposure (up to 8 mg), and residential indoor air in a prefabricated home (up to 10 mg) (NTP 2010).

Formaldehyde is an essential metabolic intermediate in the biosynthesis of purines, thymidine, and some amino acids. It is also produced via metabolism of some amino acids and a variety of xenobiotics, such as drugs, food additives, and other environmental chemicals (IARC 2006). The endogenous concentration of formaldehyde in the blood of humans, monkeys, and rats is approximately 2 to 3 μg/g (Casanova *et al.* 1988, Heck *et al.* 1985).

Occupational Exposure

In occupational environments, formaldehyde occurs mainly as a gas; however, formaldehyde particulates can be inhaled when paraformaldehyde or powdered resins are used or when formaldehyde adsorbs to other particles, such as wood dust (IARC 1995). Workers may also be exposed through contact of formalin solutions or liquid resins with the skin or eyes. Occupational exposure to formaldehyde is highly variable and can occur in numerous industries, including the manufacture of formaldehyde and formaldehyde-based resins, wood-composite and furniture production, plastics production, embalming, foundry operations, fiberglass production, construction, agriculture, firefighting, and histology, pathology, and biology laboratories, among others. In the past, the highest continuous exposure levels were measured during the varnishing of furniture and wooden floors, during the finishing of textiles, in the garment industry, during the treatment of furs, and in certain jobs in manufactured board mills and foundries. Short-term exposure to high levels of formaldehyde has been reported for embalmers, pathologists, and paper workers. Lower levels of exposure have usually been reported for the manufacture of synthetic vitreous fibers, abrasives, and rubber, and in formaldehyde production (IARC 2006). It has been suggested that because formaldehyde is ubiquitous, occupational exposure occurs in all workplaces (WHO 2002).

In the United States, high exposure levels have been reported for formaldehyde-based resin production (mean concentrations of up to 14.2 ppm), plastic product production (up to 38.2 ppm) (Stewart *et al.* 1987), embalming (up to 2.6 ppm) (Stewart *et al.* 1992), biology teaching laboratories (up to 8.3 ppm) (EPA 1981c), and pathology autopsy laboratories (up to 4.35 ppm) (NIOSH 1979). Using formaldehyde exposure data from the Occupational Safety and Health Administration (OSHA) air sampling database for various U.S. industries from 1979 to 2001, Lavoué *et al.* (2008) found the highest estimated relative indices of exposure based on time-weighted-average (TWA)

exposure data for the reconstituted wood products and lumber and wood products industries. The highest estimated relative indices of exposure based on short-term exposure data (aggregated short-term, peak, and ceiling exposure levels) were for the reconstituted wood products industry and funeral services and crematories.

In the late 1980s, OSHA estimated that over 2 million U.S. workers were exposed to formaldehyde, about 45% of whom worked in the garment industry (USDL 2009). OSHA estimated that about 1.9 million workers were exposed to formaldehyde at concentrations between 0.1 and 0.5 ppm, 123,000 at 0.5 to 0.75 ppm, and 84,000 at 0.75 to 1 ppm (WHO 2002). No current data were found for occupational exposure to formaldehyde in the United States.

Regulations

Coast Guard, Department of Homeland Security

46 CFR 150 and 151 detail procedures for shipping formaldehyde, formaldehyde solution, and 1,3,5-trioxane with incompatible chemicals.

Minimum requirements have been established for safe transport of formaldehyde solutions on ships and barges.

Consumer Product Safety Commission (CPSC)

Formaldehyde and products containing 1% or more formaldehyde are considered "strong sensitizers" and must display a warning label.

Department of Agriculture (USDA)

Limits have been established for the amount of residual formaldehyde in inactivated bacterial products and killed-virus vaccines.

Department of Transportation (DOT)

Formaldehyde, formalin, and paraformaldehyde are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials, as prescribed in 49 CFR 172.

Environmental Protection Agency (EPA)

Clean Air Act

Clean-Fuel Vehicles: Formaldehyde emissions limits have been established for various classes of clean-fuel vehicles.

Control of Emissions from New and In-Use Highway Vehicles and Engines: Formaldehyde emissions limits have been established for various classes of vehicles.

Mobile Source Air Toxics: Listed as a mobile source air toxic for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of formaldehyde is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 15,000 lb.

Regulation of Fuels and Fuel Additives: Under reformulated gasoline certification requirements, formaldehyde emissions levels must not be exceeded.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designation of Hazardous Substances: Formaldehyde and paraformaldehyde both are listed as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Formaldehyde reportable quantity (RQ) = 100 lb.

Paraformaldehyde reportable quantity (RQ) = 1,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 100 lb.

Threshold planning quantity (TPQ) = 500 lb.

Resource Conservation and Recovery Act

Listed hazardous waste: Waste codes for which the listing is based wholly or partly on the presence of formaldehyde = U122, K009, K010, K038, K040, K156, K157.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Numerous formaldehyde-based chemicals may be used as components of adhesives and coatings in packaging, transporting, or holding food, provided that conditions prescribed in 21 CFR 175 are met.

Numerous formaldehyde-based chemicals may be safely used as articles intended for use in contact with food, provided that conditions prescribed in 21 CFR 177 are met.

Numerous formaldehyde-based chemicals may be used in the production of paper products intended for use in producing, processing, preparing, treating, packaging, transporting, or holding food, provided that conditions prescribed in 21 CFR 176 are met.

Formaldehyde and formaldehyde-based chemicals may be used as adjuvants, production aids, and sanitizers that come in contact with foods, provided that conditions prescribed in 21 CFR 178 are met.

Formaldehyde-based ion-exchange resins may be used in the treatment of food, provided that conditions prescribed in 21 CFR 173 are met.

Formaldehyde may be safely used in the manufacture of animal feeds in accordance with conditions prescribed in 21 CFR 573.460.

Formalin, containing approximately 37% formaldehyde gas by weight, can be used in environmental waters for the control of fungi and parasites for certain finfish and shellfish as prescribed in 21 CFR 529.

U.S. Department of Housing and Urban Development (HUD)

All plywood and particleboard materials bonded with a resin system or coated with a surface finish containing formaldehyde shall not exceed the following emission levels when installed in manufactured homes: 0.2 ppm for plywood and 0.3 ppm for particleboard.

Manufactured homes must prominently display a notice which provides information on formaldehyde sources, levels, health effects, and remedial actions to reduce indoor levels.

Mine Safety and Health Administration

Engine exhaust from mobile diesel-powered transportation equipment must be diluted with air so that the mixture contains no more than 0.001% by volume of aldehydes, calculated as equivalent formaldehyde.

Occupational Safety and Health Administration (OSHA)

Permissible exposure limit (PEL) = 0.75 ppm [0.92 mg/m^3] (8-h TWA).

Short-term exposure limit = 2 ppm [2.46 mg/m^3] (15-min exposure).

Action level = 0.5 ppm [0.61 mg/m^3] (8-h TWA).

Comprehensive standards have been developed for occupational exposure to formaldehyde gas, its solutions, and materials that release formaldehyde.

Requirements for preventing or minimizing the consequences of catastrophic releases of toxic, reactive, flammable, or explosive chemicals are prescribed in 29 CFR 1910.119; the threshold quantity (TQ) for formaldehyde is 1,000 lb.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – ceiling (TLV-C) = 0.3 ppm [0.37 mg/m^3].

Listed as a suspected human carcinogen.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.016 ppm [0.02 mg/m^3] (10-h TWA).

Immediately dangerous to life and health (IDLH) limit = 20 ppm [24.56 mg/m^3].

Ceiling recommended exposure limit = 0.1 ppm [0.12 mg/m^3] (15-min exposure).

Listed as a potential occupational carcinogen.

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