

## Original article

# Formaldehyde: its effects on human health and management

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### Abstract:

Formaldehyde is commonly used as formalin, a mixture of 30-50% formaldehyde and 10-20% methyl alcohol in water. Formalin readily gives off irritating vapors with a strong odor. It is found in insulation materials, plywood, particle board, adhesives, glues, paint primers and fingernail products. Formaldehyde can affect us when we breathe its vapors or touch the liquid. Because formaldehyde reacts quickly with body tissues, it mainly affects the place of direct contact, such as the eyes, nose, and skin. The most common effect of overexposure is irritation of the eyes, nose and throat. The aim of this article is to summarize the various applications, potential hazards and management of formaldehyde effects in the laboratories.

**Keywords :** Formalin; Occupational Safety and Health Administration (OSHA); environmental tobacco smoke (ETS); Xenobiotics; Bacteriostatic; Micronuclei.

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### Introduction

Formaldehyde (H<sub>2</sub>C=O) is a flammable, colorless reactive and readily polymerized gas at normal room temperature and pressure, with a relative molecular mass of 30.03 and a pungent odor. Formaldehyde is the most common aldehyde in the environment. It is soluble in water, ethanol and diethyl ether and is used in solution or in polymerized form (paraformaldehyde). Formaldehyde is used as a disinfectant and sterilant, fumigant, preservative, and in embalming fluid and in some keratin-based hair smoothing treatments. It is formed naturally in the troposphere during the oxidation of hydrocarbons. The most important man-made source of formaldehyde is automotive exhaust from engines not fitted with catalytic converters. The natural background concentration is < 1 µg/m<sup>3</sup> with a mean of about 0.5 µg/m<sup>3</sup>. In urban environments, outdoor air concentrations are more variable and depend on

local conditions; annual averages are usually between 1 and 20 µg/m<sup>3</sup>. The possible routes of exposure to formaldehyde are ingestion, inhalation, dermal absorption and, rarely, blood exchange as in dialysis.

Communication standard is the Occupational Safety and Health Administration (OSHA) regulation that requires evaluation and communication to employees of all chemical hazards in the work place. OSHA and Centre for Disease Control and prevention (CDC) in 1970 gave safety regulations for clinical laboratories with numerous safety standards in a clinical set up. They insisted that each employee who works with or around hazardous chemicals must receive information about those chemicals through a comprehensive training program. The OSHA Formaldehyde Standard was written to protect employees who came into contact with formaldehyde. The formaldehyde standard is in addition to the provisions of the hazard

communication standard covering exposures to all hazardous chemicals or substances. The fact that formaldehyde is the subject of its own federal regulation should emphasize the need to protect employees from exposure.

#### **Formaldehyde exposure and regulation-**

Anatomy and pathology laboratories are the primary sources of formaldehyde exposure in India. Recently however, exposure from newly remodeled homes, offices, public settings, food, fabrics, carpets, and even from ambient air in major cities has dramatically increased. Formaldehyde levels between 0.1 and 0.5 parts per million (ppm, about 0.12–0.6 mg/m<sup>3</sup>) are detectable by human senses, between 0.5 and 1.0 ppm (0.6–1.2 mg/m<sup>3</sup>) can cause eye irritation, and above 1.0 ppm (1.23 mg/m<sup>3</sup>) can irritate the nose and throat (NICNAS, 2006).

#### **Routes of exposure**

The possible routes of exposure to formaldehyde are ingestion, inhalation, dermal absorption and, rarely, blood exchange as in dialysis. Assuming a breathing volume of 20 m<sup>3</sup>/day for an average adult, given the air levels mentioned above and making assumptions of the time spent in various environments, one can calculate inhalation exposure per day. Average time estimates lead to the conclusion that people spend

60–70% of their time in the home, 25% at work and 10% outdoors. If one assumes that normal work exposures are similar to home exposures, and the data given on the occurrence of formaldehyde in air are used, the daily exposure resulting from breathing is about 1 mg/day, with a few exposures at > 2 mg/day and a maximum of about 8 mg/day.

#### **1. Occupational exposure**

Occupational exposure may contribute considerably to total exposure. For example, a high occupational exposure (e.g. in formaldehyde or resin production, or during disinfection procedures or embalming of bodies) of 1 mg/m<sup>3</sup> for a 25% time-weighted period during which 8 m<sup>3</sup> air is breathed would give an intake of about 8 mg/day.

#### **2. Smoking**

Concentrations of 60–130 mg/m<sup>3</sup> have been measured in mainstream cigarette smoke. For a person smoking 20 cigarettes per day, this would lead to an exposure of 1 mg/day. Exposure to side-stream smoke (or environmental tobacco smoke, ETS) can be estimated from chamber measurements. When six cigarettes were smoked in a 50-m<sup>3</sup> test chamber with one air change per hour, formaldehyde levels were over 0.12 mg/m<sup>3</sup> within 15 minutes.

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S.NO.	Source	Concentration (mg/m <sup>3</sup> )	Exposure
1	Ambient air (10% of time; 2 m <sup>3</sup> /day)	0.001 – 0.02	0.002 – 0.04
2	Indoor air Home (65% of time; 10 m <sup>3</sup> /day)		
	– conventional	0.03 – 0.06	0.3 – 0.6
	– mobile home	0.1	1.0
	– environmental tobacco smoke	0.05 – 0.35	0.5 – 3.5
3	Workplace (25% of time; 8 m <sup>3</sup> /day)		
	– without occupational exposure A	0.03 – 0.06	0.2 – 0.5
	– with occupational exposure	0.1	8.0
	– environmental tobacco smoke	0.05 – 0.35	0.4 – 2.8
4	Smoking (20 cigarettes/day)	60 – 130	0.9 – 2.0 B

A - Assuming the normal formaldehyde concentration in conventional buildings.

B - Total amount of formaldehyde in smoke from 20 cigarettes.

### 3. Drinking-water

Except for accidental contamination of water with formaldehyde, concentrations in drinking water can be expected to be less than 0.1 mg/litre; intake from this source can therefore be considered negligible (below 0.2 mg/day).

### 4. Food

Formaldehyde occurs naturally in foods, and foods may be contaminated as a result of fumigation (e.g. of grain), cooking (as a combustion product) and release from formaldehyde-resin-based tableware. Formaldehyde has been used as a bacteriostatic agent in some foods, such as cheese. Fruits and vegetables typically contain 3–60 mg/kg, milk and milk products about 1 mg/kg, meat and fish 6–20 mg/kg and shellfish 1–100 mg/kg. The daily intake is difficult to evaluate, but a rough estimate from the available data is in the range of 1.5–14 mg/day for an average adult.

### 5. Other exposures

Cosmetic products containing formaldehyde, formalin and/or paraformaldehyde may come into

contact with hair (e.g. shampoos and hair preparations), skin (deodorants, bath products, skin preparations and lotions), eyes (mascara and eye make-up), oral mucosa (mouthwashes and breath fresheners), vaginal mucosa (vaginal deodorants) and nails (cuticle softeners and nail creams and lotions). Exposure from most of these sources is localized, although some formaldehyde is available for inhalation (e.g. from shaving creams). Contact with liquid barriers, as in the eyes and vagina, does not appear to lead to significant absorption. There have been reports of newborn infants being exposed to formaldehyde containing disinfectants in incubators. In certain rare events, formaldehyde in aqueous solution enters the bloodstream directly. These events are most likely to occur in dialysis or in surgery with assisted circulation, in which the dialysis machine and tubes are disinfected with formaldehyde. Formaldehyde from adsorption or backwashes can then enter the patient's bloodstream.

### Relative significance of different routes of exposure

At levels to which humans may be exposed, adverse effects are most likely to be observed primarily following inhalation. It has been shown experimentally that effects on organisms (e.g. mammals) are more closely related to concentration than to the accumulated total dose; this is due to the rapid metabolism and high reactivity and water solubility of formaldehyde. Dermal exposure predominantly affects the skin itself, and little if any formaldehyde reaches the bloodstream. There is a relatively large exposure to formaldehyde from ingestion of food, but most of it is present in a bound form. Blood exchange is a critical form of exposure but is very rare, even in the very small segment of the population at risk.

### Toxicokinetics

#### Absorption

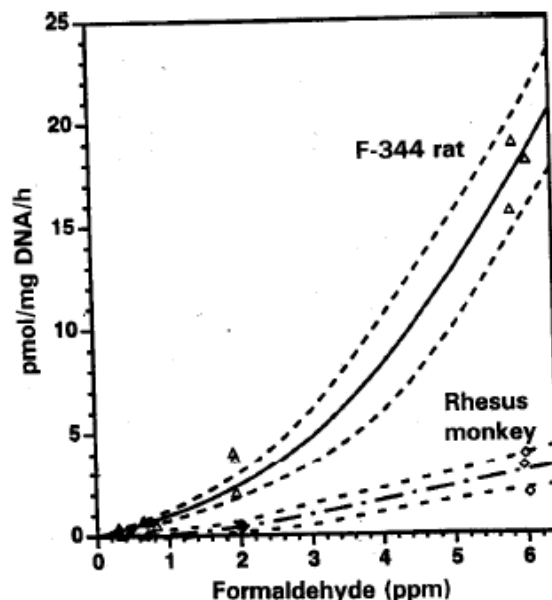
Owing to its solubility in water, formaldehyde is rapidly absorbed in the respiratory and gastrointestinal tracts and metabolized. Over 90% of inhaled formaldehyde gas is absorbed in the upper respiratory tract. It is absorbed in the nasal passages; nasopharynx, trachea and proximal regions of the major bronchi. Although formaldehyde or its metabolites can penetrate human skin – it induces allergic contact dermatitis in humans – dermal absorption appears to be very slight.

#### Distribution

Owing to its rapid metabolism, exposure of humans to formaldehyde by inhalation does not alter the concentration of endogenous formaldehyde in the blood, which is about 2–3 mg/litre. Intravenous administration of formaldehyde does not result in accumulation of formaldehyde in the blood, because of its rapid conversion to formate.

### Metabolism and elimination

Formaldehyde reacts virtually instantaneously with primary and secondary amines, thiols, hydroxyls and amides to form methylol derivatives. Formaldehyde acts as an electrophile and can react with macromolecules such as DNA, RNA and protein to form reversible adducts or irreversible cross-links. Absorbed formaldehyde can be oxidized to formate along three different pathways, and can be exhaled as carbon dioxide or incorporated into biological macromolecules via tetrahydrofolate-dependent one-carbon biosynthetic pathways. In the body, formaldehyde is produced in small quantities as a normal metabolite and also in the oxidative demethylation of xenobiotics; it may therefore be found in the liver.



Source: International Agency for Research on Cancer.

## Effects-

### A) Acute poisoning-

Employees of a pharmaceutical company who continuously inhaled formaldehyde vapors showed symptoms of irritated eyes, tearing, sneezing, coughing, chest congestion, fever, heartburn, lethargy, and loss of appetite. As a result of the poisoning, some even experienced vomiting, abdominal pain and nodal tachycardia.

#### 1) Irritation

Acute mucus membrane irritation is the most common side effect of formaldehyde poisoning, often leading to dry skin, dermatitis, tearing eyes, sneezing, and coughing. Serious formaldehyde exposure often results in eye conjunctivitis, nasal and pharyngeal diseases, and can even increase the likelihood of dangerous conditions such as laryngospasm and pulmonary edema. One man, whose face was directly exposed to a large amount of formalin, suffered from facial swelling and cornea degeneration while similarly exposed employees of a wood processing factory experienced pharyngeal congestion, chronic rhinitis, and decreased olfactory functioning

#### 2) Dermal allergies

Formaldehyde exposure is also known to directly cause dermal allergies. Dermatitis on arms and forearms, with symptoms that included red spots, swelling, irritation, pain, and burning.

#### 3) Allergic asthma

It has been shown that the likelihood for the development of allergic asthma increases proportionately with indoor formaldehyde concentration, especially when levels exceed 0.12 mg/m<sup>3</sup>. There have been many of formaldehyde induced pulmonary disorders in chronically exposed workers, all of which found abnormal pulmonary function and obstruction in the small airways of the

patients. Chronic exposure to lower concentrations of 1.3 mg/m<sup>3</sup> significantly decreased maximum mid expiratory flow and forced vital capacity values.

### B) Chronic toxicity

Long-term exposure to elevated levels of formaldehyde in the occupational setting has resulted in upper and lower airway irritation; eye irritation; and degenerative, inflammatory and hyperplastic changes of the nasal mucosa in humans. Symptoms can include coughing, wheezing, expectoration, pharyngeal congestion, chronic pharyngitis, chronic rhinitis, loss of olfactory functioning, eye irritation, lacrimation, and cornea disorder, etc. There are also reports of irritated skin, heartburn, tremor, body sores, chest pain, lethargy, abdominal pain, and loss of appetite.

#### 1) Neurotoxicity

Chronic exposure to formaldehyde can result in symptoms of neurasthenia, which include headaches, dizziness, sleep disorders, and memory loss. Many reports indicate that chronic exposure to formaldehyde increases the chances of headache and dizziness by 30–60%.

#### 2) Pulmonary function damage

There have been many reports of formaldehyde-induced pulmonary disorders in chronically exposed workers, all of which found abnormal pulmonary function and obstruction in the small airways of the patients. In one of the studies, factory workers chronically exposed to formaldehyde concentrations of 3.07±5.83 mg/m<sup>3</sup> experienced a decrease in pulmonary ventilation, relative to a control group. Chronic exposure to lower concentrations of 1.3 mg/m<sup>3</sup> significantly decreased maximum mid expiratory flow and forced vital capacity values (Zhang et al., 1999). Similarly, other studies showed amplified pulmonary damage with increased

exposure over time (Fanet al., 2006; Feng et al., 1996; Li and Chen, 2002; Wang et al., 1999), along with more abnormalities in the small airways and higher resistance to pulmonary ventilation (Hong et al., 2007).

### 3) Hematotoxicity

Hematotoxicity is defined as toxicity caused by chemical exposure to the blood and hematopoietic system, often resulting in decreased blood cell counts. In one recent case report, a previously healthy woman was diagnosed with pancytopenia (a type of anemia), which showed lower than normal white blood cell (WBC), red blood cell (RBC), platelet (Plt) and hemoglobin(Hb) counts, after just 3 months of moving into a newly remodeled apartment. (Huang et al., 2007b)

### 4) Reproductive toxicity

Formaldehyde's teratogenicity and its effects on human reproduction are still a matter of scientific controversy. Very limited research has been conducted that specifically targets formaldehyde's effects on human reproduction. To the best of our knowledge, there have been no studies on formaldehyde's effects on male reproduction; however, three general health studies included findings on menstrual disorders and heavy menstrual flow (menorrhagia) in women occupationally exposed to formaldehyde. In a food additive factory, more than 70% of the female employees exposed to formaldehyde through inhalation (0.82– 5.96 mg/m<sup>3</sup>) reported abnormal menstrual cycles, while only 17% reported this in the control group (Xu et al., 2007b).

### 5) Genotoxicity

It has been shown that formaldehyde exposure induces DNA and chromosomal damage in human peripheral blood cells (Zhang et al., 2009). Persons exposed to formaldehyde showed an increase in DNA

damage in peripheral lymphocytes measured by single cell gel electrophoresis (Comet assay) (Jiang, 2006; Tong et al., 2006; Yuet al., 2005). Another study reported elevated occurrences of chromosome aberrations such as chromatid breakage, chromosomal fragmentation, dicentric chromosome, and aneuploidy in peripheral lymphocytes of workers chronically exposed on average to 2.51 mg/m<sup>3</sup> of formaldehyde for 10.5 years (Jin and Zhu, 1992). Several studies have shown that short-term (8 weeks) exposure to high levels of formaldehyde (0.508–0.985 mg/m<sup>3</sup>) increased micronuclei (MN) frequency in nasal epithelial cells (Cheng et al., 1995), while long-term (N1 year) exposure increased MN frequency in lymphocytes (Wang et al., 1997).

### 6) Carcinogenesis

Formaldehyde has been tested for carcinogenicity by inhalation, oral administration, topical application, and subcutaneous injections in rodents. It has been proposed that, based on the weight of evidence from in vivo studies, the likely mode of action for formaldehyde induced nasal tumors in animals is relevant to humans at least qualitatively (Mc Gregor et al., 2006). Based on comprehensive research and large-scale human studies conducted internationally, the International Agency for Research on Cancer (IARC) recently classified formaldehyde as a human carcinogen that causes nasopharyngeal cancer (IARC, 2006). Popularly known as the “Cantonese Cancer”, nasopharyngeal malignancy kills as many as 13,000 Chinese people each year—more than 10 times the nasopharyngeal fatalities in the rest of the world (Jia, 2008).

### **Reducing exposure**

By law, employers must provide a safe and healthy workplace. Here are some ways employers and

workers can work together to reduce exposures to formaldehyde.

- **Use safer substitutes whenever possible-** for example-Hydrogen peroxide- based solutions, Ethyl alcohol, polyethylene glycol etc. - often can be used as disinfectants.
- **Ventilation of the work area** by installing professionally designed ventilation systems to maintain formaldehyde exposures below legal exposure limits.
- **Use of personal protective equipment like** Protective clothing, Gloves made of nitrile, neoprene, butyl rubber , Chemical safety goggles , Face shields with chemical safety goggles, Respirators, etc. Chemical resistant aprons protect against splashes to the body. Employers must ensure that employees use it.
- **Information and training of workers-** employees should be educated about formaldehyde health hazards and symptoms of overexposure. Demonstration of the proper use and maintenance of fume hoods and other local exhaust ventilation systems should be there. The purpose and limitations of personal protective clothing and equipments should be explained. Instructions should be given to employees on how to respond to spills and emergencies, and on safe clean-up procedures.
- **Establish and use safe work procedures-** regulated areas where formaldehyde concentrations exceed the minimum limit should be identified. Signs must be posted on areas where regulation is required, and limit access to persons trained on the

hazards of formaldehyde. Eyewash facilities should be provided in areas where splashing may occur with solutions that contain 0.1% or more formaldehyde. Emergency showers must be provided in areas where solutions of 1% or more formaldehyde are used.

**Minimize exposure from spills and contaminated material-**

Perform preventive maintenance on equipment and inspect frequently to detect leaks and spills. Formaldehyde neutralization pads or sheets may be used where small spills or drips may occur on work surfaces. Use of formaldehyde neutralization products that neutralize quickly and don't generate hazardous by-products must be brought into action. Contaminated material, such as towels, clothing, and sponges should be removed from the work area. Ventilate contaminated clothing and equipment in properly labeled and established storage areas. Place contaminated waste and debris for disposal in sealed, labeled containers that warn of formaldehyde hazards.

**Conclusion**

Formaldehyde remains a popular choice of tissue fixative despite of its toxic effects because of its effectiveness, low cost, and consistent results. We need to follow precautionary measures so as to reduce the toxic effects of formalin. But it is now high time to switch ourselves to a better and much safer preservative. An employer is required by law to take preventive measures to protect employees from formaldehyde protective program. It is the employer's responsibility to select, provide and maintain personal equipment.

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