

THE TOXICOLOGY OF FORMALDEHYDE

WHAT IS FORMALDEHYDE AND HOW IS IT USED?

Formaldehyde is a colorless, pungent gas which polymerizes slowly at room temperature. The four basic uses for formaldehyde include use as a bactericide or fungicide, in the production of resins, as intermediates in the production of chemicals, and as a component of end-use consumer items. Formaldehyde is also used as embalming fluid and in textile treating to impart wrinkle-resistance to clothing.

Facilities reporting the highest exposures (0.1 to above 1.0 ppm) to formaldehyde include those producing hardwood plywood, particle board, fiberboard and resins as well as foundries, laboratories and funeral services. Industries in textile finishing, apparel manufacturing, formaldehyde production and plastic molding have the next highest exposures ranging from 0.1 to 1.0 ppm. A long list of facilities have exposures to low concentrations (0.1 - 0.5 ppm), among them being pulp, paper and paperboard mills, softwood plywood manufacturers, manufacturers of various cardboard and paper products, paint, pigment and dye manufacturers, photo finishing labs, hemodialysis units, biology and veterinary labs, and various facilities dealing with electrical devices.

ACUTE TOXICITY

Formalin (aqueous formaldehyde) is highly acutely toxic with deaths occurring with as little as 30 milliliters (ml, about one ounce) ingested. The inhalation of high concentrations of formaldehyde is also extremely dangerous, with the IDLH (Immediately Dangerous to Life and Health) concentration being 100 ppm. Accidental splash exposures into the eyes may cause blindness especially in cases where immediate flushing of the eyes with water does not occur.

Irritation of eyes, nose, throat and chest is an acute response to formaldehyde that diminishes rapidly upon removal from exposure. OSHA reports that irritation complaints occur from employees manufacturing particle board and molded plastics at levels of 0.4 to 1.0 ppm, by foundry care room workers exposed to more than 1 ppm, by dialysis nurses exposed to 0.26 to 0.4 ppm, by embalmers exposed to 0.25 to 1.39 ppm, by carpenters exposed to formaldehyde treated wood at 0.35 ppm, by textile finishers exposed at 0.16 to 1.2 ppm, and by garment workers with exposures of 0.42 to 0.50 ppm. In an independent clinical study, irritation at concentrations up to 0.04 ppm in 2% to 4% of those tested was reported.

A major effect of formaldehyde on the skin is dermatitis, both irritant dermatitis and "allergic" contact dermatitis which results in a small percentage of the population. Formaldehyde had also been reported to cause hives. Although there is some absorption of formaldehyde through the skin, it is not considered significant.



Formaldehyde has also been reported to cause asthma which may develop within minutes of exposure or several hours after the exposure, either during the latter part of the work day or after returning home. The development of asthma may be influenced by continuous or intermittent exposures. Exposures to high concentrations for a short period may be more hazardous in causing asthma than exposure to low concentrations over an extended period.

CANCER EPIDEMIOLOGY

Lung Cancer

Several recently published epidemiological studies have been instrumental in the development of the new formaldehyde regulations. Perhaps the most important as well as controversial study was conducted and published by the National Cancer Institute (NCI). In one of the largest cohort mortality analyses, 26,561 workers employed prior to January 1, 1966, were studied for excess lung cancer. Investigators compared the mortality of formaldehyde-exposed workers with that of the United States population, the local population and non-exposed workers.

Although a significant increase in lung cancer was observed in the worker population, the investigators (Blair, et al.) concluded that "these data provide little evidence that mortality from cancer is associated with formaldehyde exposures at levels experienced by workers in this study" primarily due to a lack of correlation between increased cancer risk and increased dose (as measured by cumulative exposure). The investigators' comments were met with much criticism from other scientists who reviewed the raw data from the study.

A five member Advisory Panel to the study concluded that, "The finding of a significant increase in the risk for lung cancer...makes up particularly hesitant to characterize this as a study with evidence to exonerate formaldehyde as a carcinogen." Likewise, the National Institute for Occupational Safety and Health (NIOSH -- the research branch affiliated with OSHA) concluded that, "Sufficient evidence exists...to conclude that there are significant excesses of lung cancer...The absence of an exposure-response trend is not sufficient cause to discount the observed lung cancer excesses..."

Federal OSHA agreed with both the Advisory Panel and NIOSH stating that a significant increase in lung cancer can determine carcinogenicity even if the study failed to establish a dose-response curve.

Two independent researchers (Sterling and Weikam) proceeded to statistically reexamine the data from the NCI study. The researchers reconfirmed a significant lung cancer excess. Among the criticisms submitted primarily by the Formaldehyde Institute and Dupont, their analyses failed to correct for cigarette smoking as well as other items. OSHA defined their analyses by noting that the percentages of deaths resulting from lung cancer in formaldehyde-exposed workers were excessively high and significant.

Another independent researcher (Sielken) took the raw data from the NCI study and correlated the formaldehyde exposure data with the likelihood of dying from cancer of the respiratory system and lung cancer.

The United Auto Workers (UAW) reanalyzed a section of the NCI study and concluded an increasing likelihood of death due to lung cancer. They also discovered that persons exposed at the highest cumulative doses were less likely to smoke because of formaldehyde's irritant effects.

In summary, OSHA's position was that there was no dose-response relationship in the NCI study due to exposure misclassifications and due to the fact that cigarette smoking was not evident in workers with the highest cumulative doses. OSHA supported the study's finding that there was a significant increase in lung cancer in workers with 20 or more years of latency. They also noted the probability of a trend of an increased risk of lung cancer with an increase in the average level of formaldehyde exposure.

OSHA also noted a British study of lung cancer which concluded a significant excess of lung cancer among workers at the highest exposure level (greater than 2.0 ppm) after comparison with national rates of lung cancer. A significant increase in risk of death from chronic bronchitis was also observed. A possible dose-response relationship was noted. Although the authors downplayed the validity of their cancer results due to the high national rates of lung cancer, OSHA discounted their downplay and supported the study's findings.

Nasopharyngeal Cancer

The NCI study also noted an "increased risk of death from cancer of nasopharynx with an increased cumulative exposure to formaldehyde...(however) a not statistically significant (but) a striking dose-response gradient was observed by the authors." OSHA supported the importance of the study in relating formaldehyde concentration to nasopharyngeal cancer. Excursions to levels exceeding 4 ppm were noted. Cancer was also observed in workers exposed to high concentration for less than 1 year. The Formaldehyde Institute and Cyanamid Company criticized the study stating that the formaldehyde exposure was mixed with a particulate exposure, that there were only 3 cancer cases of the 7 total who were exposed for less than 1 year and that there were no cases observed in workers with the highest cumulative exposure. OSHA regarded the criticisms as insignificant.

In another study conducted by an independent researcher (Vaughan et al.) in the state of Washington, residents living in mobile homes exposed to formaldehyde through formaldehyde-treated building materials, as well as occupations dealing with resin and glue work (i.e., carpenters with less than a 0.5 ppm exposure, and furniture assemblers, cabinet makers and sewing machine operators having exposures greater than 0.5 ppm) were studied. Due to the extremely low exposure potential and cancer risk observed in most of the workers, OSHA concluded that it was inappropriate to conclude that the occupational study was negative even though excess cancer was not observed.

On the other hand, the residential exposures were greater than the workplace exposures from the standpoint of cumulative dose. Exposures lasting up to 168 hours (compared to typical 40 hour a week work exposures) were observed with concentrations in new mobile homes of years ago averaging as much as 0.5 ppm. OSHA determined that formaldehyde exposure is probably associated with the development of nasopharyngeal cancer in humans. Although rare, nasopharyngeal cancer existed with a background rate of approximately half of that seen in home residents.

Oral Cancer

The National Institute of Occupational Safety and Health (NIOSH) conducted a study on workers exposed to formaldehyde in the garment industry manufacturing permanent press garments. Workers were exposed for at least 3 months to concentrations of 0.14 to 0.17 ppm. The investigators reported excess oral cancer. OSHA, however, severely criticized the study stating that "some evidence of an association between formaldehyde exposure and oral cancer (existed) but not necessarily a causal relationship." OSHA criticized the study for limited latency periods, a middle-aged female population and a low percentage (5.5%) of deaths from cancer.

Brain Cancer

Brain cancer has been reported in pathologists, anatomists, morticians, embalmers and funeral directors exposed to embalming fluid or other tissue preservatives containing formalin. Exposure concentrations were not given. OSHA stated that the exposure "probably" contributed to the excess risk of brain cancer observed in professional workers but was unable to reach a determination that brain cancer is caused by exposure to formaldehyde.

Other Cancers

Leukemia has been reported in embalmers. OSHA's position was similar to that stated above for reports of brain cancer.

ANIMAL CANCER STUDIES

Several laboratories have studied cancer in animals. The one of greatest interest was conducted by Battelle Columbus Laboratories for the Chemical Industry Institute of Toxicology (CIIT). 120 male and female animals of each of two species, one rat and one mouse, were exposed for 6 hours/day, 5 days a week at concentrations averaging 2.0, 5.6, and 14.3 ppm in an inhalation experiment for 24 months (the average lifespan of a rodent). In the rats, there was a significant increase in nasal cancers at the highest concentration. The number of nasal cancers in mice was insufficient to show statistical significance, but were considered formaldehyde related due to pathological examination. No increase in leukemia, lymphomas, or brain cancer were observed.

Other studies support their finding of nasal cancer. New York University conducted studies in which formaldehyde was administered in a strain of rats different from that used in the CIIT study. OSHA concluded that the NYU studies confirmed that exposure to formaldehyde can cause cancer in animals. An independent inhalation animal study (Tobe et al.) also reported nasal cancer after formaldehyde exposure even though only a small number of animals were used in the experiment. An inhalation hamster study conducted by yet another independent laboratory reported no tumors, but due to the many scientific flaws in the study (decreased rodent survival time, limited experience at detecting tumors) OSHA discounted the study.

Other studies have been conducted demonstrating that formaldehyde applied topically to the skin of laboratory animals does not cause cancer.

OSHA concluded that the finding of nasal cancer in two strains of rats in three independent studies on formaldehyde alone to be extremely strong and reproducible evidence that formaldehyde is an animal carcinogen. Evidence of a dose-response relationship, finding cancers of identical cell-type and location in two species and evidence that formaldehyde is genotoxic (see below) strengthens the scientific relationship of formaldehyde exposure causing cancer.

Genotoxicity

Formaldehyde appears to be capable of binding to DNA, a well-known mechanism by which chemicals cause cancer. Formaldehyde appears to be both an initiator and a late-stage cancer causing chemical.

OSHA RISK ASSESSMENTS

OSHA believes that the CIIT study on rats provides evidence that formaldehyde causes cancer in mammals and that it is the best study on which to extrapolate cancer risk to humans. The multistage model (a mathematical model used for extrapolating the lower end of the dose-response curve to large populations and low dosages) has been endorsed by both EPA and OSHA and was used for risk assessment. The range of risks predicted is 0.56 to 264 cases per 100,000 workers for a 1 ppm exposure lasting 8 hours per day, days per week. (The previous PEL(3 ppm) ranged from 43 to 1,819 cases of cancer per 100,000 workers.) OSHA believes that the available information is not adequate to further quantitate risk for short-term exposures. The previous standard permitted ceiling exposures to 2 ppm. The new STEL requirement and other provisions of the revised standard should provide protection to employees to reduce cancer risk.

OSHA also estimated risk of sensory irritation. OSHA's assessment is based primarily on two sources of data, a study of volunteer subjects and data collected on nose and eye irritation in 17 industries. It was estimated that exposures over 3 ppm would be nearly intolerable to all workers, and between 1 and 3 ppm all workers would experience some discomfort to strong discomfort. For exposures between 0.5 and 1 ppm, 31 to 94% were expected to experience slight discomfort.

Although other scientists conducted and submitted cancer risk assessments differing from that of OSHA'S, OSHA discounted the differences as due to their use of studies other than the CIIT rat study used by OSHA and their choice of different models to fit the data. OSHA reaffirms the scientific validity of their risk assessment procedures.

Note: This guide is intended for the informational benefit of the public and may not contain all of the information pertinent to specific issue. For further information, consult the Preamble to the Formaldehyde Standard or the Consultation Education and Training Division at (517) 284-7720.