Oxidative Stress and Carcinogenic Effect of Formaldehyde Exposure: Systematic Review & Analysis

Solomon Tesfaye^{*1}, Niguse Hamba¹, Asfaw Gerbi¹, Zenebe Negeri²

¹Anatomy Unit, Department of Biomedical Sciences, Institute of Health, Jimma University, Jimma, Ethiopia;²Physiology Unit, Department of Biomedical Sciences, Institute of Health, Jimma University, Jimma, Ethiopia

ABSTRACT

Background: Evaporation of formaldehyde from embalmed cadavers cause terrific systemic hazards, from which the most frequently reported, is respiratory and testicular symptoms. Day-dependent exposure to formaldehyde can cause contact dermatitis, congenital defects like low birth weight and isolated heart disease, cytotoxicity in the respiratory tract in the form of acute lung injury, nasal obstruction, pulmonary edema, and cancer. The histopathologic and morphometric alterations in testis have a strong link with exposure duration periods and highly linked to decrease the function of both sertoli and leydig cells. Several findings ensured such exposure significantly causes and triggers tremendous health effects, but a conclusive review of findings and recommendations related to its oxidative stress and carcinogenic potential on multiple study subjects on the respiratory system and testis are lacking. This study is initiated to shade light on the risk of exposed individuals, warrant caution to those individuals and provide protective measurements in the dissection room.

Methods: We performed a systematic review using databases of Google Scholar, PubMed Central, Scopus, Medline Cochrane, and Web of Science. The search yielded 66 scientific articles out of which 26 were included in the discussion of the oxidative stress and carcinogenic effect of formaldehyde exposure on the respiratory system and testis.

Results: The review of the animal and human findings has shown significant oxidative stress and carcinogenic potential of formaldehyde exposure and anti-inflammatory responses of some novel agents. The effects of formaldehyde exposure depend on the lining tissue type, formalin concentration in embalming fluids, length of exposure, ways of exposure, animal type, sexual category, and a mixture of other aldehydes.

Conclusion: Formaldehyde causes dose-dependent oxidative stress, which is generally known to be detrimental to respiratory and testicular tissues. Formaldehyde has day-dependent carcinogenic effect in the upper respiratory tract. The possible negative manifestation of oxidative stress is due to the altered levels of trace elements in formalin treated testicular tissues and the most viable consequence of formaldehyde in testis tissue architecture is due to its potential to stimulate the reactivity of trace elements. From the review, it was concluded that females as the most sensitive, 20 minutes as the least exposure duration and 0.08 milligram per kilogram (mg/kg) as the least toxic dose of formaldehyde exposure. Regardless of the high potential of formaldehyde related tissue lesion, the reversible effects of some novel agents such as vitamin E, fish omega-3, melatonin, rose oils, flavonoids, polyphenols, Caffeic Acid Phenethyl Ester/CAPE, garlic aqueous extract were observed in reversing of the destructive property of formaldehyde. Despite complete prevention is not possible, exposed personnel should be cautious of the deleterious effects associated with occupationally exposed formaldehyde vapor.

Keywords: Systematic review; Formaldehyde; Oxidative stress; Respiratory system; Testis

ABBREVIATIONS

PPM: Parts Per Million; HCHO: Formaldehyde; HCL: Hydrochloric Acid; OSHA: Occupational Safety and Health Administration; WHO: World Health Organization; CAPE: Caffeic Acid Phenethyl Ester; IL: Interleukin; µmol/kg: micro-mole per kilogram; IgE: Imunoglobulin E; HUD: Housing and Urban Development; mg/m³: Milligram per cubic meter; HPA: hypothalamic- pituitary Axis; CRH: Corticotropin-releasing Hormone; GIT: Gastro Intestinal Tract

*Correspondence to: Solomon Tesfaye Desissa, Department of Biomedical Sciences, Jimma University, P.O. Box 378, Jimma, Ethiopia, Tel: +251911-939324; E-mail: sole.tesfaye2010@gmail.com

Received: September 07, 2020; Accepted: September 23, 2020; Published: September 30, 2020

Citation: Tesfaye S, Hamba N, Gerbi A, Neger Z (2020) Oxidative Stress and Carcinogenic Effect of Formaldehyde Exposure: Systematic Review & Analysis. Endocrinol Metab Syndr 2020; 9:319. doi: 10.35248/2161-1017.20.9.319

Copyright: ©2020 Tesfaye S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

INTRODUCTION

Formaldehyde is a highly toxic, flammable gas, slightly heavier than air and detectable at low concentrations [1]. It is truly the primary embalming elements at anatomy dissection room and funeral services. Formaldehyde has been around forever and embalming without it is just a meaningless preservation of human body [2]. Currently, formaldehyde is commercially obtainable as formalin, which contains 37% by weight or 40% by volume of formaldehyde gas in water [3].

Workers in the Anatomy department and students, embalmers in funeral homes, histopathology laboratory workers, and other biological researchers are continually exposed to the toxic vapors of formaldehyde [3]. The highest potential exposure occurs in the formaldehyde-based resins industry, where workers may be exposed to high air concentrations and also have dermal exposure from liquid formaldehyde.

The other employees at risk for exposure to formaldehyde include dentists, doctors, embalmers, nurses, pathologists, teachers, and students who handle preserved specimens in laboratories, veterinarians, and workers in the clothing industry or furniture factories [4,5].

The possible routes of exposure to formaldehyde are inhalation, ingestion, and dermal absorption and no data are available in the literature on dermal exposure, but concerning the oral pathway, exposure through food may not be negligible [6]. Formaldehyde reacts with strong oxidizers, alkalis, acids, phenols, and urea. Pure formaldehyde has a tendency to polymerize. The reaction of formaldehyde with amines forms an imine adduct via an N-methylol intermediate. The imine can react further with other amines to form methylene bridges between protein and DNA molecules, and the reaction between formaldehyde and thiols forms S-hydroxymethyl and thiazolidine adducts [1].

Formaldehyde is a notorious lining tissue irritant and carcinogenic, which can directly cause a systemic threat to humans and other animals. Animal and human studies suggested that short term exposure to formaldehyde induces erythema, itchy and burning eyes, runny and stuffy nose, poor appetite, nausea, vomiting, and confusion. Several studies carried out on Wistar albino rats showed that inhalation of formaldehyde at a low dose can result in irritation and damage to the lining of the upper respiratory tract while the lower respiratory tract responds to dose-dependent high concentrations of formaldehyde are primarily due to its toxic effects after inhalation, after direct contact with the skin or eyes by formaldehyde in liquid or vapor form, and after ingestion [6].

Long-term exposure to formaldehyde can cause contact dermatitis, congenital defects like low birth weight and isolated heart disease, cytotoxicity in the respiratory tract in the form of acute lung injury, nasal obstruction, pulmonary edema, and cancer. However, the effects of formaldehyde on asthmatics may be dependent on previous repeated exposure to formaldehyde [7-9].

Studies done in rats and mice have shown formaldehyde exposure at 3ppm to 400ppm decreased food and water intake, decreased bodyweight, gastrointestinal affect liver, and kidney effects while concentration above 6ppm in human and animal models showed nasal and eye irritation, throat irritation, change in pulmonary function decreased bodyweight, enhanced allergic responses, neurological effects (affects neuronal morphology, behavior, disturbances of biochemical parameters, and cerebral oxidative damage [10]. Formaldehyde can increase the production of reactive oxygen species in many tissues and these reactive oxygen species including singlet oxygen, hydrogen peroxide, superoxide anions, and hydroxyl radicals are important mediators of cellular injury and play an important role in oxidative damage [11,12].

Formaldehyde inhalation inflicts various harms on many organs of living bodies including the testis, brain, and liver [13-15]. Few studies showed that prolonged occupational exposure to formaldehyde in the air found more cases of nose and throat cancer while studies of laboratory rats exposed for life to formaldehyde in the air found that some rats developed only nose cancer. Species-specific effect of formaldehyde was found and humans are more prone to develop formaldehyde exposure-related cancer [1].

Formaldehyde can mimics cells and causes oxidative stress, the phenomenon of an imbalance between production and accumulation of oxygen reactive species (ROS) in cells and tissues. ROS can play, and in fact they do it, several physiological roles, and they are normally generated as by-products of oxygen metabolism; despite this, environmental stressors (i.e., UV, ionizing radiations, pollutants, and heavy metals) and xenobiotics (i.e., antiblastic drugs) contribute to greatly increase ROS production, therefore causing the imbalance that leads to cell and tissue damage (oxidative stress) [16]. Free radicals reactive oxygen species and reactive nitrogen species are generated by our body by various endogenous systems, exposure to different physiochemical conditions or pathological states, and balance between free radicals and antioxidants is necessary for proper physiological function [17].

Regardless of its use in industries and medical settings, direct exposure to formaldehyde has a potential systemic effect from which respiratory and testis related symptoms are the leading effects in animal and human studies. The aim of this review is therefore to assess the oxidative stress and the carcinogenic effect of formaldehyde exposure in the respiratory system and testis. It is initiated to shade light on the risk of exposed individuals, warrant caution to those individuals and provide protective measurements in the dissection room.

METHODS

In this review, searching strategy revealed different kinds of literature in the databases of Google Scholar, PubMed Central, Scopus, Medline Cochrane, and Web of Science to summarize oxidative stress and carcinogenic related health effects of formaldehyde exposure via comparison and discussion of investigation of different scientific works.

Illegality criteria

Inclusion criteria

All Journal articles which preferably use a peer review system and focus on the health effects of formaldehyde exposure.

All Journal articles which preferably use the peer review system and only focus on oxidative stress and carcinogenic effects of formaldehyde exposure on the respiratory system and testis.

Exclusion criteria

Journals which address the toxic effects of other aldehydes on the respiratory system and testis

Journals which are outdated and don't use a peer review system

Case report, Abstract, and a summary of the health effects of formaldehyde on the respiratory system and testis.

Data extraction

After all the Journals filling the inclusion criteria are selected by the authors, general concepts of formaldehyde, sources, routes of exposure, and its general health effects excluding the respiratory system and testis were described. Experimental researches of formaldehyde exposure effects on the Respiratory System and Testis were described on Result Section by considering methodologies used, animal models utilized, and the yield of the findings. Those journal articles using a peer review system and merely focusing on oxidative stress and carcinogenic potential of formaldehyde exposure on the respiratory system and testis were used for comparison and analysis. The search yielded 65 findings out of which 39 articles were included in the Introduction and Result section based on their general figures on formaldehyde and its health effects. But 26 articles were sorted related to the topic of the review and solely focused on the carcinogenic effects of formaldehyde on the nasopharynx and its oxidative stress potential on the lower respiratory system and testicular tissues. So, the former findings were included in the discussion section of this review. The general health effects of formaldehyde exposure on the liver, renal system, heart, nervous system, gastrointestinal tract and its adverse effects on pregnancy outcomes/ genetic effects were describe as indicated in Table 1.

RESULTS

Qualitative review of formaldehyde exposure studies in respiratory system and testis

The search on the effects of formal dehyde exposure on the respiratory

OPEN OACCESS Freely available online

system and testis yielded 66 scientific articles out of which 26 were included in the review for analysis, comparison, and discussion. Almost all were performed in rats and mice. The animal models used were Swiss mice, B6C3F1 mice, Wistar albino rats, F344 rats BN rats, Guinea pigs, and rabbits. All the investigators have evaluated and directly addressed the toxic effects of formaldehyde exposure on the respiratory system and testes. In human studies, each participant was interviewed using a questionnaire containing detailed information about their occupational history by directly focusing on the nasal cavity and throat. The doses of formaldehyde were expressed in ppm, ppb, percentage, mg/m³, and mg/kg and mol/kg. The minimum and maximum exposure duration was 15 minutes and 5 years, respectively.

Clair MB [25] investigated the relative toxicities of formaldehyde at the doses of 40, 200, 400, and 800 mM to the rat nasal epithelium following intra-nasal instillation of aqueous solutions into one nostril of male Fischer 344 (F-344) rats. The result showed formaldehyde-induced lesions included inflammation, epithelial degeneration, respiratory epithelial hypertrophy, and squamous metaplasia.

Woutersen, R.A [26] investigated long-term inhalation toxicity with formaldehyde mixed with acetaldehyde and acrolein-acetaldehyde was carried out in rats, exposed to 0, 750, 1500, and 3000/1500 ppm of the test compound for 52 weeks and killed after recovery periods of 26 or 52 weeks. Potential histopathological changes

 Table 1: Review of summing of potential health effects of formaldehyde exposure.

Studies	Formaldehyde concentration (mg/kg)	Subjects	Exposure time	Health effects	
Lang, et al. [17]	30-50	Human	4 hours	Subjective sensory irritation in eyes	
Afrin, et al. [16]	07-10	Rats and mice	10-30 days	Congestion, haemorrhages, necrosis and degeneration of liver parenchyma	
	1000, 5000, 10,000	Rats	24 hours	Renal dysfunction	
Ramos, et al. [19]				Inflammation	
				Redox imbalances	
T	0.2-4	Guinea pigs, rabbits	20-30 minutes	Negative inotropic response	
				Brady cardiac	
				Acute pumping failure	
I ani, et al. [20]				Metabolic acidosis	
				Disintegration of muscle myofibrils	
				Hypertrophic hearts	
Ahmed, et al. [21]	10 days 10 Female C3H mice	Female C3H mice	10 days	Neurotoxicity	
				Behaviours	
				Interrupts Biochemical parameters	
		Cerebral oxidant damage			
WHO [22]	251 to 300			Decrease food and water intake, body weight, GIT disturbances	
	101 to 150	Rats and Mice	24 hours		
	50 to 100				
Sari D [23]	0.08*, 0.4, 2	Rats	16 h/day, 5 days/week, for 12 weeks	Increase in number of CRH-ir neurons and in basal levels of all markers of HPA activities in Hypothalamus-pituitary-adrenal gland axis	
	Adverse pres	gnancy outcomes	s and genetic eff	ects of formaldehyde exposure	
Despite few studies ha	we reported formaldehyde in human and animal stu	provoked sponta dies has no conci	neous abortion se evidence relat	and low birth weight, a review on adverse pregnancy outcomes and ed to adverse pregnancy outcomes following formaldehyde exposure	

ormaldehyde exposure in human and animal studies has no concise evidence related to adverse pregnancy outcomes following formaldehyde exposur [24]. This study also justified such evidence as reporting biases and publication biases among the epidemiological studies.

But, there is evidence that increased frequencies of chromosome aberrations have been found in individuals with occupations that involve formaldehyde exposures in morticians, fertilizer manufacturer workers, and anatomy laboratory workers [25].

*=the least toxic dose of formaldehyde

like epistaxis, hyperplasia, loss of sensory and sustentacular cells, anosmia, hyper and metaplasia of the respiratory epithelium frequently accompanied by keratinization and occasionally by the proliferation of atypical basal cells were appeared to be more extensive in the nasal cavity, this includes both olfactory and respiratory zone of the nasal cavity.

The Animal study by Monticello, et al. [27] suggested airflow-driven formaldehyde dose showed nonlinear kinetics of formaldehyde binding to DNA accounting for the nonlinearity and site-specificity of formaldehyde-induced nasal cancer, in rats.

A human study by Boysen M, et al. showed formaldehyde related effects in nasal cavity, especially the presence of possible precancerous lesions, in the nasal mucosa of workers exposed to formaldehyde. Nasal biopsies of workers occupationally exposed to formaldehyde for more than five years showed a higher degree of metaplastic alterations, epithelial dysplasia, recurrent epistaxis, and nasal stenosis.

Purchase IFH, et al. [28] investigated formaldehyde response in nasopharyngeal cancer in men and reported there was a concern to cause a carcinogenic response in exposed populations, particularly the upper respiratory tract, in animals and man [29].

A cross-sectional approach adopted to investigate medical students reported that most frequent symptoms were unpleasant smell (91.2%), itching in the eyes (81.3%), and excessive lacrimation (76.1%). Formalin-exposed staff reported symptoms of skin disorders as drying (75%), eczema (68.8%), and allergic contact dermatitis (87.5%), besides, eye irritation (68.8%), respiratory tract irritation (93.8%), and work-related bronchial asthma (53.3%) [30].

Albert RE [31] studied carcinogenic response to the combined and separate exposures to formaldehyde (HCHO) and hydrochloric acid (HCI) in male inbred SD rats and no carcinogenic response was observed with HCI alone, but HCHO accounted for most, if not all, of the carcinogenic activity of the mixture of HCHO-HCI. Even though hydrochloric acid is tissue irritant, it is not carcinogen like formaldehyde so that it causes no carcinogenic effects in human and other animals. The carcinogenic response of the mixture of HCL and HCHO is purely due to the presence of formaldehyde.

Namavar M [32] investigated formalin effects on the Nose and Throat of Personnel of Anatomical Sciences Departments in Iran Medical Schools and validated a significant association between smell decrement and formaldehyde levels and described the occurrence of nasal irritation even below 0.75ppm.

Another study by Maronpot J [33] showed the toxicity of formaldehyde vapor in B6C3F1 mice exposed at the doses of 0, 2, 4, 10, 20, or 40 ppm for thirteen weeks. The result showed more squamous metaplasia and inflammation was shown in nasal tissues of male and female mice at the dose of 10, 20, and 40 ppm and in the larynx of treated animals at 20 and 40ppm. Clinical abnormalities (dyspnea, listlessness, and hunched posture), significant mortality, and body weight loss were observed in the 40 ppm groups. Pathologic changes were observed in the nose, larynx, trachea, and bronchi of treated males and females and in the uterus and ovaries of treated females. Squamous metaplasia and inflammation were present in the nasal tissues of male and female mice in the 10, 20, and 40 ppm groups and the larynx of males and females in the 20 and 40 ppm groups.

OPEN OACCESS Freely available online

Njoya HK, et al. [34] investigated the histopathological effects 40% formaldehyde vapor exposure on tracheal and lungs of adult Wistar rats for fifteen, twenty, twenty-five, and thirty days, in which some of the tissues were excised and assayed for Malondialdehyde (MDA) and catalase activities while others were processed for light microscopic investigation. The result showed day dependent ulceration and metaplasia of the trachea epithelium, ulceration of the alveoli, hyperkeratosis, necrotic lesions, and desquamation.

A cross-sectional study by Horvath EP, et al. [35] on 100 workers by using modified, respiratory symptom questionnaire and spirometry were administered and before and after their work shift and formaldehyde levels were determined for each test subject. The result suggested dose-dependent excess of irritant symptoms and a statistically significant decline in lung function parameters.

Kose E, et al. [36] evaluated the harmful effects of formaldehyde (FA) inhalation on sperm concentration, sperm quality, serum testosterone levels, and the rat testes with possible protective effects of rose oil against to these harmful effects, on 21 albino-Wistar rats. The epididymal sperm concentration and progressive sperm motility significantly decreased. It can be expressed that serious damages occurred via formaldehyde exposure in the male reproductive system and that the rose oil had protective effects against these damages.

Golalipoor MJ, et al. [37] investigated histopathologic and morphometric changes following exposure of formalin on Wistar rats of 6-7 postnatal weeks for 18 weeks. The result showed that a decrease in germ cells and a thickening of the basal membrane of the seminiferous tubules and these changes were related to the duration of the formaldehyde exposure. In the study by Tootian Z, et al. [38] the total number of 150 mice (60 male and 90 female) were used and subjected to the intraperitoneal treatment of formaldehyde daily at doses of 0, 2.5, 5, 7.5, and 10 mg kg/body weight in 40 days. The results showed that the formaldehyde could exert a significant effect on body weight, gonadal-somatic-index, fertility, motility, and viability of sperm. The data suggest that the formaldehyde could affect some of the testis function.

Histological study of testes mice specimens by Vosoughi S, et al. [39] revealed the displacement of germinal cells and degeneration of Leydig cells and seminiferous tubules. The result also showed serum testosterone decreased significantly (P<0.001) and the percentages of progressively motile sperm indicated a significant decrease (P<0.05) in short and long term exposure, respectively.

Exposure of 10% formaldehyde 2 hr per day in 8 male Wistar rats showed high sperm mortality and abnormality associated with a remarkable decrease in sperm count. It also revealed with decreased serum level of testosterone (p < 0.05) and down-regulated antioxidant status versus the control group. It suggested that histological adverse effects on the testicular tissue, spermatogenesis, sperm viability, count, and abnormalities can cause infertility after sexual maturation [40].

In the study of Ozen OA, et al. [41] adult albino Wistar rats were exposed to formaldehyde at sub-acute and sub-chronic and concentrations (0; 12.2; 24.4 mg.L-1). The result showed sub-acute or sub-chronic exposure to formaldehyde have caused growth retardation and altered levels of trace elements, including copper, zinc, and iron, in testicular tissue, and may induce further oxidative damage on testicular tissue leading to sperm abnormalities. The above results demonstrating formaldehyde related effects on the respiratory system and testis are summarized in Table 2.

Table 2: Short summary	of formaldehyde related	toxic effects in the respiratory system and testis.
,	1	1 , ,

Studies	Doses	Area of exposure	Duration of exposure	Animal species	Formaldehyde related toxic effects			
Clair MB [26]	40, 200, 400, and 800 mM of formaldehyde	Nostril		male Fischer 344 (F-344) rats	Inflammation, epithelial degeneration, respiratory epithelial hypertrophy, and squamous metaplasia			
Woutersen, R.A [27]	0, 750**, 1500, and 3000/1500 ppm of acetaldehyde and acrolein- acetaldehyde	Nasal cavity	52 weeks	Wistar rats	Epistaxis, hyperplasia, loss of sensory and sustentacular cells, anosmia, hyper and metaplasia			
Monticello, et al. [28]	0, 0.7**, 2, 6, 10 or 15 ppm	Nasal cavity		Wistar rats	Site-specificity of formaldehyde-induced nasal cancer,			
Boysen M et al. [29]	0.5, 2 and >2ppm	Nasal cavity	5 years	Human	Higher degree of metaplastic alterations, epithelial dysplasia, recurrent epistaxis, and nasal stenosis			
Purchase IFH, et al. [30]	2 .0**, 5 .6 or 14.3 ppm	Nasopharynx	24 months	Human	Nasopharyngeal cancer			
Noha Selim Mohamed Elshaer, et al. [31]	10%**	Respiratory system, eyes and skin	1 hr	Human	Unpleasant smell (91.2%), itching in the eyes (81.3%), and excessive lacrimation (76.1%), symptoms of skin disorders as drying (75%), eczema (68.8%), and allergic contact dermatitis (87.5%), besides, eye irritation (68.8%), respiratory tract irritation (93.8%), and work-related bronchial asthma (53.3%)			
Albert RE [32]	14 ppm** HCOH, and HCI, 10 ppm	Nasal cavity	20 months	Inbred SD rats	Carcinogenic response			
Namavar M [33]	0.75ppm	Nasal cavity		Human	occurrence of nasal irritation			
					Dyspnea, listlessness, significant mortality, and body weight loss at 40 ppm.			
Maronpot J [34]	0,2**,4,10,20,and 40ppm	Upper respiratory tract	30 weeks	B6C3F1 mice	Pathologic changes in the nose, larynx, trachea, and bronchi			
					Squamous metaplasia and inflammation in the nasal tissues at 10, 20, and 40 ppm and the larynx at 20 and 40 ppm.			
Njoya HK, et al. [35]	40% **formaldehyde	Tracheal and lungs	15, 20, 25, and 30 days	Adult Wistar rats	Ulceration and metaplasia of the trachea epithelium, ulceration of the alveoli, hyperkeratosis, necrotic lesions, and desquamation			
Horvath EP et al. [36]	10%** formaldehyde	Lungs	15 days	Human	Excess of irritant symptoms and a statistically significant decline in lung function parameters.			
Kose E, et al. [37]	10 ppm/1 h	Testis	35 days	Albino wistar rats	The epididymal sperm concentration and progressive sperm motility significantly decreased			
Golalipoor MJ, et al. [38]		Testis	18 weeks	Albino wistar rats	Decrease in germ cells and a thickening of the basal membrane of the seminiferous tubules			
Tootian Z, et al. [39]	0, 2.5**, 5, 7.5, and 10 mg kg/	Testis	40 days	Mice	Significant effect on body weight, gonadal-somatic- index, fertility, motility, and viability of sperm			
Vosoughi S, et al. [40]	10** and 20 ppm	Testis	35 days	Mice	Serum testosterone decreased significantly (P < 0.001) and the percentages of progressively motile sperm indicated a significant decrease (P < 0.05) in short and long term exposure, respectively			
Razi M, et al. [41]	10%" of formaldehyde	Testis	2 hours	Wistar rats	Adverse effects on the testicular tissue, spermatogenesis, sperm viability, count, and abnormalities can cause infertility after sexual maturation			
Ozen OA, et al. [42]	0; 12.2"; 24.4 mg.L-1	Testis		Albino wistar rats	Growth retardation and altered levels of trace elements, including copper, zinc, and iron, in testicular tissue, and may induce further oxidative damage on testicular tissue leading to sperm abnormalities			
**= the least toxic dose of formaldehyde								

DISCUSSION

The site-specific and dose-dependent effects of formaldehyde vapor on the nasal cavity

Despite the deleterious effects of formalin is the peak, in Ethiopia, observation showed negligence related to indoor formaldehyde exposure toxicity. No health and safety rules that enforce for the safety of the staff and students as well as no any safety data sheets for this chemical by the lab first aid kit and also on the notice board outside the dissection room. Due to poor laboratory setting, medical students and anatomy staff are highly exposing to formaldehyde related health symptoms. Personal protective equipment Eye/face shield, chemical safety goggles, chemical protective clothing (gloves, aprons & boots) are needed when working with formaldehyde workplace to minimize exposure routes of formaldehyde.

Inspired air is brought high into the nose so that environmental pollutants easily affect the respiratory and olfactory zone of the nasal cavity. Health risks of indoor inhaled nasal toxicants are challenging workers exposed to formaldehyde at the workplace. Animal and human studies suggested high susceptibility of the nasal cavity to environmental pollutants. There is also evidence that workers exposed to formaldehyde for a long period may develop formaldehyde tolerance, the mechanisms underlying it are still lacking. The study by Yorgancilar E, et al. [42] showed the incidence of nasal lesions after acute exposure of formaldehyde, in rats. Daydependent health symptoms were found to be itching, stuffy nose, and epistaxis. No treatment-related effects in both respiratory and olfactory epithelium at a low dose (1ppm), but marked necrosis and thickening were observed in the respiratory epithelium at high dose exposure (3ppm). This is characterized by dose, site-specific, and cell type-dependent cytotoxicity in the respiratory zone of the nasal cavity. Following severe nasal effect in an experimental animal, it is certain that nasal effects in experimental animals can be translated to potential human health risks, in the presence of infrequent personal protective equipment in the dissection room.

Similarly, the relative toxicities of formaldehyde at the doses of 40, 200, 400, and 800 mM on male Fischer 344 (F-344) rats showed formaldehyde related response only on the respiratory mucosa of anterior nasal passages and its severity was at the concentration above 200mM of dose exposure [27]. This showed that formaldehyde elicits a toxic response at a higher dose and not equally responsive at various zones of the nasal cavity. The olfactory zone remains unaltered at both low and high doses of formaldehyde exposure in animals. This can be attributed to the expression of unfolded protein response genes, transcripts Xbp1, spliced Xbp1, Chop (Ddit3), and BiP (Hspa5) and regulate defense mechanism activated by many types of insults [43]. On contrary, long-term inhalation toxicity of formaldehyde with acetaldehyde and acrolein-acetaldehyde induced rats showed marked epistaxis, hyperplasia, anosmia, and metaplasia of both the respiratory and olfactory epithelium in the nasal cavity [43,44]. This is an only a dose-dependent effect on both olfactory and respiratory epithelia of the nasal cavity, but that of other studies by Yorgancilar E, et al. [42] & Clair [25] have indicated dose, site-specific, and cellular type-dependent effects on the respiratory epithelium. The former effect is site-specific and cellular-dependent potentially marked at respiratory epithelium and more specific to the pseudo-stratified ciliated columnar epithelium, but the toxic effects of formaldehyde and other aldehydes were observed at both the olfactory and respiratory zone of the nasal cavity. This proves that the olfactory epithelium is responded to mixture exposure to aldehydes and a combination of different aldehydes at similar duration exposure more severe in the nasal cavity.

The carcinogenic effect of formaldehyde exposure in the nasopharynx

The studies showed that humans are more sensitive to indoor and outdoor air pollutants and responded to a low dose of inhaled chemicals like formaldehyde. Nasal biopsies of workers occupationally exposed to formaldehyde for more than five years showed a higher degree of metaplastic alterations, epithelial dysplasia, recurrent epistaxis, and nasal stenosis [30]. This is a long term effect and indicates that formaldehyde may be potentially carcinogenic to man. Workers in the anatomy department especially the embalmers are at risk in developing long term nasal cancer if the concentration of embalming fluid is not monitored regularly. Similarly, the carcinogenic response to the combined and separate exposures to formaldehyde (HCHO) and hydrochloric acid (HCI) was investigated in male inbred SD rats and no carcinogenic response was observed with HCI alone, but HCHO accounted for most, if not all, of the carcinogenic activity of the mixture of HCHO-HCI [31]. Even though hydrochloric acid is tissue irritant, it is not carcinogen like formaldehyde so that it causes no carcinogenic effects in human and other animals. The carcinogenic response of the mixture of HCL and HCHO is purely due to the presence of formaldehyde.

Dose and day dependent formaldehyde exposure induces a carcinogenic effect in the nasal cavity and suggests that formaldehyde as a carcinogen chemical. The combined exposure of formaldehyde with HCL induced no carcinogenic effect in the nasal cavity. HCL may induce toxicity when contact with the body, but the study showed it is not purely carcinogenic like formaldehyde.

The World Health Organization [45] stated that the presence of 2.3 to 6.1 ppm formaldehyde in a single cigarette and it was also proved that smoking of two packs of cigarettes per day corresponds to an intake of 1mg dose of formaldehyde. Therefore, the workers who are more close to gross anatomy laboratory and smokers are more vulnerable in developing health effects related to formaldehyde exposure. In the study by Kernset WD, et al. [46] 6ppm dose of formaldehyde with sufficient duration of exposure showed potential induction of substantial development of nasal tumors. Feron VJ, et al. [47] also suggested the health risk of air pollutants in open-air on the nasal mucosal tissue and smoking are risk factors for squamous cell carcinoma in the nasal cavity and paranasal air sinus. Also, tissue damage and reactive epithelial hyperplasia in nasal carcinogenesis have become extremely viable for indicating that formaldehyde exposure triggers nasal cancer in humans. Long term effects of formaldehyde with duration of time and concentration of high dose exposure most necessarily induce carcinoma in the upper respiratory tract. Increased number of cell proliferation due to formaldehyde induced damage may be potential mechanisms for the development of nasal cancer. It was also revealed that day-dependent formalin exposure in cadaver embalmers, medical students, and anatomists result in the development of blood cancer.

Ohtsuka R, et al. [48] assessed a high capacity of IgE production and hyper responsiveness to exposure to allergens and the higher responsive nasal and tracheal mucosa in BN and F344 rats after the inhalation of aerosol formaldehyde. The incidence of clinical signs such as sneezing and abnormal respiration in

formaldehyde-treated F344 rats was found to be higher than that in formaldehyde-treated BN rats, but significant tissue damage was prominent only to the nasal mucosa of BN rats. The health effect of formaldehyde-treated animals seems species-specific than sitespecific. This finding is contrary to the site-specific and cellulardependent effects of formaldehyde in the nasal cavity. It seems that BN rats have lower responsiveness to formaldehyde exposure than F344 rats. Therefore, workers having a higher sensitivity to allergies will have an increased risk of this serious allergy-induced reaction of formaldehyde. So, awareness is mandatory for people occupationally exposed to formaldehyde vapor.

A human study showed long term exposure to formaldehyde by Namavar M [32] validates a significant association between smell decrement and formaldehyde levels and the occurrence of nasal irritants at even low dose (<0.the 75ppm). The study, by Sin Eng Chia, et al. [49] stated that medical students' evaluation showed that runny nose alone as the significant association with sex (P=0.049, 2.09 times runny nose than males) in the gross anatomy laboratory. Additionally there is an evidence which stated that runny nose and direct contact with formaldehyde vapor on medical students' exposed to 0.5 to 0.74ppm formaldehyde in a gross anatomy dissection laboratory has no significant differences in the pre and post-exposure, however, there was a decreased ability to smell and throat irritation in exposed groups. Formaldehyde related health symptoms were significantly related to the time and place of occurrence. The symptoms are related to the time of exposure and place of occurrence. Indoor and outdoor concentration of formaldehyde and at different corners of the dissection room and expected health symptoms may vary. Time of exposure and distance are important variables for runny nose and sore throat in humans. For example, anatomists, embalmers, technicians, and medical students who work near the cadaver embalming room or close to the cadaver are more likely to develop a runny nose and sore throat.

The reason why females had 2.09 times runny nose than males may suggest the presence of higher susceptibility to formaldehyde vapor in female students. There is a report stating that IgE allergen sensitization rate for the 11 allergens evaluated in the blood tests was about 10% higher for adult males than adult females overall (all age groups) and including a meta-analysis of 591 studies which showed that approximately 65% of adults with allergies were women [50].

Exposure of formaldehyde below 0.74 ppm showed gradual decrements of its toxic effects but at the same dose, medical students showed no significant changes after formaldehyde exposure. The gradual over time runny nose reduction in employees in the anatomy department suggests the development of formaldehyde tolerance and it may be due to a higher duration of time in the dissection room.

The upper trachea developed squamous metaplasia at low exposure concentration, but that of the bronchial epithelium was confirmed only at a high dose of 40ppm in the mice model. It seems that formaldehyde at low doses has no definite toxic effects in treated groups, but high pathologic changes observed in the lower respiratory system are the most likely dose-dependent effect. The upper respiratory tract responds to a low dose of formaldehyde vapor, but down the lower respiratory formaldehyde easily tends to be absorbed and converted to formate [45]. Multiple scientific pieces of evidence from animal and human suggested potential effects of formaldehyde exposure causing squamous cell carcinoma, myeloid leukemia, and sinonasal squamous cell carcinoma, mostly limited to long term and high exposure concentrations of formaldehyde in the nasopharynx.

Dose-dependent and site-specific effect of formaldehyde exposure and anti-inflammatory responses in the lower respiratory system

Most of the animal studies showed dose, long-term, and sitespecific effects of formaldehyde in the lower respiratory system. A similar dose and duration of exposure, various studies showed formaldehyde toxicity differences at the lower respiratory tract and therefore such discrepancy would most likely be due to the degree of exposure and the species-specific. It provides a better understanding of the mechanism of formaldehyde induced toxicity anchored on metabolism and genotype-phenotype dependent that may define susceptibility and resistance [51].

Formaldehyde has a dose-dependent and species-specific response at the lower respiratory tract, including lung tissue architecture. As we go down to the lower respiratory tract, inhaled formaldehyde starts to be absorbed in the lungs, so that a high degree of this vapor is required to induce inflammatory or fibrogenic effects. Supporting this idea, the report by Valérie L, et al. [52] showed that interleukin-11 (IL-11) was well-known to contribute to lung inflammatory diseases, which could be involved in putative deleterious inflammatory and fibrogenic pulmonary effects of this volatile organic compound (VOC). Even though formaldehyde responds to high dose in the lower respiratory tract, in this study induction of interleukin 11 by the environmental contaminants in lung tissues and low interleukin-11 (IL- 11) receptors in the experimental animals is the major contributing effect of formaldehyde related response in the lower respiratory tract.

The hyperkeratosis and metaplasia in trachea and desquamation and necrotic lesions with significant alveolar ulceration in the lungs is supported by histopathological changes, with no any alveolar ulceration [46,53]. But significant lung weight decrement and observed only in the formed study. This difference is due to the high concentration of aqueous formaldehyde used for longduration being an extremely toxic substance causing ulceration of alveoli in rats. This ulceration of the alveoli was by excavation and desquamation of the surface epithelium and derangement with distorted supporting tissues of the alveolar wall. The significant relative weight decrement was associated with ulceration of alveoli due to damage of covering epithelium and supporting tissues of the alveolar wall by toxic effects of formaldehyde. The increment in the activities of malondialdehyde in the trachea and lungs of treated animals was the result of oxidative stress of formaldehyde and the associated link between cellular damage and oxidative stress to cause lipid peroxidation as a result of the production of free radicals [54].

Oxidative stress is highly manifested to dose-dependent formaldehyde induced toxic effects in lung tissues. Some novel agents like Caffeic Acid Phenethyl Ester (CAPE) have a potentially positive effect and might be effective in protecting the injury of remote organs caused by oxidative stress and neutrophil accumulation, in animals. In supporting this, Türkoğlu A, et al. [55] reported that CAPE is a potent inhibitor of lipoxygenase and the abolishment of leukocyte chemotaxis and inflammatory activity in damaged tissues in the lungs. On the contrary, other study showed the presence of negative effects in another species of active oxygen and some tissue injury after administration of a high dose

of CAPE (10μ mol/kg), in rats [56-59]. But, despite the effectiveness of CAPE in protecting the injury, tissue injury related to another species of active oxygen at a dose of 10μ mol/kg) was observed. This disparity observed between the two studies may be due to observer error or technical and the report of the negative effects of CAPE on other cells in formaldehyde-induced acute lung damage in rats suggested that the scientific finding of their observations mandate further studies.

Oxidative stress, following formaldehyde exposure and the reverse response of anti-inflammatory agents, in testis

Nutritional, socio-economic, lifestyle, and environmental factors have been attributed to compromising male reproductive health [59]. In recent years, a large volume of evidence by Mathur, et al. [60] suggested that decreasing male fertility (in terms of sperm count, quality, and other changes in male reproductive health) might be due to exposure to environmental toxicants. This report also indicated that such environmental toxicants like formaldehyde can easily mimic natural estrogens and target testicular spermatogenesis and harm the function of both Sertoli and Leydig cells. Many animal studies indicated oxidative stress-induced tissue damage following dose-dependent formaldehyde exposure. The study by Zhou DX, et al. [61] showed day dependent oxidative stress of formaldehyde in testicles of adult male rats. These include the disintegration of Leydig cells, edematous interstitial tissues with vascular dilations. These histopathological changes were partially reversed and showed similar normal testicular tissue features with 30mg/kg doses of vitamin E [60]. Similarly, eutrophication and reduction of seminiferous tubule diameters and decreased amount of Leydig cells were analyzed as long term effects of testicular tissue in rats and mice [37,39]. Morphometric changes in seminiferous tubules may be due to damage of Leydig cells and intercellular link damage and these effects might have led to inhibition of spermatogenesis. The histopathologic and morphometric alterations in testis have a strong link with exposure duration periods. Reduction in seminiferous tubules morphology may be due to the formaldehyde inhibitory effects on increasing the amount of collagen in testicular tissue, resulting in the thickening of interstitial and lamina propria of the seminiferous tubules which prevents the development of germinal cells.

The review report on oxidative stress (harms and benefits for human health) by Pizzino G, et al. [14] showed that environmental stressors like ultraviolet, ionizing radiations, pollutants, and heavy metals and xenobiotics contribute to greatly increase reactive oxygen species production, therefore causing oxidative stress. Like that of CAPE, more agents are responsible to reverse formaldehyde related oxidative stress. In supporting this, several antioxidants [vitamin E, flavonoids, and polyphenols) were used in a similar report by Pizzino G, et al. [14] for their definite reversible effect against oxidative stress, in testicular tissues.

Similarly, the report by Mingde, T, et al. [62] suggested that vitamin E as a powerful anti-oxidant and a scavenger of hydroxyl radicals, and it has been shown to have anti-inflammatory activities in body tissues. So, like that of CAPE; vitamin E, flavonoids, and polyphenols are favorable constituent to reverse oxidative stress in testicular tissue architecture.

The reactive oxygen species are important mediators of cellular injury and lower the antioxidant system by increasing testicular lipid peroxidation product, malondialdehyde. Likewise, the evidence of decrement percentage of motile sperms along with the percentage of sperm viability by oxidative stress by Vosoughi S, et al. [39] was clear that increasing infertility may be as a result of reduced sperm viability, not the quantity of sperm present during ejaculation.

A study by Aitken RJ et al. [63] said that testicular tissues remain vulnerable to oxidative stress as a result of abundant unsaturated fatty acids and the presence of potential reactive oxygen species (ROS). In addition to this, Tang, et al. [64] suggested that the presenting main pathological changes in testicle tissue of formaldehyde-treated animals showed degeneration of functional cells in the testicle and also the significant decline of copper and zinc in testicle tissue were high. Based on this report, the effect of lipid peroxidation may be one of the toxicity mechanisms of formaldehyde on genetic materials; because formaldehyde could induce genetic materials in spermatogenic lineage and caused degeneration and necrosis in secondary spermatocyte, spermatogenic cell which will ultimately decrease the sperm quantity and viability.

In the study by Aslan O, et al. [65] subacute or sub-chronic exposure to formaldehyde has caused growth retardation and altered levels of trace elements, including copper, zinc, and iron, in testicular tissue, and may induce further oxidative damage on testicular tissue leading to spermatozoal abnormalities. Formaldehyde has deleterious effects on testicular tissue, decreases levels of reproductive hormones, and demolishes sperm quality and quantity. There is evidence by the report of Kaba M, et al. [66] which suggested that increases in Co, Cu, Mg, and Pb levels and decreases in Zn, Mn, and Fe levels in testicular tissue can play important roles in the induction of testicular cancers. Such alterations may be, therefore, important in the pathogenesis of testicular cancers.

Animal studies showed that day dependent exposure to formaldehyde has therefore a potential effect in testis. The possible negative manifestation of oxidative stress is due to the altered levels of trace elements in formalin treated testicular tissues and the most viable consequence of formaldehyde in testis tissue architecture is due to its potential to stimulate the reactivity of trace elements.

CONCLUSION

The toxic effects of formaldehyde exposure depend on the type of lining epithelia, degree of exposure, timing, administration ways, animal models utilized, sexual category, and presenting of other mixed aldehydes. Studies showed long term carcinogenic potential of formaldehyde in the nasopharynx with cytotoxic and proliferative mechanisms. In the lower respiratory tract and testis, dose-dependent tissue damage by reactive species was common leading to oxidative stress.

Several studies concluded that long-term exposure to formaldehyde causes squamous cell carcinoma in the nasal mucosa. Most animal studies showed dose and day dependent effects of formaldehyde in the lower respiratory system and these are due to the continuous formation of reactive oxygen species in cells. High oxidative stress from reduced trace elements of formaldehyde exposed testicular tissue is apparent and may lead to male sterility which is believed to be the result of sperm viability and quantity.

Formaldehyde causes dose-dependent oxidative stress, which is generally known to be detrimental to respiratory and testicular tissues. Formaldehyde has day-dependent carcinogenic effect in the upper respiratory tract. The possible negative manifestation of oxidative stress is due to the altered levels of trace elements in

Tesfay S, et al.

formalin treated testicular tissues and the most viable consequence of formaldehyde in testis tissue architecture is due to its potential to stimulate the reactivity of trace elements. From the review, it was concluded that females as the most sensitive, 20 minutes as the least exposure duration and 0.08 milligram per kilogram (mg/ kg) as the least toxic dose of formaldehyde exposure. Moreover, the effectiveness of some antioxidants and or an anti-inflammatory such as vitamin E, fish omega-3, melatonin, rose oils, flavonoids, polyphenols, and CAPE was observed in the treatment of the harmful effects of formaldehyde induced tissue impairments. Despite complete prevention is impossible, laboratory technicians, instructors, and medical students should be cautious of the impending danger associated with formaldehyde vapor.

RECOMMENDATIONS

From the present review and analysis, the following important concerns are recommended:

Deep study should be traced to elucidate the mechanism underlying the anti-oxidative and or anti-inflammatory effects of Melatonin, fish omega-3, CAPE, rose oils, flavonoids, polyphenols and Vitamin E in repairing of formaldehyde induced tissue damage.

Further study also needed to find genetic and genomic markers that could identify individual's susceptibility to formaldehyde toxicity.

More further findings and effectiveness of alternative agents like Shellac, glutaraldehyde, formaldehyde to water ratio 1:3, ammonium carbonate, salt-containing solutions and phenoxyethanol should be ensured as these are most likely less toxic, environmentally friendly alternative agents for cadaver preservation.

More carefully designed studies need to be done on oxidative stress and carcinogenic effects of formaldehyde on the vital organs with less defined dosage, graded exposure duration periods & appropriate animal models in consideration.

The anatomy department or unit should periodically measure and accurately determine exposure limits of formaldehyde and use suitable personal protective measurements.

The university or health sector should provide extreme protection and offer potential exposure monitoring, determinations, medical surveillance and respirator fit testing in anatomy laboratories.

Anatomy laboratories are indispensable to the training of anatomists, conducting research in anatomical sciences or providing anatomical services and therefore each laboratory should be well suited and conventional. Personal protective equipment eye/face shield, chemical safety goggles, chemical protective clothing (gloves, aprons & boots) are needed when working with formaldehyde at work place to minimize exposure routes of formaldehyde.

By taking the toxic effects of formaldehyde in thought, embalmers, laboratory technicians, instructors and medical students should be thoughtful of the oxidative damage and carcinogenic effect of formaldehyde in respiratory tract and testis.

OPERATIONAL DEFINITIONS

Oxidative stress: The process of imbalance between free radicals formed and anti-oxidants/molecules the can donate an electron to a free radical, in the body.

Permissible exposure limit: When the amount of formaldehyde in work place is very low.

Short term exposure limit: The tolerable time of formaldehyde exposure at workplace.

Long term exposure limit: The maximum exposure permitted over 8-hour reference period.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

The authors contributed equally to the work:

ST: Conceptualization, Investigation, Writing- original draft, Reviewing & editing,

NH: Investigation, Writing- original draft, Reviewing & editing.

 $AG{\boldsymbol{:}}$ Structuring of the manuscript, Investigation, Reviewing & editing

ZN: Structuring of the manuscript, Investigation, Reviewing & editing

ETHICAL STATEMENT

The authors of this study confirm that they have written original work, suitably citing the work and/or word of other investigators.

COMPETING INTERESTS

The authors have declared that no competing interest exists.

FUNDING

The authors declare no funding source for this study.

REFERENCES

- 1. Agency for toxic substances and disease registry (ATSDR). Toxicological profile for formaldehyde. US department of health & human services. Atlanta, US. 2004;232-334.
- Bedino JH. Formaldehyde exposure hazards and health effects: a comprehensive review for embalmers. Expanding encyclopedia of mortuary practices. 2004;650:2653-2657.
- Raja T, Dewan S. Potential health hazards for students exposed to formaldehyde in the gross anatomy laboratory. J Environ Health 2011;33:445-447.
- 4. http://www.ehha.ca.gov/./formaldehydepr.pdf
- 5. Ki-Hyun K, Jahan SA, Lee JT. Exposure to formaldehyde and its potential human health hazards. J. Environ. Sci. Health C 2011;29:277-299.
- Kaden DA, Mandin C, Nielsen GD, Wolkoff, P. Formaldehyde. WHO Guidelines for Indoor Air Quality: Selected Pollutants. Geneva: World Health Organization; 2010;3.
- 7. Occupational Safety and Health Administration. Substance technical guidelines for formalin. 1910.
- 8. Flemming CR, Groten JP, Feron VJ. Changes in the nasal epithelium of rats exposed by inhalation to mixtures of formaldehyde, acetaldehyde, and acrolein. Toxicol Sci 1996;29:208-218.
- 9. Kita T, Fujimura M, Myou S, Ishiura Y, Abo M, Katayama N, et al. Potentiation of allergic bronchoconstriction by repeated exposure to formaldehyde in guinealpigs in vivo. Clin Exp Allergy 2003;33:1747-1753
- Slikker JW, Andersen ME, Bogdanffy MS, Bus JS, Cohen SD, Conolly RB, et al. Dose-dependent transitions in mechanisms of toxicity: case studies. Toxicol Appl Pharmacol 2004;201:226-294.

Tesfay S, et al.

- 11. Nita M, Grzybowski A. The role of the reactive oxygen species and oxidative stress in the pathomechanism of the age-related ocular diseases and other pathologies of the anterior and posterior eye segments in adults. Oxid Med Cell Longev 2016;2016:3164734.
- 12. Sydney AJ. Pharmacology of free radicals and the impact of reactive oxygen species on the testis. J Reprod Infertil 2013;14:158.
- Lee E, Hardman CA & Charlton C. Excessive s-adenosyl-I-methionine dependent methylation increases levels of methanol, formaldehyde and formic acid in rat brain striatal homogenates: Possible role in s-adenosyl-I-methionine induced Parkinson's disease-like disorders. Int J Toxicol 2008;83:821–827.
- Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative stress: harms and benefits for human health. Oxid Med Cell Longev 2017;2017:8416763.
- Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev 2010;4:118.
- Isabelle L, Bruckner T, Triebig G. Formaldehyde and chemosensory irritation in humans: a controlled human exposure study. Regul Toxicol Pharmacol 2008;50:23-36.
- Afrin M, Amin T, Karim R, Islam, MR. Effects of formaldehyde intoxication on liver of Swiss albino mice. IOSR Journal of Agriculture and Veterinary Science 2016;9:76-81
- De Oliveira Ramos C, Nardeli CR, Campos KKD, Pena KB, Machado DF, Bandeira ACB, et al. The exposure to formaldehyde causes renal dysfunction, inflammation and redox imbalance in rats. Exp Toxicol Pathol 2017;69:367-372.
- 19. Takayuki T, Horiguchi Y. Effects of formaldehyde on cardiac function. J Pharmacol Sci 1990;52:563-572.
- Ahmed S, Ozen OA, Sarsilmaz M. The toxic effects of formaldehyde on the nervous system. Reviews of environmental contamination and toxicology. Springer 2010;105-118.
- 21. World Health Organization. WHO guidelines for indoor air quality: selected pollutants. 2010.
- 22. Sari DK, Kuwahara S, Tsukamoto Y, Hori H, Kunugita N, Arashidani K, et al. Effect of prolonged exposure to low concentrations of formaldehyde on the corticotropin releasing hormone neurons in the hypothalamus and adrenocorticotropic hormone cells in the pituitary gland in female mice. Brain Res 2004;1013:107-116.
- 23. Collins JJ, Ness R, Tyl RW, Krivanek N, Esmen NA, et al. A review of adverse pregnancy outcomes and formaldehyde exposure in human and animal studies. Regul Toxicol Pharmacol 2001;34:17-34.
- 24. https://birthdefects.org/formaldehyde/
- Clair MB. Pathology and cell proliferation induced by intra-nasal instillation of aldehydes in the rat: CIIT, Research Triangle Park, North Carolina 27709. J Pathol 2008;18:353-361.
- Wouterson RA, Feron VJ. Inhalation toxicity of acetaldehyde: Progression and regression of nasal lesions after discontinuation of exposure. J Toxicol 1987;47:295-303.
- 27. Monticello TM, Swenberg JA, Gross EA, Leininger JR, Kimbell JS, Seilkop S, et al. Correlation of regional and nonlinear formaldehyde induced nasal cancer with proliferating populations of cells. J Natl Cancer Inst 1990;56:1012-1022.
- Boysen M, Zadig E, Digernes V, Abeler V, Reith A. Nasal mucosa in workers exposed to formaldehyde: A Pilot study. J Toxicol 1990;47:116-121.
- Purchase IFH, Paddle GM. Does formaldehyde cause nasopharyngeal cancer in man? Central Toxicology Laboratory and Epidemiology Unit 1989;134-144.

- Mohamed Elshaer NS, Elsayed Mahmoud MA. Toxic effects of formalin-treated cadaver on medical students, staff members, and workers in the Alexandria Faculty of Medicine. Alexandria J Med 2017;53:337-343.
- Albert RE, Sellakumar AR, Laskin S, Kuschner M, Nelson N, Snyder CA. Gaseous formaldehyde and hydrogen chloride induction of nasal cancer in the rat. J Natl Cancer Inst 1982;68:597-603.
- 32. Namavar M. Formalin effects on the nose and throat of personnel of anatomical sciences departments in Iran Medical Schools. Webmedcentral 2012;3:1-4.
- 33. Maronpot J. Evaluation of the toxicity of formaldehyde vapour in b6c3f1 mice. Int J Toxicol 2012;3:388–391.
- 34. Njoya HK, Ofusori DA, Nwangwu SC, Amergoro, Akinyeye AJ, Abayomi TA. Histopathological effect of exposure of formaldehyde vapor on the trachea and lungs of adult wistar rats. Int J Integr Biol 2009;7:160-165.
- 35. Horvath EP, Anderson H, Pierce WE, Hanrahan L, Wendlick JD. Effects of formaldehyde on the mucous membranes and lungs: A study of an industrial population. JaMa, 1988;259:701-707.
- Kose E, Sarsilmaz M, Tas U, Kavakli A, Turk G, OzlemD. Rose oil inhalation protects against formaldehyde-induced testicular damage in rats. Andrologia 2012;44:342-348.
- Golalipoor MJ, Azarhoosh R, Ghafari S, Gharravi AM, Fazel SA, Davarian A. Formaldehdye exposure enduces histopathologic and morphometric chnges in rat testis. Int J Morphol 2007;66:167-178.
- Tootian Z, Tajik P, Fazelipour S, Taghava M. Effect of formaldehyde injection on function of mice testis. Int. J. Pharmacol 2007;3:421-424.
- Vosoughi S, Khavanin A, Salehnia M, Asilian HM, Soleimanian A. Effects of simultaneous exposure to formaldehyde vapor on mice testicular tissue and sperm parameters. International Quarterly Journal, 2012;3: 114-116.
- 40. Razi M, Malekinejad H, Sayrafi R, Hosseinchi MR, Feyzi S, Moshtagion SM, et al. Adverse effects of long-time exposure to formaldehyde vapour on testicular tissue and sperm parameters in rats. Vet Res Forum 2013;4:213.
- Ozen OA, Yaman M, Sarisilmaz M, Songur A, Kus I. Testicular zinc, copper and iron concentrations in male rats exposed to sub-acute and sub-chronic formaldehyde inhalation. J Trace Elem Med Biol 2002;16:119–122.
- 42. Yorgancilar E, Deveci E, Deveci S. Effects of formaldehyde on respiratory mucosa in rats. Int J Morphol 2012;30:521-523.
- Sammeta N, McClintock ST. Chemical stress induces the unfolded protein response in olfactory sensory neurons. J Comp Neurol 2010;10:1825-1836.
- 44. Flemming C, Groten J, Feron V. Changes in the nasal epithelium of rats exposed by inhalation to mixtures of formaldehyde, acetaldehyde, and acrolein: Division of toxicology, nutrition and food research institute, Zeist, the Netherlands. J Toxicol 1996;29:208-218.
- WHO. International Programme on Chemical Safety (IPCS) (1989). Environmental Health Criteria 1989;222-333.
- 46. Kernset WD, Pavkov KL, Donofrio DJ, Gralla EJ, Swenberg JA. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. J Natl Cancer Inst 1983;43:4382-4392.
- Feron VJ, Arts JH, Kuper CF, Slootweg PJ, Woutersen RA. Health risks associated with inhaled nasal toxicants. Crit Rev Toxicol 2001;31:313-47.
- 48. Ohtsuka R, Shuto Y, Fujie H, Takeda M, Harada T, Itagaki S, eta l. A further comparative study on early histological changes in respiratory tract of brown Norway and fischer-344 rats after short-term inhalation of formaldehyde aerosol. J Toxicol Pathol 1998;11:235-240.

Tesfay S, et al.

- 49. Chia SE, Ong CN, Foo S, Lee HP. Medical students exposure to formaldehyde in a gross anatomy dissection laboratory. J Am Coll Health 1992;41:115-119.
- 50. https://www.medicalnewstoday.com/articles/327318
- 51. Nagaishi C. Functional Anatomy and Histology of the Lungs. Baltimore University Park Press 1972:223-244.
- 52. Valérie L, Matthieu A, Sarah A, Noémie H, Marc LV, Jouneaua S et al. Mapk- and pkc/creb-dependent induction of interleukin- 11 by the environmental contaminant formaldehyde in human bronchial epithelial cells. Int J Toxicol 2012;292:13–22.
- 53. Dinsdale D, Riley RA, Verschoyle RD. Pulmonary cytochrome P450 in rats exposed to formaldehyde vapor. J Environmental Toxicol 1993;62:19-27.
- Javedan M, Entezarizaher T. Cytotoxic effect of formaldehyde vapor on rat nasal mucosa during 3- and 30- day periods. J Pathol 1999;2:17-23.
- 55. Türkollu A, Sarsilma M, Colakollu N, Zararsiz I, Kulollu T, Pekmez H, et al. Formaldehyde-induced damage in lungs and effects of caffeic acid phenethyl ester: A Light Microscopic Study. Eur J Intern Med 2008;5:152-156.
- Mirzoeva OK, Calder PC. The effect of propolis and its components: An eicosanoid production during the inflammatory response. Cent Eur J Med 1996;55:441- 449.
- 57. Armutcu F, Temel S, Özen S, Uzun A, Akyol Ö. Inhibitory effect of caffeic acid phenethyl ester on bleomycine-induced pulmonary fibrosis, in rats. Iran J Pharm Sci 2004;339:65-75.

- Calikoglu M, Tamer L, Sucu N. The effects of caffeic acid phenethyl ester on tissue damage in lung after hind limb ischemia-reperfusion. J Pharmacol 2003;48:397-403.
- 59. Sharma R, Biedenharn KR, Fedor JM, Agarwal A. Lifestyle factors and reproductive health: taking control of your fertility. Reprod Biol Endocrinol 2013;11:66.
- 60. Mathur, Premendu P, D'cruz SC. The effect of environmental contaminants on testicular function. Asian J Androl 2011;13:585.
- 61. Zhou DX, Qiu SD, Zhang J, Tian H, Wang HX. The protective effect of vitamin E against oxidative damage caused by formaldehyde in the testes of adult rats. Asian J Androl 2006;8:584-588.
- 62. Mingde T, Xie Y, Yi Y, Wang W. Effects of formaldehyde on germ cells of male mice. Wei sheng yan jiu Journal of hygiene research 2003;32:544-548.
- 63. Aitken RJ, Roman SD. Antioxidant systems and oxidative stress in the testes. Oxid Med Cell Longev 2008;1:15-24.
- 64. Ashok A, Virk G, Ong C, Du Plessis SS. Effect of oxidative stress on male reproduction. World J Mens Health 2014;32:1-17.
- 65. Ozen OA, Yaman M, Sarsilmaz M, Songur A, Kus I. Testicular zinc, copper and iron concentrations in male rats exposed to subacute and subchronic formaldehyde gas inhalation. J Trace Elem Med Biol 2002;16:119-122.
- 66. Kaba M, Pirinççi N, Yüksel MB, Geçit I, Günel M, Demir M, et al. Serum levels of trace elements in patients with testicular cancers. Int Braz J Urol 2015;41:1101-1107.