

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 data on mechanisms of carcinogenesis. Formaldehyde was first listed in the *Second Annual Report on Carcinogens* in 1981 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals. Since that time, additional cancer studies in humans have been published, and the listing status was changed to *known to be a human carcinogen* in the *Twelfth Report on Carcinogens* (2011).

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 lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding. The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia.

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. Most of the studies, including all of the large cohort studies and the studies of professional groups, reported cancer mortality. For types of cancer with higher survival rates, such as lymphohematopoietic cancer, studies reporting mortality are less informative than studies reporting incidence, because mortality studies will miss cases of cancer that do not result in death.

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.* (2009) 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 (which can be related to genetic susceptibility and/or common environmental factors). 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 ($P_{\text{trend}} = 0.033$), duration of exposure ($P_{\text{trend}} = 0.014$), 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 time since first exposure (West *et al.* 1993) or who died at an older age (Roush *et al.* 1987); risk was increased four-fold 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 ($P_{\text{trend}} = 0.025$ across exposed subjects), peak exposure ($P_{\text{trend}} < 0.001$), and average exposure ($P_{\text{trend}} = 0.066$) (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 workers 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 significantly elevated risk for ever having worked in silversmithing jobs before or after employment at Plant 1; however, silversmithing was not correlated with formaldehyde exposure levels at this plant and therefore was not a confounding factor 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); however, the statistical power of these studies was inadequate to evaluate the risks of rare types of cancer.

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 for evaluation of 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 did 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, 2002). 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; however, the statistical power of these studies was inadequate to evaluate the risks of types of cancer.

Lymphohematopoietic Cancer

Evidence that demonstrates an association between formaldehyde exposure and combined lymphohematopoietic cancer is as follows: (1) in the NCI cohort of industrial workers, risk was significantly higher for the highest peak-exposure group than the lowest peak-exposure group, and a positive exposure-response relationship based on peak exposure was found (Beane Freeman *et al.* 2009), (2) increased risks were found in all of the cohort studies of professional groups (NTP 2010), and (3) a significant risk was reported (relative risk [RR] = 1.25, 95% CI = 1.12 to 1.39) in the meta-analysis by Zhang *et al.* (2009). In the NCI cohort study of industrial workers, the risks of Hodgkin's lymphoma and multiple myeloma also were significantly higher among individuals with the highest peak exposure than those with the lowest peak exposure, and a positive exposure-response relationship was found for Hodgkin's lymphoma (Beane Freeman *et al.* 2009). The other studies gave conflicting results for these two types of cancer. In the meta-analyses by Zhang *et al.* (2009), a significant association was found for multiple myeloma, but not for Hodgkin's lymphoma. Because the evidence for these two types of cancer is mainly limited to the NCI cohort study, a causal association is not established.

Increased risks for leukemia (all types combined) were found in all of the professional studies and some of the industrial cohort studies

(NTP 2010). Among studies that evaluated subtypes of lymphohematopoietic cancer or leukemia, the strongest associations were observed for myeloid leukemia. For example, in the nested case-control study of embalmers (Hauptman *et al.* 2009), the excess risk of non-lymphoid lymphohematopoietic cancer was explained by a strong association with myeloid cancer, and in other studies, the magnitudes of the effect estimates were higher for myeloid leukemia than for all leukemia or other subtypes of leukemia (Pinkerton *et al.* 2004, Beane Freeman *et al.* 2009, NTP 2010).

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 ($P_{\text{trend}} = 0.020$) and with increasing average exposure level ($P_{\text{trend}} = 0.058$), in addition to increasing peak exposure level ($P_{\text{trend}} = 0.036$). 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 long 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 (RR = 2.79, 95% CI = 1.08 to 7.21) than for the lowest exposure category, and risk increased with increasing peak exposure ($P_{\text{trend}} = 0.02$) (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 follow-up period longer than the optimal latency period for cancer, as has been seen with other leukemia-inducing agents (Silver *et al.* 2002). 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 time since first exposure (≥ 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 time since first exposure 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.* 2009) 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.* (2010) 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 are 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 B6C3F₁ mice (Kerns *et al.* 1983). Nasal tumors were also 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.

Long-term exposure of adult rats to formaldehyde in drinking water caused benign tumors of the forestomach (squamous-cell papilloma) in male Wistar rats (Takahashi *et al.* 1986) and testes (interstitial-cell adenoma) (Soffritti *et al.* 2002, statistics reported in IARC 2006) in male Sprague-Dawley rats. Increased incidences of intestinal tumors (primarily leiomyosarcoma, which are rare malignant tumors of the muscle of the intestine) were observed in female Sprague-Dawley rats exposed to formaldehyde *in utero* starting on gestational day 13 and throughout life via the drinking water (Soffritti *et al.* 1989, statistics reported in IARC 2006). Leiomyosarcoma of the stomach and intestines was also observed in the formaldehyde-exposed groups, but not the concurrent control groups (untreated animals and control animals given methanol), in Sprague-Dawley rats exposed as adults. Although the findings were not statistically significant, they are of concern because of the rarity of these tumors. Hemolymphoreticular tumors (combined types) in rats of both sexes also were significantly increased after long-term exposure of adults; however, it is unclear whether these tumors were exposure-related, because of limitations in the reporting of these tumors (Soffritti *et al.* 2002, IARC 2006). 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; however, it is poorly absorbed via the skin (NTP 2010). 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 pure formaldehyde is a gas at room temperature, it hydrates rapidly and is in equilibrium with its hydrated form, methanediol (Fox 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

The mechanisms by which formaldehyde causes cancer are not completely understood and most likely involve several modes of action. Formaldehyde exposure is associated with key events 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). Understanding of the mechanisms is more advanced for nasal tumors than for lymphohematopoietic cancer. There is evidence for a genotoxic mode of action for both types of cancer. 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 *Salmonella typhimurium* 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.* 2010a). Cells deficient in FANC genes were hypersensitive to formaldehyde exposure and had increased frequencies of micronuclei and cancer (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 (Casanova *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 nasopharyngeal). 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-hydroxymethyl-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 levels were positively correlated with mutant *p53* protein levels. Higher levels of DNA-protein crosslinks in lymphocytes were significantly associated with increased risk of higher serum *p53* levels (Shaham *et al.* 2003). However, *p53* mutations were not observed in rat nasal mucosa exposed to formaldehyde for 13 weeks, suggesting that they may be a later event in the progression of cancer (Meng *et al.* 2010). Numerous studies of industrial workers and professional groups exposed to formaldehyde found that formaldehyde exposure increased the frequency of micronuclei 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).

Leukemia

Lymphohematopoietic cancers are a heterogeneous group of cancers that arise from damage to stem cells during hematopoietic and lymphoid development (Greaves 2004). Blood cells arise from a common stem cell, which forms two progenitor cells, the common myeloid stem cell and the common lymphoid stem cell. 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.* 2010a). Because formaldehyde is highly reactive and rapidly metabolized, a key question is how it can reach the bone marrow or cause toxicity or genotoxicity at distal sites. 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, systemic effects have been observed after inhalation or oral exposure, and although the mechanisms by which formaldehyde causes myeloid leukemia in humans are not known, a number of plausible mechanisms have been advanced. These include (1) theoretical mechanisms for the distribution of formaldehyde to distal sites and (2) proposed mechanisms of leukemogenesis that do not require formaldehyde to reach the bone marrow. In addition, there is some evidence that formaldehyde causes adverse hematological effects in humans.

Systemic Effects Observed After Inhalation or Oral Exposure

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), micronucleus formation (Surruda *et al.* 1993, He *et al.* 1998, Orsière *et al.* 2006, Costa *et al.* 2008), and chromosomal aberrations (albeit not in all studies) (Jakab *et al.* 2010, NTP 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 tes-

tes (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 gland (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).

Theoretical Mechanisms for the Distribution of Formaldehyde to Distal Sites

The mechanisms by which formaldehyde causes toxicity at distal sites are unknown. The formation of methanediol (discussed above) from formaldehyde helps to explain how a reactive chemical could be distributed and undergo metabolism throughout the body (Fox 1985, Matubayasi *et al.* 2007). The upper respiratory tissues are covered by an aqueous mucous membrane, through which formaldehyde could be transported as methanediol (Georgieva *et al.* 2003). 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. However, there is no experimental evidence to support these potential mechanisms.

Other Potential Mechanisms of Formaldehyde-Induced Leukemia

Zhang *et al.* (2009) 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 cytogenetic 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 the olfactory epithelium of the nasal passages of rats contained multipotent stem/progenitor cells that were able to repopulate the hematopoietic tissues of irradiated rats and to form progenitor cells of multiple lineages.

Hematotoxicity

Damage to hematopoietic stem or progenitor cells would result in adverse hematological effects, which 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.* (2010b) found that formaldehyde-exposed workers had lower counts of white blood cells, granulocytes, platelets, red blood cells, and lymphocytes than did non-exposed workers. Furthermore, myeloid progenitor cells cultured from the blood of 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. 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

^aHSDB 2009, ^bO'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, plas-

tics, 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 its use as a disinfectant or antimicrobial agent in various consumer products, as a medical treatment for some skin conditions, as a tissue preservative for pathologists and embalmers, and as a biocide and preservative in food and cosmetic products. Formaldehyde is registered as a materials preservative for use in consumer products such as laundry detergents, general-purpose cleaners, and wallpaper adhesives (ATSDR 1999, IARC 2006, EPA 2008). The main uses for paraformaldehyde are as foundry resins and in applications where the presence of water could interfere with a production process. Paraformaldehyde is also used as an antimicrobial agent for in-drawer fumigation of hair-cutting equipment and as a mildewcide in closets and unoccupied vacation homes (EPA 2008).

Production

Formaldehyde is produced by catalytic oxidation of methanol via a silver or metal-oxide catalyst process. 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). In 2009, formaldehyde was produced by 12 companies and their subsidiaries at 39 U.S. manufacturing plants (Bizzari 2007, SRI 2009), and paraformaldehyde and trioxane each were produced at one U.S. manufacturing plant (SRI 2009). Formaldehyde was available from 36 U.S. suppliers, paraformaldehyde from 25, and trioxane from 11. Internationally, formaldehyde was available from 152 suppliers in 25 countries, paraformaldehyde from 59 in 15 countries, and trioxane from 21 in 9 countries (ChemSources 2009). 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 (11,000 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. Formaldehyde concentrations in the environment generally are reported in parts per billion, but exposure levels are much higher in the workplace, occurring in the range of parts per million. 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). The general population can be exposed to formaldehyde primarily from breathing indoor or outdoor air, from tobacco smoke, from use of cosmetic products containing formaldehyde, and, to a more limited extent, from ingestion of food and water. For the general population, the major sources of airborne formaldehyde exposure include combustion sources, off-gassing from numerous construction and home-furnishing products, and off-gassing 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). Form-

aldehyde 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); daily exposure from outdoor air has been estimated at 0.1 mg or less (HSDB 2009).

Formaldehyde levels can be higher in indoor air than in outdoor air. Important determinants of indoor air levels include the sources of the formaldehyde, the age of the source materials, temperature, humidity, and ventilation rates (IARC 2006). Although daily formaldehyde exposure from residential indoor air in conventional homes has been reported to range from 0.5 to 2.0 mg, daily exposure in a prefabricated home was as high as 10 mg (Fishbein 1992). Temporary housing provided by the Federal Emergency Management Agency as shelter for residents of Louisiana and Mississippi displaced by Hurricanes Katrina and Rita had formaldehyde concentrations ranging from 3 to 590 ppb (0.003 to 0.59 ppm) (CDC 2008, 2009). Most of the housing was at least two years old at the time of sampling, which occurred during the winter months. Formaldehyde levels were higher in travel trailers than park models or mobile homes. Higher concentrations of formaldehyde than were found by the Centers for Disease Control and Prevention have been reported by others (for example, see COGR 2007). There are no federal guidelines for formaldehyde levels in residential housing for indoor air quality (CDC 2008).

Daily exposure to formaldehyde was estimated at up to 2 mg from smoking 20 cigarettes per day, up to 3.5 mg from environmental tobacco smoke in the home, and 2.8 mg from environmental tobacco smoke in the workplace (WHO 2000).

The general population could also be exposed to formaldehyde by handling consumer products that contain formaldehyde as an antimicrobial agent (such as laundry detergents, wallpaper adhesive, or sanitizers) or from its use as a mildewcide for clothing and linens or in vacation homes (EPA 2008). Although formaldehyde *per se* now is rarely used in cosmetics, the use of formaldehyde releasers is common. An analysis of data from the U.S. Food and Drug Administration's Voluntary Cosmetic Registration Program Database indicated that nearly 20% (6,463 of 33,212) of cosmetic products contained formaldehyde (including formalin) or any of eight formaldehyde-releasing preservatives (benzylhemiformal, 5-bromo-5-nitro-1,3-dioxane, 2-bromo-2-nitropropane-1,3-diol, diazolidinyl urea, 1,3-dimethylol-5,5-dimethylhydantoin, imidazolidinyl urea, quaternium-15, or sodium hydroxymethylglycinate) (De Groot and Veenstra 2010, De Groot *et al.* 2010). Absorption of formaldehyde from hand cream or suntan lotion was estimated at up to 0.1 mg for a typical application, assuming 5% absorption through the skin (ATSDR 1999). Other products that often contain formaldehyde releasers are industrial and household cleaning agents, soaps, shampoos, paints, lacquers, and cutting fluids (WHO 2002).

Food and water contain measureable concentrations of formaldehyde (WHO 2002, Mutsuga *et al.* 2006), but the significance of ingestion as a source of formaldehyde exposure for the general population is questionable. Formaldehyde in food exists mostly in a bound form (IPCS 1989, Fishbein 1992), and it is considered to be unstable in aqueous solution (ATSDR 1999). Formaldehyde present in food can occur naturally or through inadvertent contamination; it can also be added as a preservative, disinfectant, or bacteriostatic agent and can result from cooking or smoking of foods (Howard 1989, IPCS 1989, ATSDR 1999). Generally, higher levels were reported in fish, seafood, and smoked ham than in other foods (Li *et al.* 2007, NTP 2010). Formaldehyde in treated drinking water occurs primarily through the oxidation of organic matter during ozonation or chlorination; con-

centrations of up to 30 µg/L were reported (WHO 2005). Formaldehyde can also be present in the water before treatment; it was found in 16 of 35 influent samples at concentrations ranging from 1.2 to 13 µg/L (Krasner *et al.* 1989).

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 (Heck *et al.* 1985, Casanova *et al.* 1988).

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). Daily formaldehyde intake from occupational exposure has been estimated at up to 8 mg (WHO 2000).

In the United States, high exposure levels were 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 1981), and pathology autopsy laboratories (up to 4.35 ppm) (Moseley *et al.* 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 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 (USDOL 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 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.

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

Formaldehyde and paraformaldehyde 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.

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)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.75 ppm (0.92 mg/m³) (8-h TWA).

Short-term exposure limit (STEL) = 2 ppm (2.46 mg/m³) (15-min exposure).

Action level = 0.5 ppm (0.61 mg/m³) (8-h TWA).

Comprehensive standards have been developed for occupational exposure to formaldehyde gas, its solutions, and materials that release formaldehyde. These standards identify the permissible exposure limits and prescribe requirements for monitoring exposures, using respiratory protection, conducting medical evaluations, housekeeping, and other activities at 29 CFR 1910.1048 (General Industry), 29 CFR 1926.1148 (Construction Industry), and 29 CFR 1915.1048 (Shipyards).

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/m³).

Listed as a suspected human carcinogen.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.016 ppm (0.02 mg/m³) (10-h TWA).

Immediately dangerous to life and health (IDLH) limit = 20 ppm (24.56 mg/m³).

Ceiling recommended exposure limit = 0.1 ppm (0.12 mg/m³) (15-min exposure).

Listed as a potential occupational carcinogen.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://ull.chemistry.uakron.edu/erd> and search on CAS number. Last accessed: 5/19/09.
- Appelman LM, Woutersen RA, Zwart A, Falke HE, Feron VJ. 1988. One-year inhalation toxicity study of formaldehyde in male rats with a damaged or undamaged nasal mucosa. *J Appl Toxicol* 8(2): 85-90.
- Armstrong RW, Imrey PB, Lye MS, Armstrong MJ, Yu MC, Sani S. 2000. Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. *Int J Epidemiol* 29(6): 991-998.
- Aslan H, Songur A, Tunc AT, Ozen OA, Bas O, Yagmurca M, Turgut M, Sarsilmaz M, Kaplan S. 2006. Effects of formaldehyde exposure on granule cell number and volume of dentate gyrus: a histopathological and stereological study. *Brain Res* 1122(1): 191-200.
- ATSDR. 1999. *Toxicological Profile for Formaldehyde*. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp111.pdf>.
- Bachand A, Mundt KA, Mundt DJ, Montgomery RR. 2010. Epidemiological studies of formaldehyde exposure and risk of leukemia and nasopharyngeal cancer: A meta-analysis. *Crit Rev Toxicol* 40(2): 85-100.
- Ballarin C, Sarto F, Giacomelli L, Bartolucci GB, Clonfero E. 1992. Micronucleated cells in nasal mucosa of formaldehyde-exposed workers. *Mutat Res* 280(1): 1-7.
- Beall JR, Ulsamer AG. 1984. Formaldehyde and hepatotoxicity: a review. *J Toxicol Environ Health* 14(1): 1-21.
- Beane Freeman LE, Blair A, Lubin JH, Stewart PA, Hayes RB, Hoover RN, Hauptmann M. 2009. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. *J Natl Cancer Inst* 101(10): 751-761.
- Bizzari SN. 2007. Formaldehyde. In *Chemical Economics Handbook*. Menlo Park, CA: SRI Consulting. Online edition. 106 pp.
- Blair A, Zheng T, Linos A, Stewart PA, Zhang YW, Cantor KP. 2001. Occupation and leukemia: a population-based case-control study in Iowa and Minnesota. *Am J Ind Med* 40(1): 3-14.
- Bonassi S, Norppa H, Ceppi M, Stromberg U, Vermeulen R, Znaor A, et al. 2008. Chromosomal aberration frequency in lymphocytes predicts the risk of cancer: results from a pooled cohort study of 22 358 subjects in 11 countries. *Carcinogenesis* 29(6): 1178-1183.
- Bosetti C, McLaughlin JK, Tarone RE, Pira E, La Vecchia C. 2008. Formaldehyde and cancer risk: a quantitative review of cohort studies through 2006. *Ann Oncol* 19(1): 29-43.
- Bray F, Haugen M, Moger TA, Tretli S, Aalen OO, Grotmol T. 2008. Age-incidence curves of nasopharyngeal carcinoma worldwide: bimodality in low-risk populations and aetiological implications. *Cancer Epidemiol Biomarkers Prev* 17(9): 2356-2365.
- Burgaz S, Cakmak G, Erdem O, Yilmaz M, Karakaya AE. 2001. Micronuclei frequencies in exfoliated nasal mucosa cells from pathology and anatomy laboratory workers exposed to formaldehyde. *Neoplasma* 48(2): 144-147.
- Burgaz S, Erdem O, Cakmak G, Erdem N, Karakaya A, Karakaya AE. 2002. Cytogenetic analysis of buccal cells from shoe-workers and pathology and anatomy laboratory workers exposed to n-hexane, toluene, methyl ethyl ketone and formaldehyde. *Biomarkers* 7(2): 151-161.
- Casanova M, Heck HD, Everitt JI, Harrington WW Jr, Popp JA. 1988. Formaldehyde concentrations in the blood of rhesus monkeys after inhalation exposure. *Food Chem Toxicol* 26(8): 715-716.

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- Casanova M, Deyo DF, Heck HD. 1989. Covalent binding of inhaled formaldehyde to DNA in the nasal mucosa of Fischer 344 rats: analysis of formaldehyde and DNA by high-performance liquid chromatography and provisional pharmacokinetic interpretation. *Fundam Appl Toxicol* 12(3): 397-417.
- Casanova M, Morgan KT, Steinhagen WH, Everitt JJ, Popp JA, Heck HD. 1991. Covalent binding of inhaled formaldehyde to DNA in the respiratory tract of rhesus monkeys: pharmacokinetics, rat-to-monkey interspecies scaling, and extrapolation to man. *Fundam Appl Toxicol* 17(2): 409-428.
- Casanova M, Morgan KT, Gross EA, Moss OR, Heck HA. 1994. DNA-protein cross-links and cell replication at specific sites in the nose of F344 rats exposed subchronically to formaldehyde. *Fundam Appl Toxicol* 23(4): 525-536.
- CDC. 2008. *Final Report on Formaldehyde Levels in FEMA-Supplied Travel Trailers, Park Models and Mobile Homes*. Centers for Disease Control and Prevention. <http://www.cdc.gov/nceh/ehhe/trailerstudy/pdfs/FEMAFinalReport.pdf>.
- CDC. 2009. *Evaluation of Mitigation Strategies for Reducing Formaldehyde Concentrations in Unoccupied Federal Emergency Management Agency-Owned Travel Trailers*. Centers for Disease Control and Prevention. http://www.cdc.gov/nceh/ehhe/trailerstudy/pdfs/Evaluation_of_Mitigation_Strategies_FEMA_Trailers.pdf.
- Chang JC, Gross EA, Swenberg JA, Barrow CS. 1983. Nasal cavity deposition, histopathology, and cell proliferation after single or repeated formaldehyde exposures in B6C3F1 mice and F-344 rats. *Toxicol Appl Pharmacol* 68(2): 161-176.
- ChemSources. 2009. *Chemical Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on formaldehyde, paraformaldehyde, and trioxane. Last accessed: 4/30/09.
- Cikmaz S, Kutoglu T, Kanter M, Mesut R. 2010. Effect of formaldehyde inhalation on rat livers: a light and electron microscopic study. *Toxicol Ind Health* 26(2): 113-119.
- Coggon D, Harris EC, Poole J, Palmer KT. 2003. Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. *J Natl Cancer Inst* 95(21): 1608-1615.
- COGR. 2007. *FEMA's Toxic Trailers*. Hearing Before the Committee on Oversight and Government Reform, House of Representatives, Congress of the United States. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_house_hearings&docid=f:40851.pdf.
- Costa S, Coelho P, Costa C, Silva S, Mayan O, Santos LS, Gaspar J, Teixeira JP. 2008. Genotoxic damage in pathology anatomy laboratory workers exposed to formaldehyde. *Toxicology* 252(1-3): 40-48.
- Dallas CE, Scott MJ, Ward JB Jr, Theiss JC. 1992. Cytogenetic analysis of pulmonary lavage and bone marrow cells of rats after repeated formaldehyde inhalation. *J Appl Toxicol* 12(3): 199-203.
- Dean JH, Lauer LD, House RV, Murray MJ, Stillman WS, Irons RD, Steinhagen WH, Phelps MC, Adams DO. 1984. Studies of immune function and host resistance in B6C3F₁ mice exposed to formaldehyde. *Toxicol Appl Pharmacol* 72(3): 519-529 (as cited in IARC 2006).
- De Groot AC, Venstra M. 2010. Formaldehyde-releasers in cosmetics in the USA and in Europe. *Contact Dermatitis* 62(4): 221-224.
- De Groot AC, White IR, Flyvholm MA, Lensen G, Coenraads PJ. Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy. Part 1. Characterization, frequency and relevance of sensitization, and frequency of use in cosmetics. *Contact Dermatitis* 62(1): 2-17.
- EPA. 1981. *Technical Document: Formaldehyde*. Office of Toxic Substances. Washington, DC: U.S. Environmental Protection Agency.
- EPA. 2008. *Registration Eligibility Decision for Formaldehyde and Paraformaldehyde*. U.S. Environmental Protection Agency. <http://www.epa.gov/oppsrtd1/reregistration/REDS/formaldehyde-red.pdf>.
- Feron VJ, Bruyntjes JP, Woutersen RA, Immel HR, Appelman LM. 1988. Nasal tumours in rats after short-term exposure to a cytotoxic concentration of formaldehyde. *Cancer Lett* 39(1): 101-111.
- Fishbein L. 1992. Exposure from occupational versus other sources. *Scan J Work Environ Health* 18: 5-16.
- Fox EM. 1985. Urea formaldehyde foam insulation: defusing a timebomb. *Am J Law Med* 11(1): 81-104.
- Fritsch G, Stimpfl M, Kurz M, Printz D, Buchinger P, Fischmeister G, Hoecker P, Gadner H. 1996. The composition of CD34 subpopulations differs between bone marrow, blood and cord blood. *Bone Marrow Transplant* 17(2): 169-178.
- Georgieva AV, Kimbell JS, Schlosser PM. 2003. A distributed-parameter model for formaldehyde uptake and disposition in the rat nasal lining. *Inhal Toxicol* 15(14): 1435-1463.
- Golalipour MJ, Azarhoush R, Ghafari S, Gharravi AM, Fazeli SA, Davarian A. 2007. Formaldehyde exposure induces histopathological and morphometric changes in the rat testis. *Folia Morphol (Warsz)* 66(3): 167-171.
- Golalipour MJ, Kord H, Ghafari S, Gharravi AM, Davarian A, Fazeli SA, Azarhoush R. 2008. Morphometric alterations of the rat spleen following formaldehyde exposure. *Folia Morphol (Warsz)* 67(1): 19-23.
- Golden R, Pyatt D, Shields PG. 2006. Formaldehyde as a potential human leukemogen: an assessment of biological plausibility. *Crit Rev Toxicol* 36(2): 135-153.
- Greaves MF. 2004. Biological models for leukaemia and lymphoma. In *Mechanisms of Carcinogenesis: Contributions of Molecular Epidemiology*. Buffler P, Rice J, Baan R, Bird M, Boffetta P, eds. IARC Scientific Publication 157. Lyon, France: IARC Press. pp. 351-372.
- Guyton KZ, Kyle AD, Aubrecht J, Cogliano VJ, Eastmond DA, Jackson M, et al. 2009. Improving prediction of chemical carcinogenicity by considering multiple mechanisms and applying toxicogenomic approaches. *Mutat Res* 681(2-3): 230-240.
- Hansen J, Olsen JH. 1995. Formaldehyde and cancer morbidity among male employees in Denmark. *Cancer Causes Control* 6(4): 354-360.
- Hansen J, Olsen JH. 1996. [Occupational exposure to formaldehyde and risk of cancer] [in Danish; English translation]. *Ugeskr Laeger* 158(29): 4191-4194.
- Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. 2003. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries. *J Natl Cancer Inst* 95(21): 1615-1623.
- Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. 2004. Mortality from solid cancers among workers in formaldehyde industries. *Am J Epidemiol* 159(12): 1117-1130.
- Hauptmann M, Stewart PA, Lubin JH, Beane Freeman LE, Hornung RW, Herrick RF, et al. 2009. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. *J Natl Cancer Inst* 101(24): 1696-1708.
- Hayes RB, Raatgever JW, de Bruyn A, Gerin M. 1986. Cancer of the nasal cavity and paranasal sinuses, and formaldehyde exposure. *Int J Cancer* 37(4): 487-492.
- He JL, Jin LF, Jin YH. 1998. Detection of cytogenetic effects in peripheral lymphocytes of students exposed to formaldehyde with cytokinesis-blocked micronucleus assay. *Biomed Environ Sci* 11(1): 87-92.
- Heck H, Casanova M. 2004. The implausibility of leukemia induction by formaldehyde: a critical review of the biological evidence on distant-site toxicity. *Regul Toxicol Pharmacol* 40(2): 92-106.
- Heck HD, White EL, Casanova-Schmitz M. 1982. Determination of formaldehyde in biological tissues by gas chromatography/mass spectrometry. *Biomed Mass Spectrom* 9(8): 347-353.
- Heck HD, Chin TY, Schmitz MC. 1983. Distribution of [¹⁴C] formaldehyde in rats after inhalation exposure. In *Formaldehyde Toxicity*. Gibson JE, ed. Washington, DC: Hemisphere Publishing. pp. 26-36.
- Heck HD, Casanova-Schmitz M, Dodd PB, Schachter EN, Witek TJ, Tosun T. 1985. Formaldehyde (CH₂O) concentrations in the blood of humans and Fischer-344 rats exposed to CH₂O under controlled conditions. *Am Ind Hyg Assoc J* 46(1): 1-3.
- Heck HD, Casanova M, Steinhagen WH, Everitt JJ, Morgan KT, Popp JA. 1989. Formaldehyde toxicity: DNA-protein cross-linking studies in rats and nonhuman primates. In *Nasal Carcinogenesis in Rodents: Relevance to Human Risk*. Feron VJ, Bosland MC, eds. Wageningen, Netherlands: Pudoc. pp. 159-164.
- Hildesheim A, Dosemeci M, Chan CC, Chen CJ, Cheng YJ, Hsu MM, et al. 2001. Occupational exposure to wood, formaldehyde, and solvents and risk of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* 10(11): 1145-1153.
- Howard PH. 1989. *Handbook of Environmental Fate and Exposure Data for Organic Chemicals* Chelsea, MI: Lewis Publishers, Inc. pp. 342-350.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 5/18/09.
- Hubal EA, Schlosser PM, Conolly RB, Kimbell JS. 1997. Comparison of inhaled formaldehyde dosimetry predictions with DNA-protein cross-link measurements in the rat nasal passages. *Toxicol Appl Pharmacol* 143(1): 47-55.
- IARC. 1995. Formaldehyde. In *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Wood Dust and Formaldehyde*, vol. 62, Lyon, France: International Agency for Research on Cancer. pp. 217-362.
- IARC. 2006. Formaldehyde. In *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxypropan-2-ol*, vol. 88, Lyon, France: International Agency for Research on Cancer. pp. 39-325.
- Im H, Oh E, Mun J, Khim JY, Lee E, Kang HS, et al. 2006. Evaluation of toxicological monitoring markers using proteomic analysis in rats exposed to formaldehyde. *J Proteome Res* 5(6): 1354-1366.
- IPCS. 1989. *Environmental Health Criteria No. 89: Formaldehyde*. International Programme on Chemical Safety. <http://www.inchem.org/documents/ehc/ehc/ehc89.htm>.
- Jakab MG, Klupp T, Besenyi K, Biro A, Major J, Tompa A. 2010. Formaldehyde-induced chromosomal aberrations and apoptosis in peripheral blood lymphocytes of personnel working in pathology departments. *Mutat Res* 698(1-2): 11-17.
- Johnson E, Cotter FE. 1997. Monosomy 7 and 7q—associated with myeloid malignancy. *Blood Rev* 11(1): 46-55.
- Kamata E, Nakadate M, Uchida O, Ogawa Y, Suzuki S, Kaneko T, Saito M, Kurokawa Y. 1997. Results of a 28-month chronic inhalation toxicity study of formaldehyde in male Fisher-344 rats. *J Toxicol Sci* 22(3): 239-254.
- Kerns WD, Pavkov KL, Donofrio DJ, Gralla EJ, Swenberg JA. 1983. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. *Cancer Res* 43(9): 4382-4392.
- Kimbell JS, Gross EA, Richardson RB, Conolly RB, Morgan KT. 1997. Correlation of regional formaldehyde flux predictions with the distribution of formaldehyde-induced squamous metaplasia in F344 rat nasal passages. *Mutat Res* 380(1-2): 143-154.
- Kitaeva LV, Kitaev EM, Pimenova MN. 1990. [The cytopathic and cytogenetic sequelae of chronic inhalational exposure to formaldehyde on female germ cells and bone marrow cells in rats] [in Russian; English translation]. *Tsitologiya* 32(12): 1212-1216.
- Kitaeva LV, Mikheeva EA, Shelomova LF, Shvartsman PY. 1996. Genotoxic effects of formaldehyde in somatic human cells *in vivo*. *Genetika* 32: 1287-1290.
- Krasner SW, McGuire MJ, Jacangelo JG, Patania NL, Reagan KM, Aieta EM. 1989. The occurrence of disinfection by-products in United States drinking water. *J Amer Water Works Assoc* 81(8): 41-53.
- Lavoue J, Vincent R, Gerin M. 2008. Formaldehyde exposure in U.S. industries from OSHA air sampling data. *J Occup Environ Hyg* 5(9): 575-587.
- Li JR, Zhu JL, Ye LF. 2007. Determination of formaldehyde in squid by high-performance liquid chromatography. *Asia Pacific J Clin Nutr* 16(Suppl 1): 127-130.

Report on Carcinogens, Twelfth Edition (2011)

- Li W, Ray RM, Gao DL, Fitzgibbons ED, Seixas NS, Camp JE, et al. 2006. Occupational risk factors for nasopharyngeal cancer among female textile workers in Shanghai, China. *Occup Environ Med* 63(1):39-44.
- Liteplo RG, Meek ME. 2003. Inhaled formaldehyde: exposure estimation, hazard characterization, and exposure-response analysis. *J Toxicol Environ Health B Crit Rev* 6(1): 85-114.
- Liu YR, Zhou Y, Qiu W, Zeng JY, Shen LL, Li AP, Zhou JW. 2009. Exposure to formaldehyde induces heritable DNA mutations in mice. *J Toxicol Environ Health A* 72(11): 767-773.
- Lu K, Boysen G, Gao L, Collins LB, Swenberg JA. 2008. Formaldehyde-induced histone modifications *in vitro*. *Chem Res Toxicol* 21(8): 1586-1593.
- Lu K, Collins LB, Ru H, Bermudez E, Swenberg JA. 2010. Distribution of DNA adducts caused by inhaled formaldehyde is consistent with induction of nasal carcinoma but not leukemia. *Toxicol Sci* 116(2): 441-451.
- Lu Z, Li CM, Qiao Y, Yan Y, Yang X. 2008. Effect of inhaled formaldehyde on learning and memory of mice. *Indoor Air* 18(2): 77-83.
- Luce D, Gérin M, Leclerc A, Morcet JF, Brugère J, Goldberg M. 1993. Sinonasal cancer and occupational exposure to formaldehyde and other substances. *Int J Cancer* 53(2): 224-231.
- Luce D, Leclerc A, Bégin D, Demers PA, Gérin M, Orłowski E, et al. 2002. Sinonasal cancer and occupational exposures: a pooled analysis of 12 case-control studies. *Cancer Causes Control* 13(2): 147-157.
- Marsh GM, Youk AO. 2005. Reevaluation of mortality risks from nasopharyngeal cancer in the formaldehyde cohort study of the National Cancer Institute. *Regul Toxicol Pharmacol* 42(3): 275-283.
- Marsh GM, Youk AO, Buchanich JM, Erdal S, Esmen NA. 2007. Work in the metal industry and nasopharyngeal cancer mortality among formaldehyde-exposed workers. *Regul Toxicol Pharmacol* 48(3): 308-319.
- Matubayasi N, Morooka S, Nakahara M., Takahashi H. 2007. Chemical equilibrium of formaldehyde and methanediol in hot water: free-energy analysis of the solvent effect. *J Molec Liq* 134: 58-63.
- McMartin KE, Martin-Amat G, Noker PE, Tephly TR. 1979. Lack of a role for formaldehyde in methanol poisoning in the monkey. *Biochem Pharmacol* 28(5): 645-649.
- Meng F, Bermudez E, McKinzie PB, Andersen ME, Clewell HJ 3rd, Parsons BL. 2010. Measurement of tumor-associated mutations in the nasal mucosa of rats exposed to varying doses of formaldehyde. *Regul Toxicol Pharmacol* 57(2-3): 274-283.
- Monticello TM, Morgan KT, Everitt JJ, Popp JA. 1989. Effects of formaldehyde gas on the respiratory tract of rhesus monkeys. Pathology and cell proliferation. *Am J Pathol* 134(3): 515-527.
- Monticello TM, Miller FJ, Morgan KT. 1991. Regional increases in rat nasal epithelial cell proliferation following acute and subchronic inhalation of formaldehyde. *Toxicol Appl Pharmacol* 111(3): 409-421.
- Monticello TM, Swenberg JA, Gross EA, Leininger JR, Kimbell JS, Seilkop S, Starr TB, Gibson JE, Morgan KT. 1996. Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells. *Cancer Res* 56(5): 1012-1022.
- Moseley CL, Singal M, Murphy L. 1979. *HHE Determination, Report No. HHE-78-116-557, Commonwealth Trading Company, Stoughton, Massachusetts*. Washington, DC: National Institute for Occupational Safety and Health.
- Murgia E, Ballardini M, Bonassi S, Rossi AM, Barale R. 2008. Validation of micronuclei frequency in peripheral blood lymphocytes as early cancer risk biomarker in a nested case-control study. *Mutat Res* 639(1-2): 27-34.
- Murrell W, Feron F, Wetzig A, Cameron N, Splatt K, Bellette B, et al. 2005. Multipotent stem cells from adult olfactory mucosa. *Dev Dyn* 233(2): 496-515.
- Mutsuga M, Kawamura Y, Sugita-Konishi Y, Hara-Kudo Y, Takatori K, Tanamoto K. 2006. Migration of formaldehyde and acetaldehyde into mineral water in polyethylene terephthalate (PET) bottles. *Food Addit Contam* 23(2): 212-218.
- NTP. 2010. *Report on Carcinogens Background Document for Formaldehyde*. National Toxicology Program. http://ntp.niehs.nih.gov/ntp/roc/twelfth/2009/November/Formaldehyde_BD_Final.pdf.
- O'Neil MJ, Heckelman PE, Koch CB, Roman KJ, Kenny CM, D'Areca MR, eds. 2006. *The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals*, 14th ed. Whitehouse Station, NJ: Merck. pp. 726, 1211, 1672.
- Olsen JH, Jensen SP, Hink M, Faurbo K, Breum NO, Jensen OM. 1984. Occupational formaldehyde exposure and increased nasal cancer risk in man. *Int J Cancer* 34(5): 639-644.
- Olsen JH, Asnaes S. 1986. Formaldehyde and the risk of squamous cell carcinoma of the sinonasal cavities. *Br J Ind Med* 43(11): 769-774.
- Orsiere T, Sari-Minodier I, Iarmarcovai G, Botta A. 2006. Genotoxic risk assessment of pathology and anatomy laboratory workers exposed to formaldehyde by use of personal air sampling and analysis of DNA damage in peripheral lymphocytes. *Mutat Res* 605(1-2): 30-41.
- Ozen OA, Akpolat N, Songur A, Kus I, Zararsiz I, Ozacmak VH, Sarsilmaz M. 2005. Effect of formaldehyde inhalation on Hsp70 in seminiferous tubules of rat testes: an immunohistochemical study. *Toxicol Ind Health* 21(10): 249-254.
- Pala M, Ugolini D, Ceppi M, Rizzo F, Maiorana L, Bolognesi C, et al. 2008. Occupational exposure to formaldehyde and biological monitoring of Research Institute workers. *Cancer Detect Prev* 32(2): 121-126.
- Patel KG, Bhatt HV, Choudhury AR. 2003. Alteration in thyroid after formaldehyde (HCHO) treatment in rats. *Ind Health* 41(3): 295-297.
- Paulsson K, Johansson B. 2007. Trisomy 8 as the sole chromosomal aberration in acute myeloid leukemia and myelodysplastic syndromes. *Pathol Biol (Paris)* 55(1): 37-48.
- Pesch B, Pierl CB, Gebel M, Gross I, Becker D, Johnen G, et al. 2008. Occupational risks for adenocarcinoma of the nasal cavity and paranasal sinuses in the German wood industry. *Occup Environ Med* 65(3): 191-196.
- Pinkerton LE, Hein MJ, Stayner LT. 2004. Mortality among a cohort of garment workers exposed to formaldehyde: an update. *Occup Environ Med* 61(3): 193-200.
- Pyatt D, Natelson E, Golden R. 2008. Is inhalation exposure to formaldehyde a biologically plausible cause of lymphohematopoietic malignancies? *Regul Toxicol Pharmacol* 51(1): 119-133.
- Recio L, Sisk S, Pluta L, Bermudez E, Gross EA, Chen Z, Morgan K, Walker C. 1992. p53 mutations in formaldehyde-induced nasal squamous cell carcinomas in rats. *Cancer Res* 52(21): 6113-6116.
- Ridpath JR, Nakamura A, Tano K, Luke AM, Sonoda E, Arakawa H, et al. 2007. Cells deficient in the FANCD1/BRCA pathway are hypersensitive to plasma levels of formaldehyde. *Cancer Res* 67(23): 11117-11122.
- Roush GC, Walrath J, Stayner LT, Kaplan SA, Flannery JT, Blair A. 1987. Nasopharyngeal cancer, sinonasal cancer, and occupations related to formaldehyde: a case-control study. *J Natl Cancer Inst* 79(6): 1221-1224.
- Sarsilmaz M, Kaplan S, Songur A, Colakoglu S, Aslan H, Tunc AT, Ozen OA, Turgut M, Bas O. 2007. Effects of postnatal formaldehyde exposure on pyramidal cell number, volume of cell layer in hippocampus and hemisphere in the rat: a stereological study. *Brain Res* 1145: 157-167.
- Sellakumar AR, Snyder CA, Solomon JJ, Albert RE. 1985. Carcinogenicity of formaldehyde and hydrogen chloride in rats. *Toxicol Appl Pharmacol* 81(3 Pt 1): 401-406.
- Shaham J, Bomstein Y, Gurvich R, Rashkovsky M, Kaufman Z. 2003. DNA-protein crosslinks and p53 protein expression in relation to occupational exposure to formaldehyde. *Occup Environ Med* 60(6): 403-409.
- Silver SR, Rinsky RA, Cooper SP, Hornung RW, Lai D. 2002. Effect of follow-up time on risk estimates: a longitudinal examination of the relative risks of leukemia and multiple myeloma in a rubber hydrochloride cohort. *Am J Ind Med* 42(6): 481-489.
- Soffritti M, Maltoni C, Maffei F, Biagi R. 1989. Formaldehyde: an experimental multipotential carcinogen. *Toxicol Ind Health* 5(5): 699-730.
- Soffritti M, Belgoggi F, Lambertin L, Lauriola M, Padovani M, Maltoni C. 2002. Results of long-term experimental studies on the carcinogenicity of formaldehyde and acetaldehyde in rats. *Ann N Y Acad Sci* 982: 87-105.
- Songur A, Ozen OA, Sarsilmaz M. 2010. The toxic effects of formaldehyde on the nervous system. *Rev Environ Contam Toxicol* 203: 105-118.
- Speit G, Schütz P, Merk O. 2000. Induction and repair of formaldehyde-induced DNA-protein crosslinks in repair-deficient human cell lines. *Mutagenesis* 15(1): 85-90.
- SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 4/30/09.
- Stewart P, Cubit D, Blair A. 1987. Formaldehyde levels in seven industries. *Appl Ind Hyg* 2(6): 213-236.
- Stewart PA, Schairer C, Blair A. 1990. Comparison of jobs, exposures, and mortality risks for short-term and long-term workers. *J Occup Med* 32(8): 703-708.
- Stewart PA, Herrick RF, Feigley CE, Utterback DF, Hornung R, Mahar H, Hayes R, Douthit DE, Blair A. 1992. Study design for assessing exposures of embalmers for a case-control study. Part I. Monitoring results. *Appl Occup Environ Hyg* 7: 532-540.
- Suruda A, Schulte P, Boeniger M, Hayes RB, Livingston GK, Steenland K, et al. 1993. Cytogenetic effects of formaldehyde exposure in students of mortuary science. *Cancer Epidemiol Biomarkers Prev* 2(5): 453-460.
- Takahashi M, Hasegawa R, Furukawa F, Toyoda K, Sato H, Hayashi Y. 1986. Effects of ethanol, potassium metabisulfite, formaldehyde and hydrogen peroxide on gastric carcinogenesis in rats after initiation with N-methyl-N'-nitro-N-nitrosoguanidine. *Jpn J Cancer Res* 77(2): 118-124.
- Tang X, Bai Y, Duong A, Smith MT, Li L, Zhang L. 2009. Formaldehyde in China: Production, consumption, exposure levels, and health effects. *Environ Int* 35(8): 1210-1224.
- Thompson CM, Sonawane B, Grafstrom RC. 2009. The ontogeny, distribution, and regulation of alcohol dehydrogenase 3: implications for pulmonary physiology. *Drug Metab Dispos* 37(8): 1565-1571.
- Titenko-Holland N, Levine AJ, Smith MT, Quintana PJ, Boeniger M, Hayes R, Suruda A, Schulte P. 1996. Quantification of epithelial cell micronuclei by fluorescence *in situ* hybridization (FISH) in mortuary science students exposed to formaldehyde. *Mutat Res* 371(3-4): 237-248.
- USDL. 2009. *Occupational Exposure to Formaldehyde*. OSHA Fact Sheet no. 92-27. U.S. Department of Labor. <http://ehs.okstate.edu/training/OSHAHYD.HTM>. Last accessed: 12/18/09.
- Vaughan TL, Strader C, Davis S, Daling JR. 1986. Formaldehyde and cancers of the pharynx, sinus and nasal cavity: I. Occupational exposures. *Int J Cancer* 38(5): 677-683.
- Vaughan TL, Shapiro JA, Burt RD, Swanson GM, Berwick M, Lynch CF, Lyon JL. 1996. Nasopharyngeal cancer in a low-risk population: defining risk factors by histological type. *Cancer Epidemiol Biomarkers Prev* 5(8): 587-593.
- Vaughan TL, Stewart A, Teschke K, Lynch CF, Swanson GM, Lyon JL, Berwick M. 2000. Occupational exposure to formaldehyde and wood dust and nasopharyngeal carcinoma. *Occup Environ Med* 57(6): 376-384.
- Wang B, Liu DD. 2006. [Detection of formaldehyde induced developmental toxicity assessed with single cell gel electrophoresis] [in Chinese; English translation]. *Fen Zi Xi Bao Sheng Wu Xue Bao* 39(5): 462-466.
- Wang M, Cheng G, Balbo S, Carmella SG, Vailata PW, Hecht SS. 2009. Clear differences in levels of a formaldehyde-DNA adduct in leukocytes of smokers and nonsmokers. *Cancer Res* 69(18): 7170-7174.
- West S, Hildesheim A, Dosemeci M. 1993. Non-viral risk factors for nasopharyngeal carcinoma in the Philippines: results from a case-control study. *Int J Cancer* 55(5): 722-727.
- WHO. 2000. *Air Quality Guidelines for Europe*, 2nd ed. World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf.
- WHO. 2002. *Formaldehyde: Concise International Chemical Assessment Document 40*. World Health Organization. <http://www.inchem.org/documents/cicads/cicads/cicad40.htm>.

Report on Carcinogens, Twelfth Edition (2011)

WHO. 2005. *Formaldehyde in Drinking-water. Background Document for Development of WHO Guidelines for Drinking-water Quality*. World Health Organization. http://www.who.int/water_sanitation_health/dwq/chemicals/formaldehyde130605.pdf.

Ye X, Yan W, Xie H, Zhao M, Ying C. 2005. Cytogenetic analysis of nasal mucosa cells and lymphocytes from high-level long-term formaldehyde exposed workers and low-level short-term exposed waiters. *Mutat Res* 588(1): 22-27.

Ying CJ, Yan WS, Zhao MY, Ye XL, Xie H, Yin SY, Zhu XS. 1997. Micronuclei in nasal mucosa, oral mucosa and lymphocytes in students exposed to formaldehyde vapor in anatomy class. *Biomed Environ Sci* 10(4): 451-455.

Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT. 2009a. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. *Mutat Res* 681(2-3): 150-168.

Zhang L, Freeman LE, Nakamura J, Hecht SS, Vandenberg JJ, Smith MT, Sonawane BR. 2010a. Formaldehyde and leukemia: Epidemiology, potential mechanisms, and implications for risk assessment. *Environ Mol Mutagen* 51(3):181-191.

Zhang L, Tang X, Rothman N, Vermeulen R, Ji Z, Shen M, *et al.* 2010b. Occupational exposure to formaldehyde, hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells. *Cancer Epidem Bio Prev* 9(1):80-88.