

## **Review Article**

### **EFFECTS OF FORMALDEHYDE EXPOSURE ON HUMAN BODY – A REVIEW ARTICLE**

#### **Abstract**

Formaldehyde, a ubiquitous volatile organic compound, is used extensively in the manufacture of many products and processes across industries, yet little is known of its inherent risks in the occupations. Because of formaldehyde public health significance, many countries and regulatory agencies have issued guidelines, advisories, and regulations for its exposure. These permissible exposure limits are different for different countries and institutions, suggesting that there is currently no global agreement on what comprises safe formaldehyde exposure levels. Formaldehyde has a wide range of chronic toxicity effects affecting different cells, tissues and organs of the body including, but not limited to, neuronal, pulmonary, immunological, haematological, genetic and reproductive and developmental systems. It is also carcinogenic, nephrotoxic and hepatotoxic. Most of the mechanisms through which formaldehyde exerts its toxic effects are not clearly understood. Due to its global economic importance, formaldehyde has clearly come to stay despite its known toxicities. It is proposed that well-designed epidemiologic, in addition to mechanistic and animal studies, need to be carried out to better appreciate the systemic effects of formaldehyde exposure.

**Keywords:** Formaldehyde; Toxic; Toxicity; Exposure; Acute; Chronic; Public Health; Occupational; Volatile Organic Compound

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#### **1. Introduction**

Formaldehyde is a very volatile, highly reactive chemical that is helping to boost the world economy. It is used extensively in the manufacture of many products and processes (Miller & Collins, 2017). For example, it is used widely in the wood processing, textile, construction, furniture, chemical, automotive, aircraft, healthcare, cosmetics, carpeting, and other industries (Organization for Economic Co-operation and Development [OECD], 2018). It is catalogued as a volatile organic

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compound (VOC) due to its high vapour pressure at standard temperature (Nowshad et al., 2018). Presently, formaldehyde is becoming increasingly used across an array of end-user industries globally. It has been forecasted that the global formaldehyde market is expected to reach 36.6 million tons towards the end of 2026 (Transparency Market Research, 2017).

Formaldehyde is a colourless, pungent, and flammable gas that is highly ubiquitous as it exists in both the physical environment and in biologic systems (Razi et al., 2013). This abundance of formaldehyde even extends to the galaxy, and research has shown that it is likely to be the source of organic carbon solids in the solar system (Cody et al., 2011). This implies that it helped to create the organic compounds and molecules that manifested life on earth. It dissolves very well in water, alcohols, and other polar solvents (Subasi, 2020). It is easily oxidized by sunlight to carbon dioxide, and at high temperatures (above 150°C) it decomposes to methanol and carbon monoxide (Subasi, 2020). In terms of its physical and chemical properties, formaldehyde is made up of hydrogen, carbon, and oxygen with a chemical formula of CH<sub>2</sub>O or HCOH. The molecular weight is 30.026g/mol, with a boiling point of -21.1°C at 760mmHg; a melting point of -92.2°C and a vapour pressure above 1atm (National Institute for Occupational Safety and Health [NIOSH], 2016).

In living systems, formaldehyde plays a role as an important metabolic intermediate in cells, body fluids and tissues (National Centre for Biotechnology Information [NCBI], 2019). In other instances, it may act as a building block in the production of biological compounds (Kalapos, 1999). It is also a methyl donor through the 1-carbon pool (Su & He, 2017).

This article is aimed at calling attention to the widespread effects of formaldehyde exposure on the various tissues and organs of the human body. To achieve this, we shall look at the formaldehyde regulations, advisories and guidelines for some countries and regulatory agencies. We shall also consider the environmental exposures to formaldehyde, including indoor and outdoor exposures; formaldehyde metabolism; the production of formaldehyde within and outside the body; and the medical uses of formaldehyde. These considerations will help to elucidate the acute and chronic impacts of formaldehyde exposure on the human body.

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## 2. Formaldehyde Regulation and Public Health

Although occupational and environmental exposure to formaldehyde is of public health importance, there appears to be less attention to the health effects of chronic exposure than to those of acute exposure (Kim et al., 2011; Tang et al., 2009). Exposure to formaldehyde should be a global concern due to its public health significance (Kim et al., 2011). Many countries and regulatory agencies have instituted advisories, guidelines, and regulations for formaldehyde exposure (Table 1). These occupational exposure limits (OEL) are the time-weighted average (TWA), the short-term exposure limits (STEL), and the threshold limit value (TLV) (ILO, 2011). The Occupational Safety and Health Administration (OSHA) stipulates that TWA is the worker's exposure to formaldehyde on a daily basis in an 8-hour workday, which is 0.75ppm (0.92mg/m<sup>3</sup>). Similarly, the STEL is the allowable average exposure to formaldehyde in a 15-minute time period, although the timing can vary based on jurisdiction. STEL is given as 2ppm (2.46mg/m<sup>3</sup>). Lastly, TLV is the level of formaldehyde a worker can be exposed to on a daily basis throughout his working career with no adverse effects (OSHA, 2011).

Table 1

*Formaldehyde regulations, advisories and guidelines for some countries and agencies*

Country or Agency	Concentration (ppm)	Type
Australia	1	TWA
	2	STEL
European Union	0.3	TWA
	0.6	STEL
South Africa	2	STEL
	1	TWA
United Kingdom	2	STEL
	2	TWA
United States	- ACGIH	0.3 TLV
	- NIOSH	0.016 TWA
	- OSHA	0.1 Ceiling*
	- OSHA	0.75 TWA
	- EPA	2 STEL
	0.7 TLV	
WHO	0.08	Ceiling

\*Ceiling, or maximum allowable concentration (MAC), the value that should never be exceeded during any length of time. Adapted from Kim et al., 2011 and Zhang, 2018.

## 2.1 Indoor Exposure

The World Health Organization (WHO) recommends an indoor formaldehyde concentration limit of 0.08ppm ( $0.1\text{mg}/\text{m}^3$ ) for short-term exposure (30 minutes) (WHO, 2010). However, in reality, most modern houses contain indoor formaldehyde levels exceeding this permissible limit. This comes from building materials and house furnishings such as paneling of walls with plywood, furniture, fibreboard, fiberglass, urea-formaldehyde foam insulation (UFFI), paints, floor finishes, varnishes and other interior decoration products (Li et al., 2019). In older houses, incomplete combustion of fuels, e.g. from kerosene stove and firewood, is also a source of formaldehyde pollution (WHO, 2010). Modern buildings are designed to be energy-efficient, making it so airtight as to increase indoor formaldehyde levels due to poor ventilation (Li et al., 2019). Cigarette smoking in the indoor environment also increases indoor formaldehyde concentrations (Masjedi et al., 2019). However, factors such as the age of the building (and furnishings), the rate of air exchange (ventilation) and the weather generally affect indoor formaldehyde concentration. The age of the building is inversely proportional to the indoor formaldehyde concentration. This is so because indoor formaldehyde concentration dissipates with time. The indoor concentration of formaldehyde is low in properly ventilated buildings. Formaldehyde concentration is more in hot weather than in cold season due to the high vapour pressure of formaldehyde (WHO, 2010).

## 2.2 Outdoor Exposure

Several sources are responsible for the pollution of the environment with formaldehyde, mainly from anthropogenic sources. The commonest source of environmental formaldehyde is automobile engines due to incomplete combustion of fossil fuel (NCBI, 2019). Other sources include cigarette smoking (WHO, 2010), bush burning and manufactured wood products (Zhang, 2018). Formaldehyde is also a product of residual decomposition of plants in the soil. As part of smog pollution, formaldehyde is produced when hydrocarbons react with hydroxyl radicals during oxidation in the troposphere (International Programme on Chemical Safety [IPCS], 1989). Formaldehyde is as well produced in large quantities in the industries, and used in numerous applications (Li et al., 2019).

Statistics of outdoor levels of formaldehyde are non-existent in Nigeria and other developing countries, although it is envisaged that the levels may be higher than in developed countries where outdoor levels are regulated (Zhang, 2018). Outdoor levels of formaldehyde are higher in the cities than in the rural areas because of the concentration of industries more in the cities than in the rural

areas. The higher the altitude, the lower the formaldehyde concentration in the environment (NCBI, 2019) because formaldehyde is slightly heavier than air.

### 2.3 Other Types of Exposure

Other types of exposures are those due to formaldehyde contamination of seafood, fruits and other foods where diluted formaldehyde is illegally used as a preservative to increase their shelf life (Nowshad et al., 2018). Aspartame is a popular artificial sweetener, although it has its health hazard – it is metabolized into formaldehyde which may accumulate in the human body to toxic levels (Zafar et al., 2017). When humic matter is oxidized during ozonation and chlorination, it gives rise to formaldehyde which may contaminate groundwater (Can & Gurol, 2003). Additionally, formaldehyde may leach from polyacetal plastic fittings into drinking water if the insulating coating has been breached (Crous & Haarhoff, 2011). The WHO recommends 0.9mg/L (0.9ppm) as the maximum level of formaldehyde in drinking water (WHO, 2017). Children are also exposed to formaldehyde through the childhood vaccination programmes. This is possible because formaldehyde is a constituent of most vaccines where it serves to inactivate viruses and detoxify bacterial toxins (Destefano et al., 2017).

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### 3. Formaldehyde Metabolism

The role of formaldehyde as a metabolic intermediate has been mentioned. It is essential for the biogenesis of purines, thymidine and several amino acids (NCBI, 2019). There are three metabolic pathways for the metabolism of formaldehyde. The first is the detoxification of formaldehyde with glutathione as a cofactor. This reaction depends on the presence of the enzyme *formaldehyde dehydrogenase* (FDH) (Inci et al., 2013). The second pathway is the detoxification of formaldehyde in the absence of glutathione. This normally happens at high levels of formaldehyde exposure when the glutathione levels have been depleted. This pathway depends on the presence of the enzyme *aldehyde dehydrogenase* (ALDH1 & ALDH2) (Tulpule et al., 2013). These detoxification processes work efficiently as long as the concentration of formaldehyde in the blood is low. High concentrations of formaldehyde in the blood cause acidosis and tissue damage (NCBI, 2019). The third pathway is the oxidation of formaldehyde in the presence of hydrogen peroxide, which is also important after glutathione depletion. It is catalyzed by *catalase* (Zhang, 2018).

In these three pathways, the end-product is formic acid which is eliminated either through the urine or through exhalation, depending on the route of absorption. Usually, when formaldehyde is absorbed by ingestion, the mode of elimination is through the urine and faeces as its sodium salt. But if absorbed through the respiratory system, the formic acid is broken down into carbon dioxide (CO<sub>2</sub>) and water (H<sub>2</sub>O) and eliminated by exhalation (National Toxicological Program [NTP], 2011).

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Formaldehyde is also known to bind tetrahydrofolate (THF) to become incorporated into the one-carbon pool and the formation of adducts. In this process, formaldehyde becomes a metabolic donor (NTP, 2011). Paradoxically, when THF is oxidized, the one-carbon pool also serves as a source of endogenous formaldehyde (Burgos-Barragan et al., 2017).

In addition, formaldehyde can bind to biological macromolecules like DNA and protein to form DNA-protein crosslinks and protein-protein crosslinks or DNA-DNA crosslinks. It can also bind to small molecules such as cysteine, urea and glutathione to form their corresponding adducts (Ortega-Atienza et al., 2016).

#### 4. Endogenous Production of Formaldehyde

Formaldehyde is present in humans and most other living things as byproducts of metabolism in body fluids, cells, and tissues (Obahiagbon & Obahiagbon, 2015; Burgos-Barragan et al., 2017). It is usually produced via various mechanisms, namely methanol metabolism, demethylation of DNA, RNA and histone, amino acid metabolism and lipid peroxidation (European Food Safety Authority [EFSA], 2014). The presence of formaldehyde in cells necessitates its use as either a building block molecule or a methyl donor in the metabolism of several biological processes. However, science is yet to fully appreciate its complete role in physiology (Swenberg et al., 2011; EFSA, 2014).

Formaldehyde has also been found in some seafood, some types of mushrooms, chicken, egg, beer, and fruits, where it may be a contaminant or a naturally occurring constituent (Andrews, 2013).

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#### 5. Exogenous Production of Formaldehyde

Formaldehyde is produced in the industry either through the oxidation process, which is highly exothermic, or through the dehydrogenation process, which is highly endothermic and more cost-effective. In the oxidation process of formaldehyde production, methanol is oxidized using a metal

catalyst acidified with dilute sulphuric acid (Gupta, 2011) as shown in equation 5.1. In the dehydrogenation process, methanol is dehydrogenated to produce formaldehyde (Gupta, 2011) as shown in equation 5.2. Its many industrial applications have already been highlighted in Section 1.



## 6. Medical Uses of Formaldehyde

Formaldehyde is the commonest chemical used for embalment (Raja & Sultana, 2012). In this case, it is employed as an aqueous solution, called formalin, containing 37% by weight of dissolved formaldehyde and 10% methanol to prevent oxidation and polymerization of the solution (Manoonkitiwangsa & Schultz, 2002). Formaldehyde is used as a tissue preservative since it destroys germs and kills insects and other microbes. It also doubles as a bactericide in hospital laboratories (Ferreira et al., 2017). Formaldehyde is an active ingredient of formocresol which is used to treat inflammation of the dental pulp resulting from dental caries in children (Lewis, 2010). Formaldehyde is also used in vaccine production as a preservative and additive (Organization for Economic Cooperation and Development, 2018). Minute amounts (usually not more than 0.1mg) can be found in certain vaccines, e.g. for Polio and Hepatitis A virus (Sanders et al., 2015). It is also applied as an active ingredient in anti-infective drugs and hard-gel capsules, and in pharmaceutical research (Niculescu et al., 2012).

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## 7. Health Effects of Formaldehyde

### 7.1 Toxicological Effects

#### 7.1.1 Acute Toxicity

Acute toxicity refers to the adverse effect of formaldehyde exposure occurring within a period of 24 hours following oral or dermal exposure, or within a period of 4 hours following inhalation exposure (OSHA, 2012). The main acute toxicity effects of formaldehyde are varying degrees of severity and intensity of acute poisoning and irritation (Elshaer & Mahmoud, 2017).

##### 7.1.1.1 Acute poisoning

Acute poisoning is common where formaldehyde is used as a food preservative or where there is continuous inhalation of formaldehyde vapour. Due to its high reactivity with the mucous membrane, symptoms of acute formaldehyde poisoning include chest congestion, coughing, fever, heartburn, eye irritation, lethargy, sneezing and tearing of eyes (Agency for Toxic Substances and Disease Registry [ATSDR], 2019). Some people may experience abdominal pain, vomiting and nodal tachycardia (Zhang, 2018). When ingested accidentally, symptoms may include abdominal pain, bloody stools, bloody vomiting and a high level of *alanine amino transferase* (ALT). In severe cases, cyanosis and degeneration of the gastric mucosa may result (ATSDR, 2019).

#### **7.1.1.2 Acute Mucous Membrane Irritation**

Acute mucous membrane irritation is a prominent reaction of formaldehyde poisoning which often leads to cough, skin inflammation and dryness of the skin, sneezing and tearing (Zhang, 2018). Formaldehyde is a known allergen that causes *allergic contact dermatitis* (Lyapina et al., 2012). The symptoms include burning sensation, red spots, pain, irritation and swelling (Uter et al., 2020). In recent times, many case reports have described *allergic reactions* in people with contact dermatitis secondary to formaldehyde and other components of face masks (Dhamija et al., 2020).

#### **7.1.2 Chronic Toxicity**

Chronic toxicity is the appearance of long-term or sustained adverse health effects due to prolonged exposure to formaldehyde (Zhang, 2018). Chronic toxicity is commonly correlated with occupational exposures (Saeidnia, 2014; Salthammer et al., 2010). Sustained exposure to high levels of formaldehyde can lead to eye and upper and lower airway irritation in humans. In the nasal mucosa, it can also lead to hyperplasia, degeneration, and inflammation of the mucosal cells (Kedar et al., 2019). All these can subsequently lead to the following symptoms: coughing and expectoration, lacrimation, anosmia, pharyngeal congestion, corneal disorder, chronic pharyngitis and wheezing (ATSDR, 2019; Fenech et al., 2016).

##### **7.1.2.1 Neurotoxicity**

Neurotoxicity refers to the damage to the central nervous system which includes the brain and the peripheral nervous system. Chronic formaldehyde exposure to the nervous system may lead to physical and mental exhaustion (neurasthenia) symptomized by headache, irritability, amnesia, and

sleep disturbances (Ülker & Ülker, 2019). A significant dose-response relationship has been found to exist with increasing years of formaldehyde exposure (Seals et al., 2017).

Chronic formaldehyde exposure can also lead to neurodegenerative disorders (NDDs) which include, inter alia, amyotrophic lateral sclerosis (ALS), Huntington's disease, Alzheimer's disease, and Parkinson's disease (Reddy et al., 2010). NDDs are a group of slow, chronic, gradually debilitating and selective disorders of the neuronal cells which ultimately result to an incurable nervous system derangement (Berman & Bayati, 2018). NDDs are of unknown etiologies. However, collectively, they share common risk factors. These risk factors include age, gender, vitamin deficiencies, tumors, depression, head injury, infection, immunodeficiency and metabolic conditions, oxidative stress, diabetes mellitus, hypertension, cerebrovascular accident, lack of education, chemical exposure, inflammation and smoking (Hipkiss, 2017; National Institute of Health [NIH], 2016; Peters et al., 2017; Tulpule & Dringen, 2013; Zhang, 2018). While the association of chronic formaldehyde exposure and neurotoxicity have been established, its mechanism of action in the onset of neurodegeneration is yet to be fully appreciated (Tulpule & Dringen, 2013). Chronic formaldehyde exposure has also been linked to memory, behavioural and learning changes (Hipkiss, 2017; Tong et al., 2011).

#### **7.1.2.2 Abnormal Pulmonary Function**

Prolonged formaldehyde exposure can lead to abnormal lung function and airway obstruction (Uthiravelu et al., 2015). Chronic formaldehyde exposure also significantly decreases forced vital capacity and maximum mid-expiratory flow values (Dhar & Chaudhuri, 2019). Similarly, chronic exposure to formaldehyde has been shown to cause severe pulmonary damage along with more anomalies in the bronchioles, and higher resistance to breathing (National Toxicological Program [NTP], 2014).

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#### **7.1.2.3 Allergic Asthma**

Chronic exposure to formaldehyde is associated with asthma and other inflammatory disorders of the respiratory system, and this association is directly proportional to the concentration of indoor and occupational formaldehyde (Lino-dos-Santos-Franco et al., 2011). Nonetheless, there is no known association between formaldehyde concentration and the severity of asthma (Kim et al., 2011). Meanwhile, a link has been found between formaldehyde and childhood asthma (McGwin et al.,

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2010). It is thought that this association is due to formaldehyde's ability to increase sensitization to mite antigen (Nair et al., 2016). Exposure to formaldehyde can also cause occupational asthma and an impaired lung function (Ren et al., 2013).

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#### 7.1.2.4 Immune System Effects

The sensitization caused by formaldehyde has been shown to be immunoglobulin-E (IgE)-mediated, especially in children (Zhan, 2018). A significant increase in IgG (including formaldehyde-specific IgG), IgA and IgM and other immuno-markers have been found in children with high exposure to formaldehyde (Calderon-Garciduenas et al., 2015). The association of formaldehyde exposure to the immune system is not defined in adults. Both reduction and increase in immunoglobulin and other immune-markers have been observed (Rhomberg, 2011; Zhang, 2018).

## 7.2 Haematotoxicity

Toxicity of the haematopoietic system manifests through alteration of the haematopoietic cell number or function. The haematotoxic effects of formaldehyde affect cells in the peripheral blood, bone marrow, spleen, lymph node and other tissues (National Toxicological Program [NTP], 2014). Several studies report inconsistent findings in the measured haematological indices. Some studies have shown a decrease in leucocyte count (Elshaer & Mahmoud, 2017; Zhang et al., 2013). Other studies have demonstrated a reduction in erythrocytes and platelets (Elshaer & Mahmoud, 2017; Ji et al., 2013). An increase in monocytes, eosinophils and some T-cell subsets, with a decrease in neutrophils and haemoglobin concentration and an attenuation of T-cell function have all been observed (Abd-Elhakima et al., 2016; Hosgood et al., 2013).

Odiegwu et al. (2018) found a statistically significant difference ( $p < 0.05$ ) between the exposed group and the unexposed group with lower white blood cell (WBC) and mixed differential counts, and a higher neutrophil count in the former. They also observed that the negative correlation between total WBC count and duration of exposure was statistically significant. In terms of morphology of the WBC, RBC and platelets in the peripheral blood, no significant alteration was observed. Bassig et al. (2016) also found that formaldehyde elicited a reduction in granulocyte, lymphocyte and platelet counts which were statistically significant.

These conflicting findings may be due to the different sources of formaldehyde, the different formaldehyde exposure levels, and the time span of the different studies. However, taken as a whole,

and supported by other studies in animals, the findings confirm that human exposure to formaldehyde vapour is causally associated with several haematological effects (NTP, 2014). However, contrary to these findings, Mundt et al. (2017) evaluated haematological parameters in relation to quantitative exposure measures of formaldehyde with linear regression analyses and showed that the observed differences in haematological parameters were not exposure dependent.

### 7.3 Genotoxicity

Formaldehyde exerts its genotoxic effects by disrupting the genetic information in a cell. This disruption of genetic information may lead to mutation during replications, ultimately leading to accelerated senescence and cancer, if the lesions are not repaired (Rhomberg et al., 2011; Stingelli et al., 2017). The various mechanisms of DNA damage include DNA adduct formation, DNA protein crosslinks, chromosomal changes such as chromosomal aberrations, exchanges of sister chromatids, ~~micronuclei~~micronuclei, and aneuploidy (Zhang, 2018). However, Jimenez-Villarreal et al. (2017) also observed other mechanisms of formaldehyde genotoxicity namely oxidative stress, DNA methylation, and production of reactive oxygen species. Nonetheless, the ubiquity of formaldehyde in all cells of the body makes it very challenging to gauge the contribution of exogenous formaldehyde exposure to genotoxicity (Leng et al., 2019).

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#### 7.3.1 DNA Adducts

A DNA adduct is formed when a section of DNA binds to a carcinogenic chemical like formaldehyde. DNA adducts are the determining factors in the development of mutations and cancer when a cell is replicating, unless a repair takes place (Swenberg et al., 2011). For this reason, adducts have been proposed as potential biomarkers for cancer risk (Ma et al., 2019).

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#### 7.3.2 Cytogenetic Aberrations

Several researchers have found that formaldehyde is involved in cellular genetic alterations. Such alterations include chromosomal aberrations, ~~micronuclei~~micronuclei, and sister chromatid exchanges (Katsnelson et al., 2013; Lan et al., 2015; Zhang et al., 2010b). Chromosomal aberrations occur when there is a deviation in the number of chromosome sets, number of individual chromosomes or changes in appearance of individual chromosomes due to mutations (Crawford, 2017). These may later manifest as genetic diseases or species anomalies.

Sister chromatid exchanges are said to occur when there is an interchange of chromatin between two corresponding sister chromatids, usually due to error in replication or blocking of DNA replication (Jain et al., 2018). On the other hand, micronuclei are tiny extra nuclear fragments containing damaged chromosomes, or even complete chromosomes that were not incorporated into the nucleus during mitosis (Jain et al., 2018). According to Musak et al. (2013), these cytogenetic aberrations may be used to predict future risk of carcinogenesis, especially cancers of the haematological system.

#### **7.4 Carcinogenesis**

The cancer-causing effects of formaldehyde are well established in the literature. In 2005, the International Agency for Research on Cancer (IARC) categorized formaldehyde as a human carcinogen. In 2012, the IARC also categorized formaldehyde as a leukemogen (IARC, 2012; Kwon et al., 2018). This fact has also been confirmed by other regulatory agencies, including the European Union Occupational Diseases Classification, Labelling and Packaging of Substances and Mixtures (EU CLP) guidelines (European Composite Industry Association [ECIA], 2014), the United States Environmental Protection Agency (EPA) (EPA, 2010), and the American Conference of Government Industrial Hygienists (ACGIH) (ACGIH, 2009). In some countries such as Denmark, Malaysia, France and Taiwan, cancers caused by formaldehyde have been recognized as occupational diseases (Kwon et al., 2018).

Many studies have linked formaldehyde exposure with increased risk of certain cancers such as sinonasal, nasopharyngeal and blood-related cancers, including myeloid leukaemia (Fenech et al., 2015; Kim et al., 2011; Kwon et al., 2018; Salthammer et al., 2010). The National Toxicological Program (2016) has also shown that exposure to formaldehyde can cause cancers in diverse tissues and organs such as the pharyngolaryngeal cavity, lungs, pancreas and brain. Despite the overwhelming significant associations between formaldehyde exposure and nasopharyngeal cancers and leukemia, the International Labour Organization (ILO) could not reach an agreement on the possibility of formaldehyde causing such cancers (ILO, 2010).

In contrast, in a recent animal study using highly sensitive and accurate nanoscale liquid chromatography coupled to tandem mass spectrometry (nano LC-MS/MS), researchers examined the cancer-causing potential of inhaled formaldehyde, in doses more likely to be experienced in humans, and found that the risk of developing cancer was significantly lower than previously expected (Leng

et al., 2019). However, whether this finding can be extrapolated to the human population remains to be seen.

### 7.5 Reproductive and Developmental Toxicity

Formaldehyde has long been suspected to have adverse effects on the reproductive system and development. However, earlier studies on this subject were inconclusive partly due to poor study designs involving human populations. But Duong et al. (2011) in their systematic review and meta-analysis, found evidence of an association between exposure to formaldehyde and reproductive and developmental toxicity. Their research involved both retrospective human population studies and *in vivo* animal experiments. These reproductive and developmental events may include spontaneous abortions, low birth weight, congenital abnormalities, premature births and stillbirths (Duong et al., 2011).

Formaldehyde teratogenicity is commonly characterized by changes in structure and function of the male or female reproductive organs, the endocrine system associated with reproduction, pregnancy outcomes, altered growth or death (Chinedu et al., 2017; Wang et al., 2012). These can occur at any time in the life of the organism.

In the past, most of these studies on the reproductive toxicity of formaldehyde focused on women. However, Wang et al. (2012) have shown evidence of male reproductive toxicity in males occupationally exposed to formaldehyde. A significant increase in the risk of miscarriage has been demonstrated in the wives of occupationally exposed male workers. Also, wives of men exposed to formaldehyde took three times longer to get pregnant than wives of men not exposed to formaldehyde, after adjustments for other factors (Wang et al., 2012). The study final noted that formaldehyde reproductive toxicity appeared to be dose-dependent as infertility occurred three times as high in wives of men exposed to higher concentrations than in wives of men not exposed (Wang et al., 2012).

Although the exact mechanisms of formaldehyde reproductive toxicity isare unknown, it is thought that formaldehyde causes toxicity through DNA and chromosomal alterations, decreased dehydrogenase activity, increased cell death, decreased sex hormones, abnormal methylation and

stress-induced effects in those organs of reproduction and associated endocrine organs (de Graaf et al., 2009; Tang et al., 2009; Wang et al., 2012).

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## 7.6 Nephrotoxicity and Hepatotoxicity

Research has shown that workers occupationally exposed to formaldehyde had a significant increase in the incidence of cancers of the kidney (Inci et al., 2013). Earlier studies had essentially found acute renal failure caused by either tubular necrosis or edematous obstruction after instillation of formal (Merimsky & Jossiphor, 1980) and acute renal failure secondary to hypotension in an individual who had ingested 150 ml in a suicide attempt (Shimizu et al., 2003). Later findings have corroborated that, indeed, in very severe acute poisoning, there may be haematuria, proteinuria and acute renal failure (ATSDR, 2019; Li et al., 2019).

In the liver, Olooto (2010) has demonstrated that exposure to formaldehyde significantly reduces total serum protein, albumin and total globulin levels. This suggests an impairment of the synthetic function of the liver, including that of humoral immunity.

## 8. Conclusion

Formaldehyde is a very versatile chemical with a wide range of applications in the industries globally, and has helped to boost the world economy. But despite its versatility, it can be seen from the foregoing that formaldehyde is harmful to many cells, tissues and organs. ~~Thus~~ ~~Thus~~, it is capable of causing acute poisoning and chronic damage to nervous, respiratory, immune, haematological and the chromosomal systems. Most of the mechanisms through which formaldehyde exerts its toxicity remain unknown, and require further studies. However, given the commercial importance of formaldehyde, its ubiquity in the environment, and the fact that it is also produced within the body, precise hazard classification and risk evaluation of whether exposure to formaldehyde is from occupational, consumer products or residential sources are crucial.

In view of the economic relevance of formaldehyde to the global economy, it may not be possible to substitute an alternative to this ubiquitous chemical with contemporary scientific knowledge. In the meantime, many countries and regulatory agencies have established advisories, guidelines and regulations for occupational and industrial contexts. It is worthy of note that these permissible exposure limits are different for different countries and institutions since there is currently no global agreement on what comprises safe formaldehyde exposure levels.

To elucidate these findings, well-designed epidemiologic, in addition to mechanistic and animal studies, need to be carried out to better appreciate the systemic effects of formaldehyde exposure.

### REFERENCES

- Abd-Elhakima, Y.M., Mohamed, A.A. & Mohamed, W.A. (2016). Hemato-immunologic impact of subchronic exposure to melamine and/or formaldehyde in mice. *Journal of Immunotoxicology*, 13(5): 713 – 722.
- Berman, T. & Bayati, A. (2018). What are neurodegenerative diseases and how do they affect the brain? *Frontiers for Young Minds*. 6:70. doi: 10.3389/frym.2018.00070.
- Burgos-Barragan, G., Wit, N., Meiser, J., Dingler, F.A., Pietzke, M., Mulderrig, L., Pontel, L.B., Rosado, I.B., Brewer, T.F., Cordell, R.L., Monks, P.S., Chang, C.J., Vazquez, A., & Patel, K.J. (2017). Mammals divert endogenous genotoxic formaldehyde into one-carbon metabolism. *Nature*, 548, 549 – 554.
- Calderon-Garciduenas, L., Vojdani, A., Blaurock-Busch, E., Busch, Y., Friedle, A., Franco-Lira, M., Sarathi-Mukherjee, P., Martinez-Aguirre, X., Park, S.-B., Torres-Jardon, R. & D'Angiulli, A. (2015). Air pollution and children: Neural and tight junction antibodies and combustion metals, the role of barrier breakdown and brain immunity in neurodegeneration. *Journal of Alzheimer's disease*; 43: 1039 – 1058.
- Can, Z.S. & Gurol, M. (2003) Formaldehyde formation during ozonation of drinking water. *Science & Engineering*, 25:1, 41-51.
- Chinedu, I.A., Chukwuemeka, E.O., Ndumnworo, O.D.F., Kalu, A.U, Nwabunwanne, O.V. & Igube, N.A. (2017). Effect of short-term exposure to formalin on male reproductive hormones of students in Nnewi. *IOSR Journal of Dental and Medical Sciences*, 16: 33 – 36.

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- Cody, G. D., Heying, E., Alexander, C. M. O., Nitter, L. R., Kilcoyne, A. L. D., Sanford, S. A. & Stroud, R. M. (2011). Establishing a molecular relationship between chondritic and cometary organic solids. *PNAS*, 108(48) 19171 – 19176. doi: 10.1073/pnas.1015913108
- Crawford, A.C. (Ed.) (2017). Principles of Biology. Ipswich, MA: Salem Press.
- Crous, P. A., & Haarhoff, J. (2011). The Effect of Formaldehyde Use in Sanitation. Report to the Water Research Commission. WRC Report No. KV 274/11
- Destefano, F., Offit, P. A. & Fisher, A. (2017). Vaccine Safety. In S. A. Plotkin, W. A. Orenstein, P. A. Offit and K. M. Edwards (Eds.). *Plotkin's Vaccines* (7<sup>th</sup> ed.) (pp. 1584 – 1600.e10). Amsterdam: Elsevier. <https://doi.org/10.1016/B978-0-323-35761-6.00082-1>
- Dhamija, Y., Khan, N. and Schmidlin, K. (2020). Facial contact dermatitis due to masks in the covid-19 era. *Annual of Allergy Asthma and Immunology*; 125(5): S104.
- European Food Safety Authority [EFSA] (2014). Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sources. *EFSA J.*, 12, 3550.
- Fenech, M., Nersesyan, A. & Knasmueller, S. (2016). A systematic review of the association between occupational exposure to formaldehyde and effects on chromosomal DNA damage measured using the cytokinesis-block micronucleus assay in lymphocytes. *Mutation Research*, 770(Pt A): 46 – 57.
- Ferreira, J.R., Rezende, L.C., Barbosa, A.S., De Carvalho, P., De Lima, N.E. and Carvalho A.A. (2017). Economic, human and environmental health benefits of replacing formaldehyde in preservation of corpses. *Ecotoxicology and Environmental Safety*; 145: 490 – 495.
- Hipkiss, A.R. (2017). Depression, diabetes and dementia: Formaldehyde may be a common causal agent: could carnosine, a pluripotent peptide, be protective? *Ageing and Disease*, 8(2): 128–130.
- Hosgood, H.D., Zhang, L., Tang, X., Vermeulen, R., Hao, Z., Shen, M., Qiu, C., Ge, Y., Hua, M., Ji, Z., Li, S., Xiong, J., Reiss, B., Liu, S., Xin, K.X., Azuma, M., Xie, Y., Freeman, L.B., Ruan, X. ... Lan Q. (2013). Occupational exposure to formaldehyde and alterations in lymphocyte subsets. *American Journal of Industrial Medicine*; 56(2): 252 – 257.

[https://www.ilo.org/global/topics/safety-and-health-at-work/areasofwork/chemical-safety-and-the-environment/WCMS\\_151534/lang--en/index.htm](https://www.ilo.org/global/topics/safety-and-health-at-work/areasofwork/chemical-safety-and-the-environment/WCMS_151534/lang--en/index.htm)

International Programme on Chemical Safety (1989). Environmental health criteria 89, Formaldehyde, <http://www.inchem.org/documents/ehc/ehc/ehc89.htm>

Jain, A.K., Singh, D., Dubey, K., Mittal, S. & Pandey, A.K. (2018). Models and methods for *in vitro* toxicity. In A. Dhawan and S. Kwon (Eds.). *In vitro toxicology* (pp. 45 – 65). Amsterdam: Elsevier Inc.

Ji, Z., Li, X., Fromowitz, M., Mutter-Rottmayer, E., Tung, J., Smith, M. & Zhang, L. (2013). Formaldehyde induces micronuclei in mouse erythropoietic cells and suppresses the expansion of human erythroid progenitor cells. *Toxicology Letters*, 224(2): 233 – 239.

Kalapos, M. P. (1999). A possible Evolutionary role of formaldehyde. *Exp. Mol. Med.*, 31, 1 – 4.

Katsnelson, B.A., Degtyareva, T.D., Privalova, L.I., Minigaliyeva, I.A., Slyshkina, T.V., Ryzhov, V.V. & Beresneva, O.Y. (2013). Attenuation of sub-chronic formaldehyde inhalation toxicity with oral administration of glutamate, glycine and methionine. *Toxicology Letters*, 220: 181–186.

Kedar, S., Nagle, S., Khairnar, P., Jagade, M.V., Parelkar, K. (2014). Effect of formaldehyde on nasal mucosa in workers exposed to formaldehyde. *International Journal of Recent Trends in Science and Technology*; 13(1): 225 – 227

Kim, K-H., Jahan, S.A. & Lee, J-T. (2011). Exposure to formaldehyde and its potential human health hazards. *Journal of Environmental Sciences and Health, Part C*; 29:277 – 299.

Lan, Q., Smith, M.T., Tang, X., Guo, W., Vermeulen, R., Ji, Z., ... Zhang, L. (2015). Chromosome-wide aneuploidy study of cultured circulating myeloid progenitor cells from workers occupationally exposed to formaldehyde. *Carcinogenesis*, 36:160–167.

Leng, J., Liu, C-W., Hartwell, H.J., Yu, R., Lai, Y., Bodnar, W.M., ... Swenberg, J.A. (2019). Evaluation of inhaled low-dose formaldehyde-induced DNA adducts and DNA-protein cross-links by liquid chromatography-tandem mass spectrometry. *Archives of Toxicology*; 93(3):763–773. doi:10.1007/s00204-019-02393-x.

- Lewis, B. (2010). The obsolescence of formocresol. *Journal of California Dental Association*, 38: 102–107.
- Lyapina, Kisselova-Yaneva, Krasteva, Tzekova-Yaneva and Dencheva-Garova (2012). Allergic contact dermatitis from formaldehyde exposure. *Journal of IMAB - Annual Proceeding (Scientific Papers) 18(4)*
- Masjedi, M. R., Taghizadeh, F., Hamzehali, S., Ghaffari, S., Fazlzadeh, M., Jafari, A. J., Niazi, S., Mehrizi, E.A., Moradi, M., Pasalari, H., & Arfaeinia, H. (2019). Air pollutants associated with smoking in indoor/outdoor of water pipe cafés in Tehran, Iran: Concentrations, affecting factors and health risk assessment. *Scientific Reports*, 9, 3110. <https://doi.org/10.1038/s41598-019-39684-3>
- Merimsky, E., Jossiphov, J. (1980). L'action toxique sur le rein des instillations endovésicales de formaldéhyde. Diffusion hématogène ou reflux [Toxic effects on the kidney by endovesical instillations of formol. Hematogenic diffusion or reflux (author's translation)]. *Journal of Urology (Paris)*. 86(7): 527-9. French. PMID: 7452051.
- Mundt, K.A., Gallagher, A.E., Dell, L.D., Natelson, E.A., Boffetta, E. & Gentry, P.R. (2017). Does occupational exposure to formaldehyde cause haematotoxicity and leukaemia-specific chromosome changes in cultured myeloid progenitor cells? *Critical Reviews in Toxicology*. DOI: 10.1080/10408444.2017.1301878
- Musak, L., Smerhovsky, Z., Halasova, E., Osina, O., Letkova, L., Vodickova, L., Polakova, V., Buchancova, J., Hemminki, K., & Vodicka, P. (2013). Chromosomal damage among medical staff occupationally exposed to volatile anesthetics, antineoplastic drugs, and formaldehyde. *Scandinavian Journal of Work Environment and Health*, 39(6): 618 – 630.
- National Institute of Health (2016). The dementias: Hope through research. <https://www.nia.nih.gov/sites/default/files/the-dementias-hope-through-research.pdf>
- National Toxicological Program (2014). Review of the formaldehyde assessment in the National Toxicology Program 12th report on carcinogens.

- Niculescu, M., Ghituleasa, C., Mocioiu, A-M., Nicula, G. & Surdu, L. (2012). Formaldehyde in clothing and interior textiles. Proceedings of the 4th International Conference on Advanced Materials and Systems, ICAMS: 153-158
- Nowshad, F., Islam, N. and Khan, M. S. (2018). Concentration and formation behavior of naturally occurring formaldehyde in foods. *Agricultural & Food Security*, 7:17 <https://doi.org/10.1186/s40066-018-0166-4>
- Obahiagbon, F. I. & Obahiagbon I. (2015). Formaldehyde: A review of occurrence, chemical characteristics, exposures, metabolism, kinetics and health effects in man and animals. *International Journal of Molecular Biology & Chemistry*. 3(1): 43 – 54
- Occupational Safety and Health Administration (2012). OSHA Hazard Communication Standard (HCS), Paragraph A.1.1., Appendix A to 29 CFR 1910.1200
- Olooto, W.E. (2010). Assessment of the effect of formaldehyde exposure on the liver in mortuary workers in south western Nigeria. *Nigerian Medical Practitioner*, 57(4): 65-68
- Organization for Economic Cooperation and Development (2018). Economic valuation in formaldehyde regulation by Alistair Hunt and Nick Dale. University of Bath, Environment Directorate.
- Peters, T.L., Kamel, F., Lundholm, C., Feychting, M., Weibull, C.E., Sandler, D.P., Wiebert, P., Sparén, P., Ye, W., & Fang, F. (2017). Occupational exposures and the risk of amyotrophic lateral sclerosis. *Occupational and Environmental Medicine*, 74: 87–92.
- Reddy, N.J., Sudini, M. & Lewis, L.D. (2010). Delayed neurological sequelae from ethylene glycol, diethylene glycol and methanol poisonings. *Clinical Toxicology (Phila)*, 48: 967e973.
- Ren, X., Ji, Z., McHale, C.M., Yuh, J., Bersonda, J., Tang, M., Smith, M.T., & Zhang, L. (2013). The impact of FANCD2 deficiency on formaldehyde-induced toxicity in human lymphoblastoid cell lines. *Archive of Toxicology*, 87: 189–196.
- Rhomberg, L.R., Bailey, L.A., Goodman, J.E., Hamade, A.K. & Mayfield, D. (2011). Is exposure to formaldehyde in air causally associated with leukemia? – A hypothesis-based weight-of-evidence analysis. *Critical Reviews in Toxicology*, 41(7): 555 – 621.

- Saeidnia, S. (2014). Turpentine. In P. Wexler (Ed.) *Encyclopaedia of Toxicology* (3<sup>rd</sup> ed) pp 860 – 865. Boston MA: Academic Press.
- Sanders, B., Koldijk, M. & Schuitemaker, H. (2015). In *Vaccine Analysis: Strategies, Principles, and Control*. K. B. Nunnally, E. V. Turula and D. R. Sitrin (Eds). Springer Berlin Heidelberg, Berlin, Heidelberg, 45–80.
- Seals, R.M., Kioumourtoglou, M.A., Gredal, O., Hansen, J. and Weisskopf, M.G. (2017). Occupational formaldehyde and amyotrophic lateral sclerosis, *European Journal of Epidemiology*, 32, 893 – 899.
- Shimizu, K., Sugita, M., Yokote, R., Sekii, H., Miyake, Y. and Kiyota, K. (2003). Intestinal edema caused by ingested formalin. *Chudoku Kenkyu*; 16: 447 – 51.
- Stingele, J., Bellelli, R. & Boulton, S.J. (2017). Mechanisms of DNA–protein crosslink repair. *Nature Reviews Molecular Cell Biology*, 18:563 – 573.
- Su, T. and He, R. (2017). Formaldehyde playing a role in (de)methylation for memory. In: *Formaldehyde and cognition*. Springer, Dordrecht. [https://doi.org/10.1007/978-94-024-1177\\_3](https://doi.org/10.1007/978-94-024-1177_3)
- Subasi, N. T. (2020). Formaldehyde Advantages and Disadvantages: Usage areas and harmful effects on human beings. *Biochemical Toxicology – Heavy Metals and Nanomaterials*. doi: <http://dx.doi.org/10.5772/intechopen.89299>
- Tang, X., Bai, Y., Duong, A., Smith, M.T., Li, L. & Zhang L. (2009). Formaldehyde in China: Production, consumption, exposure levels, and health effects. *Environment International*, 35: 1210–1224.
- Transparency Market Research (2017). <https://www.transparencymarketresearch.com/formaldehyde-market.html>
- Tulpule, K. & Dringen, R. (2013). Formaldehyde in brain: An overlooked player in neurodegeneration? *Journal of Neurochemistry*, 127: 17 – 21.

- Tulpule, K., Hohnholt, M. C. & Dringen, R. (2013). Formaldehyde metabolism and formaldehyde-induced stimulation of lactate production and glutathione export in cultured neurons. *Journal of Neurochemistry*, 125, 260 – 272.
- Ülker, O. C., & Ulker, O. (2019). Toxicity of formaldehyde, polybrominated diphenyl ethers (PBDEs) and phthalates in engineered wood products (EWPs) from the perspective of the green approach to materials: A review. *BioResources*, 14(3), 7465-7493.
- Uter, Werfel, Lepoittevin and White (2020). Contact Allergy: Emerging Allergens and Public Health Impact. *International Journal of Environmental Research in Public Health* 2020, 17, 2404; doi:10.3390/ijerph17072404
- Uthiravelu, P., Saravanan, A., Kumar, C.K., & Vaithiyanandane, V. (2015). Pulmonary function test in formalin exposed and non-exposed subjects: A comparative study. *Journal of Pharmacy and Bioallied Sciences*, 7(Suppl 1): S35–S39. doi: 10.4103/0975-7406.155787
- Wang, H., Zhou, D., Zheng, L., Zhang, J., Huo, Y., Tian, H., Han, S., Zhang, J. and Zhao, W. (2012). Effects of paternal occupation exposure to formaldehyde on reproductive outcomes. *Journal of Occupational and Environmental Medicine*, 54(5): 518 – 524.
- WHO (2017). Guidelines for drinking-water quality, 4<sup>th</sup> ed., incorporating the first addendum.
- Zafar T., Naik, Q. A. B., Shrivastava V. K. (2017). Aspartame: Effects and awareness. *MedCrave Online Journal of Toxicology*, 3(2):23–26. DOI: 10.15406/mojt.2017.03.00046
- Zhang, L. (2018). Formaldehyde: Exposure, toxicity and health effects. California, CA: Royal Society of Chemistry. [www.rsc.org](http://www.rsc.org)
- Zhang, L., Tang X., Rothman N., Vermeulen R., Ji Z., Shen M., Qiu, C., Guo, W., Liu, S., Reiss, B., Freeman, L.B., Ge, Y., Hubbard, A.E., Hua, M., Blair, A., Galvan, N., Ruan, X., Alter, B.P., ... Lan Q. (2010b). Occupational exposure to formaldehyde haematotoxicity and leukaemia-specific chromosome changes in cultured myeloid progenitor cells. *Cancer Epidemiology Biomarkers Preview*, 19(1): 80 – 88.

Zhang, Y., Liu, X., McHale, C., Li, R., Zhang, L., Wu, Y., Ye, X., Yang, X., & Ding S. (2013). Bone marrow injury induced via oxidative stress in mice by inhalation exposure to formaldehyde. *PLoS One*, 8(9):e74974.

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