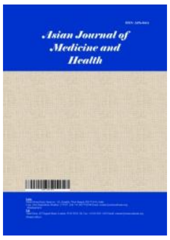

Asian Journal of Medicine and Health

19(12): 131-142, 2021; Article no.AJMAH.78998
ISSN: 2456-8414

Effects of Formaldehyde Exposure on Human Body-A Review Article

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJMAH/2021/v19i1230425
Editor(s):
(1) Dr. P. Veera Muthumari, V.V.Vanniaperumal College for Women, India.
Reviewers:
(1) Rashad E.M. Said, Al-Azhar University, Egypt.
(2) Asmaa Mohammed Tolba, Zagazig University, Egypt.
Complete Peer review History, details of the editor(s), Reviewers and additional Reviewers are available here:
https://www.sdiarticle5.com/review-history/78998

Review Article

Received 20 October 2021
Accepted 22 December 2021
Published 23 December 2021

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 exposure; acute; chronic; toxic; 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 [1]. It is catalogued as a volatile organic compound (VOC) due to its high vapour pressure at standard temperature [2]. 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 [3].

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 [4]. 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 [5]. It is easily oxidized by sunlight to carbon dioxide, and at high temperatures (above 150^oC) it decomposes to methanol and carbon monoxide [5]. In terms of its physical and chemical properties, formaldehyde is made up of hydrogen, carbon, and oxygen with a chemical formula of CH_2O or HCOH. The molecular weight is 30.026g/mol, with a boiling point of -21.1^oC at 760mmHg; a melting point of -92.2^oC and a vapour pressure above 1atm (National Institute for Occupational Safety and Health [6].

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 [7]. It is also a methyl donor through the 1-carbon pool [8].

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.

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 [9-10]. Exposure to formaldehyde should be a global concern due to its public health significance [9]. 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 ($0.92mg/m^3$). 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 ($2.46mg/m^3$). 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).

2.1 Indoor Exposure

The World Health Organization (WHO) recommends an indoor formaldehyde concentration limit of 0.08ppm ($0.1mg/m^3$) 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

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	
	0.6	TWA
		STEL
South Africa	21	STEL
		TWA
United Kingdom	22	STEL
		TWA
United States	0.3	TLV
ACGIH	0.016	TWA
NIOSH	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. [9] and Zhang, [11]*

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 [12]. 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 [11]. 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 [13]. 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 [11]. 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 [2]. 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 [14]. When humic matter is oxidized during ozonation and chlorination, it gives rise to formaldehyde which may contaminate groundwater [15]. Additionally, formaldehyde may leach from polyacetal plastic fittings into drinking water if the insulating coating has been breached [16]. The WHO recommends 0.9mg/L (0.9ppm) as the maximum level of formaldehyde in drinking water [17]. 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 [18].

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) [19-20]. 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* [11].

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_2) and water (H_2O) and eliminated by exhalation (National Toxicological Program [NTP], 2011).

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 [21].

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 [22,21]. 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 [23]. 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; [23]. 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).

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.

$$2CH_3OH + O_2 \rightarrow 2CH_2O + 2H_2O \text{ (oxidation) (5.1)}$$

$$CH_3OH \rightarrow CH_2O + H_2 \text{ (dehydrogenation) (5.2)}$$

6. MEDICAL USES OF FORMALDEHYDE

Formaldehyde is the commonest chemical used for embalmment (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 [24]. Formaldehyde is an active ingredient of formocresol which is used to treat inflammation of the dental pulp resulting from dental caries in children [25]. Formaldehyde is also used in vaccine production as a preservative and additive [1]. Minute amounts (usually not more than 0.1mg) can be found in certain vaccines, e.g. for Polio and Hepatitis A virus [26]. It is also applied as an active ingredient in anti-infective drugs and hard-gel capsules, and in pharmaceutical research [27].

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 [28]. 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 [11]. 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 [11]. Formaldehyde is a known allergen that causes *allergic contact dermatitis* [29]. The symptoms include burning sensation, red spots, pain, irritation and swelling [30]. In recent times, many case reports have described *allergic reactions* in people with contact dermatitis secondary to formaldehyde and other components of face masks [31].

7.1.2 Chronic toxicity

Chronic toxicity is the appearance of long-term or sustained adverse health effects due to prolonged exposure to formaldehyde [11]. Chronic toxicity is commonly correlated with occupational exposures [32] 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 [33]. All these can subsequently lead to the following symptoms: coughing and expectoration, lacrimation, anosmia, pharyngeal congestion, corneal disorder, chronic pharyngitis and wheezing (ATSDR, 2019; [34].

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) symptomatized by headache, irritability, amnesia, and sleep disturbances [35]. A significant dose-response relationship has been found to exist with increasing years of formaldehyde exposure [36].

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 [37]. 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 [38]. NNDs 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 [39, 6, 40, 19,20,11]. 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 [19-20]. Chronic formaldehyde exposure has also been linked to memory, behavioural and learning changes [39] Tong et al., 2011).

7.1.2.2 Abnormal pulmonary function

Prolonged formaldehyde exposure can lead to abnormal lung function and airway obstruction [41]. 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 [42].

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 [9]. Meanwhile, a link has been found between formaldehyde and childhood asthma (McGwin et al., 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 [43].

7.1.2.4 Immune system effects

The sensitization caused by formaldehyde has been shown to be immunoglobulin-E (IgE)-mediated, especially in children [11]. 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 [44]. 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 [45,11].

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 [23]. Several studies report inconsistent findings in the measured haematological indices. Some studies have shown a decrease in leucocyte count (Elshaer & Mahmoud, 2017; [46]. Other studies have demonstrated a reduction in erythrocytes and platelets (Elshaer & Mahmoud, 2017; [47]. 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 [48] [49].

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 [14]. However, contrary to these findings, Mundt et al. [50] 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.

Although the International Agency for Research on Cancer (IARC) had classified formaldehyde as a Group 1 carcinogen in 2012 based on leukemogenic studies (IARC, 2012), the correlation between exposure to formaldehyde and the incidence of leukemia has remained a controversial one. To better understand this association, Kang et al. [51] summarized qualitative associations between formaldehyde and leukemia through the literature-based network approached. They concluded that the genetic changes caused by formaldehyde, via oxidative, stress could interrupt the haematopoietic system, suggesting a potential leukemia-inducing mechanism of formaldehyde as well as major genes associated with formaldehyde and leukemia.

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 [45, 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, and aneuploidy [11]. 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 [52].

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).

7.3.2 Cytogenetic aberrations

Several researchers have found that formaldehyde is involved in cellular genetic alterations. Such alterations include chromosomal aberrations, micronuclei, and sister chromatid exchanges [53,54, 55]. 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 [56]. 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 [57]. 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 [57]). According to Musak et al. [58], 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 [34, 9, 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 [52]. 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 [59,60]. 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. [60] 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 [60]. 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 [60].

Although the exact mechanisms of formaldehyde reproductive toxicity are 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; [10]; [60].

In an earlier work, Thrasher and Kilburn [61] showed that in pregnant rats, formaldehyde crossed the placenta and entered the fetal tissues. This was achieved by incorporating formaldehyde with radioactive C14 which was demonstrated to be higher in fetal organs, particularly the brain and the liver, than in maternal tissues. This led to increased fetal anomalies, enzyme abnormalities in cell organelles, decreased ascorbic acid concentration, and increased embryo mortality, among others.

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 formol [62] and acute renal failure secondary to hypotension in an individual who had ingested 150 ml in a suicide attempt [63]. 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 [64] 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 [65].

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, it can cause 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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