

A Review of the Health Effects of Formaldehyde Toxicity

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Running Headline: Effects of formaldehyde on health

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Summary:

Anatomists, technicians, medical or veterinary students and embalmers are among the people who have a great risk for formaldehyde toxicity. Inhaled formaldehyde primarily affects the airways; the severity and extent of physiological response depends on its concentration in the air. Acute inhalation exposure to formaldehyde causes histopathologic damage and DNA-protein cross-linking in the nasal mucosa of rats and rhesus monkeys. Although not definitely established, formaldehyde is a potential agent to cause carcinoma in the nasal cavity of human beings, but the carcinogenic effect of it is experimentally proven in rats. Accidental or suicidal ingestion of formaldehyde solution is an indication for emergency esophagoscopy and laparotomy. However, no significant embryoletality nor malformations were observed in the offspring of mice, dogs or hamsters exposed to formaldehyde orally or percutaneously during the major period of organogenesis. Additionally, no evidence of immunosuppression was observed in mice and rats exposed to a high concentration of formaldehyde. As a result, the concentration of formaldehyde in the working environment must be controlled continuously and occupational exposure limits for this compound, existing in some countries must always be remembered.

Key Words: Formaldehyde, effects on health

Formaldehyde was discovered by Butlerov in 1859, and it has been manufactured commercially since the early 1900s. It is produced by the oxidation of methanol with air in the presence of a silver or an iron oxide - molybdenum oxide catalyst. Anhydrous gaseous formaldehyde is not available commercially. Most formaldehyde is sold in the form of aqueous solutions containing 30-56% formaldehyde with 0.5-15% methanol as an inhibitor of polymerization (Gerberich et al.,1980). Approximately 30 years following its discovery, formaldehyde was introduced to the medical world as a disinfectant and tissue hardener (Walker,1964; Cox,1984). It has been a popular constituent of embalming solutions since about 1900 (Plunkett and Barbella,1977).

Formaldehyde is a highly reactive one-carbon compound (Fielder et al.,1981). It has a characteristic odour in air in the 0.1-1.0 ppm concentration range (Loomis,1979; Brabec,1981). In biological systems formaldehyde undergoes hydration in the presence of water, reacts with the active hydrogen of many compounds such as ammonia, amines, amides, thiols, phenols and nitro-alkanes, and condenses with hydrogen chloride in the presence of water to form chloromethyl ether, an acknowledged carcinogen in both humans (Weiss et al.,1979) and animals (Van Duuren et al.,1958).

Gross anatomy laboratories are environments of chronic exposure to formaldehyde vapors. Additionally, formaldehyde is widely used in the manufacture of resins and plastics and in the synthesis of intermediates in the chemical industry. It is also used as a fumigant in agriculture, in embalming fluids and in the manufacture of crease-resistant garments.

The toxicity of formaldehyde is of concern to all who work closely with it. Embalmers, anatomists, technicians and medical or veterinary students are among the people who have high exposure to formaldehyde.

Early users were aware of formaldehyde's pungent odour and local irritant qualities (Yodaiken,1981). More recently, it has been recognized as an allergic skin sensitizer (Loomis,1979; Bernstein et al.,1984) and a potential carcinogen (Kerns et al.,1983; Holmström et al.,1989a). Nevertheless, its popularity and use continues. This has stimulated further research into the detection and toxicity of formaldehyde so that the benefits of use may be weighed against the risks (Bernstein et al.,1984; Skisak,1983).

The presence of formaldehyde in biologically active concentrations in several occupational and environmental atmospheres has created concern about the hazards of exposure to these contaminated atmospheres. A review of the clinical and animal toxicologic data demonstrate both primary irritant and sensitizing actions of the compound. The minimal concentration of formaldehyde that can be detected by odour is similar to the level that produces minimal irritant effects on the eyes and in the pulmonary airway, thereby serving as a warning of exposure to the compound. The irritant effects are reversible when exposure is discontinued. Some people show allergic type responses to concentrations of the compound that are well below the odour threshold (Loomis,1979).

Formaldehyde is a noxious gas and classed as an upper respiratory irritant, because it has a high solubility in water and is therefore held by the moisture covering the respiratory passages (Gross et al.,1967). During respiration through the nose, most of the formaldehyde in the inhaled air is absorbed into the nasal mucosa and the remaining small amount reaches the lower airway tract (Andersen and Proctor,1982). Because formaldehyde is an irritant for mucous membranes, as it travels to the lower airway tract in the inhaled air, it causes irritation in the mucous membranes of the nose, pharynx, larynx and lower airways. Andersson and Mölhavé (1983) concluded that, a formaldehyde concentration higher than 0.5 mg/m³ caused dose related symptoms like dryness in the nose, throat and conjunctiva. As exposure levels increase, formaldehyde also causes lower respiratory tract irritation. Additionally, chronic exposure may cause burning and tightness of chest and some vegetative and neurobehavioral changes including headache, nausea and irritability (Kilburn et al.,1985). Increasing levels of exposure to formaldehyde may lead to discomfort starting from mild tingling, sensation in the eyes, nasal cavity and pharynx to lacrimation, severe burning sensation in the nose, throat and trachea and coughing (Kulle and Cooper,1975). Respiration is reflexly inhibited by formaldehyde through its action on trigeminal nerve endings in the nasal deposition especially after long terms of exposure (Cham,1985).

The effect of formaldehyde on respiratory tract was shown with rhinomanometry which revealed more pronounced obstruction in formaldehyde exposed objects. Mucociliary clearance was slower, sense of smell was decreased and spirometric analysis had lower FVC (Forced Vital Capacity) values than expected in the formaldehyde exposed objects (Holmström and Wilhelmsson,1988).

Inhaled formaldehyde primarily effects the airways; the severity and extent of physiological response depend on its concentration in the air. As the concentration increases, cell proliferation and cell death increase and, as in animals, there is a dose-dependent decrease in mucociliary activity (Morgan et al.,1986a). The relatively low threshold of response and the disagreeable, irritating odour of formaldehyde prevent one from breathing intolerable amounts of the gas. In rare massive acute exposures, victims have suffered pulmonary edema and even death. Relatively low concentrations have provoked or exacerbated asthmatic symptoms in some individuals (Wilhelmsson and Holmström,1987).

Acute inhalation exposure to formaldehyde causes histopathologic damage (Chang et al.,1983) and DNA-protein cross-linking in the nasal mucosa of rats and rhesus monkeys (Auerbach et al.,1977; Martin et al.,1978; Griesemer et al.,1982; Casanova et al.,1989). At formaldehyde concentrations 5.6 ppm and over, rats developed squamous cell carcinomas in the nasal cavity (Kerns et al.,1983), again exclusively in the respiratory epithelial regions (Morgan et al.,1986b). Chronic exposure to formaldehyde may lead to conditions like a decrease in the sense of smell, pharyngitis, laryngitis and emphysema. Besides, formaldehyde exposure for a long period of time may cause carcinomas although not proven in human objects (Halperin et al.,1983; Holmström et al.,1989a). During chronic irritation of respiratory tract mucosa, hyperplasia of mucous glands and goblet cells of the epithelium may arise. Mononuclear infiltration, loss of cilia and metaplastic changes of the epithelium may be seen (Holmström et al.,1989a).

Rabbits, mice and guinea pigs, which are exposed to 16 ppm of formaldehyde vapor for 10 hours led to edema and hemorrhage in lungs, consolidation, distention of alveoli and rupture of alveolar septa with death of some animals. Formaldehyde inhalation of 35 ppm for 18 hours resulted in irritation in eye and nose, and dyspnea in rats (Kulle and Cooper,1975).

Although not definitely established, formaldehyde is a potential agent to cause carcinoma in the nasal cavity of human beings. Since the most pronounced effects of formaldehyde is observed in the nasal mucosa, most of its carcinogenic effect is assumed to occur in the nasal cavity, although some indicates its effects in the oral cavity and pharynx (Hayes et al.,1986).

These not definitely proven conditions are supported by the positive findings obtained from animal experiments, especially from those in which rats are used. The

carcinogenic effect of formaldehyde exposure is experimentally proven in rats. When rats are exposed to formaldehyde gas, most of it is absorbed in the nasal mucosa during inhalation. This may lead to squamous cell metaplasia and eventually to squamous cell carcinomas in the nasal mucosa of rats, besides other types of neoplasms (Holmström et al.,1989a; Feron et al.,1988; Swenberg et al.,1980). Carcinomas in the nasal cavity of rats are mostly localized in the anterior portion of the lateral surface of the nasoturbinates and adjacent lateral wall or midventral septum (Morgan et al.,1986b).

The effects of formaldehyde on the electrical activity of the nasopalatine nerve was studied in anesthetized rats. When formaldehyde was presented continuously for one hour, it produced a decrease in nasopalatine nerve response to amyl alcohol that varied directly with the formaldehyde concentrations employed. Perfusion of the nasal cavities with air for one hour following the formaldehyde exposure resulted in a partial recovery of the neural response to amyl alcohol (Kulle and Cooper,1975).

Accidental or suicidal ingestion of formaldehyde solution is an indication for emergency esophagoscopy and laparotomy. If necessary, total gastrectomy without immediate reanastomosis can be safely done, leaving reconstruction of the intestine for a later date when the suitability of tissues for anastomosis can be determined (Allen et al.,1970). Roy et al. (1962) reported a case of corrosive gastritis after 240 ml of 37% formaldehyde ingestion. The severity of corrosive injuries are directly related to the agent ingested and its concentration and duration of contact with the viscus (Daly and Cardona,1961).

No significant embryolethality nor malformations were observed in the offspring of mice, dogs or hamsters exposed to formaldehyde orally (mice, dogs) or percutaneously (hamsters) during the major period of organogenesis (Hurni and Ohder,1973; Marks et al.,1980; Overman,1985). Saillenfait et al. (1989) examined the effects of maternally inhaled formaldehyde on embryonal and foetal development in rats and the results of their study show that formaldehyde is slightly foetotoxic at 20 ppm. Neither embryolethal nor teratogenic effects were observed following inhalation exposure at levels up to 40 ppm.

Holmström et al. (1989b) vaccinated the rats with pneumococcal polysaccharide antigens and tetanus toxoid to evaluate the immunologic effects of long-term formaldehyde exposure. The antibody response to vaccination was measured three to four weeks later by enzyme-linked immunosorbent assay and as a

result there were no signs of impaired B-cell function in rats exposed to a high concentration (12.6 ppm) of formaldehyde for nearly two years. Following a 21-day (6 hr/day) inhalation exposure to 15 ppm of formaldehyde, no evidence of immunosuppression was observed in mice (Dean et al.,1984).

In an effort to understand the susceptibility or resistance of cells to formaldehyde toxicity, it is of interest to investigate the capability of specific cell types to detoxify formaldehyde. Formaldehyde may be detoxified principally via action of formaldehyde dehydrogenase (FDH), a specific enzyme that catalyzes the conversion of formaldehyde, glutathione and NAD⁺ to S-formylglutathione and NADH (Uotila and Mannervik,1979; Pourmotabbed and Creighton,1986). Since FDH is a glutathione requiring enzyme, the pool of glutathione available for formaldehyde binding is important in regulating FDH activity. FDH activity is present in tissues lining the nasal airways and is especially prominent in the luminal epithelial cells of the olfactory and respiratory mucosae. Only a weak reaction product is observed in the epithelial lining of the trachea and major bronchi, being present in both ciliated and non-ciliated cells. However, in the terminal bronchioles there is prominent FDH activity, especially in the apical cytoplasm of Clara cells. In the liver, hepatocyte cytoplasm shows a high FDH activity, while reaction product is absent from hepatocyte nuclei and a narrow perinuclear zone. However, centrilobular hepatocytes close to central veins show weaker staining. Sinusoidal epithelium and Kupffer cells show no evidence of FDH activity. In kidney, prominent deposits of FDH reaction product are present throughout the renal cortex, being especially strong in epithelial cells lining proximal convoluted tubules. Glomeruli, distal tubules and collecting ducts have little or no FDH activity. In the brain, FDH activity is especially strong in white matter associated with myelinated axons, prominent but less distinct in the neuropil of gray matter and very weak or absent in neuronal perikarya. Muscle tissue show a characteristic pattern of FDH activity. In bone, osteocytes and periosteum show distinct FDH activity (Keller et al.,1990).

Conclusion:

A review of the literature in this study demonstrates the primary irritant and sensitizing actions of the formaldehyde. These effects are of concern to all, who work closely with it. Additionally, the carcinogenic effect of formaldehyde exposure is experimentally proven in rats and there are also a few indefinitely established reports about the carcinogenic effect of this compound in human beings. Therefore, the concentration of formaldehyde in the working environment must be minimal and it must be controlled continuously. Secondly, the exposure time to formaldehyde must

also be taken into consideration by the workers and occupational exposure limits for this compound, existing in some countries must always be remembered.

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