VOC MIXTURES: TOXICITY AND ADVERSE HEALTH EFFECTS ASSOCIATED WITH COEXPOSURE TO XYLENE AND FORMALDEHYDE

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ABSTRACT

Volatile organic compounds (VOCs) are organic chemicals characterized by high vapor pressure which causes molecules to readily evaporate and escape into the environment. Two common VOCs with wide and varying applications are xylene and formaldehyde. Significant exposures to these two chemicals commonly occur in occupational settings, particularly in medical and scientific laboratories. Although the health effects and some of the toxicological mechanisms of xylene and formaldehyde individually are known, few studies have been conducted to evaluate the combined effects of these two compounds. The purpose of this research project is to investigate and analyze the potential health effects of a combined exposure to xylene and formaldehyde. Our findings indicate that coexposure to xylene and formaldehyde affects cells at the molecular level, causing various detrimental health effects. Several studies that have been conducted in the animal model combing the exposures of formaldehyde and xylene and have shown potential adverse effects to the urinary (kidneys), digestive (liver) and neurological (brain) systems. Some of the mechanisms for the coexposures include increasing antioxidant levels in the liver and kidneys and increasing the production of reactive oxygen species in the brain. However, to date there is not enough research on this topic to determine the extent of the toxicological effects from coexposure to formaldehyde and xylene.

INTRODUCTION

Xylene and formaldehyde are often used in industrial and commercial processes, scientific and medical laboratories, and agriculture. [27][24][3] While these two chemicals share several common applications, their structures are quite different. Xylene (C_8H_{10}) is a flammable aromatic hydrocarbon; it is found in 3 isomeric forms: ortho-, para-, and meta-xylene. [27][8] Formaldehyde (CH_2O) is a simple aldehyde and does not consist of a carbon ring; it is also a natural product of metabolism in humans and animals.[23] Because of their volatile nature, both chemicals are readily absorbed into the body through inhalation exposure, though exposure through dermal contact and the gastrointestinal tract are possible as well. [27][28][24][3] Both chemicals pose many similar known and potential health risks, including neurological, dermal, and respiratory effects. [27] [28][24][2]

Both chemicals can be found outside of the occupational setting. Xylene is released into the environment through solid waste and the application of pesticides. [19] It has been found to contaminate ground water and ground soil. [5] Once introduced into the environment, xylene is broken down by biodegradation but has been found to persist in the environment for up to 198 days. [5][21] Xylene has also been detected in ground soil through bio-indicators such as plants and trees. [21][30] The soil degradation rates agree with the idea that lower water tables increase aerobic biodegradation of xylene. [21][30]

Formaldehyde is released into the environment by industrial processes and combustion.[10] Once the compound reaches the environment, it is mainly found in the atmosphere after being released in a gaseous phase and therefore not usually found in ground soil or ground water. [1] In the atmosphere, formaldehyde undergoes a photochemical reaction, transforming into a nitrogen oxide (⟦NO⟧x). [1] The concentration of formaldehyde in the atmosphere is directly correlated with the yearly seasonal pattern. [1][10] Formaldehyde is broken up in the environment through photochemical reactions and biodegradation. [10]

Xylene is primarily metabolized by oxidation which occurs in the liver, producing methylhippuric acid which is finally excreted in urine [27]. Although Formaldehyde can be metabolized by various pathways, it is mostly metabolized into formic acid by formaldehyde dehydrogenase (FDH) [12]. The formic acid is then excreted in urine as formate [12]. Multiple mechanisms of toxicity are known for both formaldehyde and xylene; however, little information is known about the toxicological effect of these two chemicals resulting from a coexposure. Despite these knowledge gaps, a few studies have been conducted that show combined effects from coexposure to formaldehyde and xylene on the liver, kidneys, and brain in the animal model [15,16,29].

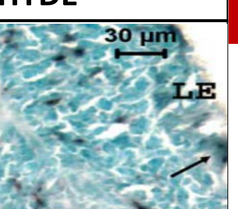
EXPOSURE

CHEMICAL	ROUTES OF EXPOSURE
XYLENE	• **Dermal** contact (slow absorption) [27] - lack of PPE (i.e. gloves)[28] • **Inhalation** (rapid absorption) [27] - lack of PPE (i.e. mask)[28] • **Gastrointestinal tract** [28] • **Oral** [27] Xylene is more readily absorbed through oral and inhalation exposure and to a lesser extent through dermal contact [27][8]
FORMALDEHYDE	• **Dermal** contact [24] • **Inhalation** [24] • **Gastrointestinal tract** [24][3] • **Fetal** through **maternal** exposure [3] [23]

SOURCES OF EXPOSURE IN COMMON

INDUSTRIAL/COMMERCIAL
-furniture [27][24][3]
-rubber [27][24]
-cleaning and disinfecting products [27][24]

SCIENTIFIC/MEDICAL LABORATORY
-**xylene** as solvent: makes tissues translucent [27][8]
-**formaldehyde** for embalming, cadavers, and scientific specimen preservation [24]



[3]

AGRICULTURAL
-pesticides [8][24]

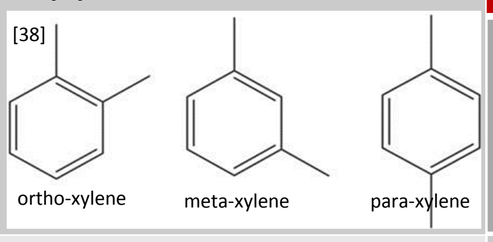
OTHER
-tobacco, cigarette smoke [27][3][13]


[3]

HEALTH EFFECTS

CHEMICAL	KNOWN
XYLENE	• Neurological: headache, fatigue, depression, cognitive, dizziness [28][27] • Eyes: color vision impairment (indicates neurotoxicity), irritation [18] • Reproductive: spontaneous abortion [27] • Dermal: eczema, urticaria [27] • Respiratory: lung damage (bleeding, swelling, congestion), decreased function [27] • Gastrointestinal discomfort: vomiting, nausea [27] • Kidney [27] • Liver [27] • Nasal and throat irritation [27] • Auditory damage [8]
FORMALDEHYDE	• Neurological: central nervous system damage [24] [2]; cognitive, depression, and anxiety [20] • Eyes: irritation, blindness [24] • Reproductive: spontaneous abortion [24][3], testicular autophagy [11], premature birth [3], teratogenic/birth defects [3], inhibited hormone production and abnormal trophoblast differentiation [23] • Cancer (known carcinogen): bone marrow damage and leukemia [31], nasopharyngeal [24] • Dermal: dermatitis, lesions [24] • Respiratory: airway irritation, pneumonia, respiratory disease [24] • Nasal irritation [24]

[38]



POSSIBLE FROM COEXPOSURE TO XYLENE AND FORMALDEHYDE

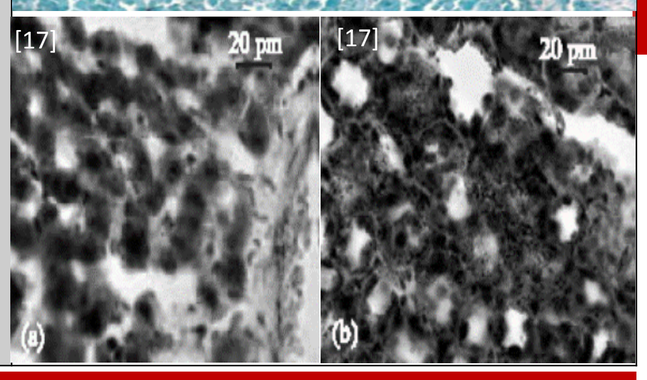
IMMUNE SYSTEM
- Significantly correlated with an increase in CD4- and CD8-positive T cells in bronchus-associated lymphoid tissue (BALT) in developing and adult rats. Implication: **affects immunity**. [26]
- Considerable increases in T cells containing alpha-naphthyl acetate esterase (ANAE) in the BALT of adult rats; concentrations of these cells also increased significantly in the peripheral blood of rats in all exposure groups. Implication: **may affect immunity** in both **BALT and at the systemic cellular level** (pictured). [25]

LIVER AND KIDNEY
- With rats, body and liver weights were measured and activity levels of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and malondialdehyde (MDA) were determined. Implication: **hepatotoxic**, causing **decreased liver weight** and **affecting oxidative stress levels**, particularly in embryos and very young rats. [15]
- Using Sprague-Dawley rats, researchers measured activity levels of SOD, CAT, GSH, MDA, and glutathione peroxidase (GSH-Px). Nephrotoxicity was investigated by measuring serum concentrations of creatinine and urea. Total albumin and protein levels were also determined. Implication: alone and combined, **cause kidney toxicity**; xylene more nephrotoxic. [16]
- After 6 weeks of exposure, fine granular fat deposits developed in both the livers and kidneys in growing and adult rats. Implication: leads to **fatty liver and kidney** (pictured). [17]

REPRODUCTIVE SYSTEM
- Formaldehyde alone and xylene + formaldehyde appeared to decrease seminiferous epithelial height. These findings indicate that xylene-formaldehyde co-exposure can **negatively affect** the **male reproductive system**. [9]

[25]

[17]

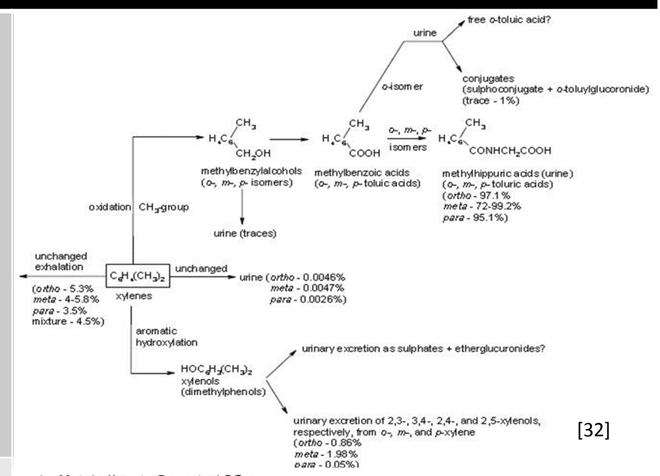


REGULATORY

STANDARD	FORMALDEHYDE	XYLENE
Cal/OSHA PEL [34]	0.75 ppm	100 ppm
Cal/OSHA STEL [34]	2 ppm	150 ppm
Cal/OSHA AL [34]	0.5 ppm	-
Cal/OSHA C [34]	-	300 ppm
NIOSH IDLH [35]	20 ppm	900 ppm
EPA MCL [36]	-	10 mg/L
CDPH NL [37]	0.1 mg/L	-

METABOLISM

CHEMICAL	METABOLIC PATHWAY(S)
XYLENE	• A chain methyl group of Xylene is oxidized by mixed function oxidases in the liver which form methyl benzoic acids which then are conjugated with glycine to yield methylhippuric acid. [27] Proceeding metabolism and biotransformation methylhippuric acid is excreted in urine. This metabolic pathway occurs regardless of exposure route or isomer. [27] • Small amounts of Xylene are excrete unchanged in exhaled breath and urine. [22] • Although Xylene is metabolized and excreted quickly in the body, accumulation in muscle and adipose tissue can occur with chronic exposure. [27]
FORMALDEHYDE	• Metabolism from formaldehyde to formate occurs in all of the tissues of the body and the formate is removed form the body by the surrounding blood supply. [12] • Formaldehyde dehydrogenase (FDH) is the major metabolic enzyme that oxidizes formaldehyde to form formic acid [4] • The primary metabolites of the FDH pathway are formate and CO_2 [12] • Formaldehyde can also form cross linkages between protein and between protein and single stranded DNA if it is not metabolized by FDH [4] • Formaldehyde can also bind to tetrahydrofolate and enter the C_1 intermediary metabolic pool [4]. • Formaldehyde is rapidly metabolized in the body and therefore storage of formaldehyde in the body is not considered to have an effect on toxicity [12]



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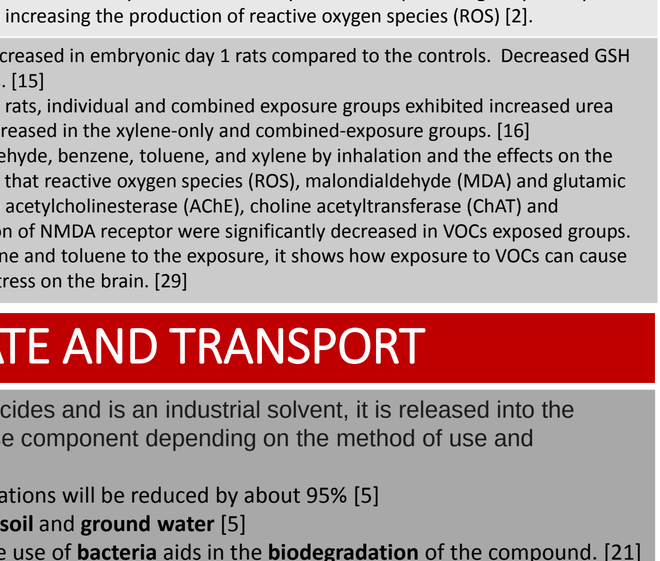

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MECHANISMS OF TOXICITY

CHEMICAL	MECHANISMS
XYLENE	• The lipophilicity of Xylene is responsible for its irritant and narcotic effects by it ability to dissolve lipid membranes. [6] • Inhaled m-Xylene disrupted $GABA_A$ receptor binding in one study, it was determined that m-Xylene was distributed unevenly in the rat brain with an infinity for the cerebellum and altered the [^{35}S] TBPS binding which may have effected changes in $GABA_A$ receptor binding. This mechanism may explain the adverse effect of m-Xylene on motor coordination. [14]
FORMALDEHYDE	• Forms crosslinks between DNA and proteins and is incorporated into macromolecules in respiratory and olfactory mucosa [12] • Nucleophilic sites on cell membranes, such as the amino groups in protein and DNA, react easily with the electrophilic carbonyl atom of the formaldehyde molecule [7] • In one study, acute oral exposure to formaldehyde caused DNA damage, apoptosis, and neuronal injury in rabbit brains. Further, the regulation of the cytotoxic action of formaldehyde is carried out by free radical producing enzymes by inhibiting antioxidant systems and therefore increasing the production of reactive oxygen species (ROS) [2].
XYLENE + FORMALDEHYDE	• In rat livers, CAT activities and MDA levels increased in embryonic day 1 rats compared to the controls. Decreased GSH levels were detected in day-old infantile rats. [15] • Regarding kidney toxicity in Sprague-Dawley rats, individual and combined exposure groups exhibited increased urea concentrations, and GSH and MDA levels increased in the xylene-only and combined-exposure groups. [16] • In one study, mice were exposed to formaldehyde, benzene, toluene, and xylene by inhalation and the effects on the brain were analyzed. The researchers found that reactive oxygen species (ROS), malondialdehyde (MDA) and glutamic acid (Glu) were increased significantly, while acetylcholinesterase (AChE), choline acetyltransferase (ChAT) and acetylcholine (ACh) levels, and the expression of NMDA receptor were significantly decreased in VOCs exposed groups. [29] Although this study also includes benzene and toluene to the exposure, it shows how exposure to VOCs can cause neurotransmitter disruption and oxidative stress on the brain. [29]

ENVIRONMENTAL FATE AND TRANSPORT

XYLENE	• Since xylene is a component of pesticides and is an industrial solvent, it is released into the environment as a solid or liquid-phase component depending on the method of use and application. [19] • After **day 198**, the total xylene concentrations will be reduced by about 95% [5] • Has been found to contaminate **ground soil** and **ground water** [5] • Takes a long time to break down, but the use of **bacteria** aids in the **biodegradation** of the compound. [21] • Can be detected in ground soil through **bio-indicators** such as **plants** and **trees** [21][30]
FORMALDEHYDE	• Released into the **atmosphere** and is not typically found in soil and ground water [1] • Released into the environment through **gas-phase** releases from many industrial processes such as vehicle and industrial combustion, natural soil, water treatment, and road dust. **Secondary formations** of formaldehydes come from oil combustion and vegetative burning [10] • Once introduced into the atmosphere, it undergoes a **photochemical reaction**, transforming into a nitrogen oxide (⟦NO⟧x). [1] • **Broken up** in the environment through **photochemical reactions** and **biodegradation** [10]

CONCLUSION

Xylene and formaldehyde pose a legitimate threat to human health, particularly in occupational settings in which workers are subjected to chronic exposures to these two VOCs. These substances enter the body through similar routes of exposure and produce many similar negative health effects. What is not as clear, however, are the toxicological mechanisms taking place at the molecular level as a result of coexposure to formaldehyde and xylene. Studies show that such exposures appear to affect various biomarkers involved in oxidative stress. Of particular interest is a study which investigated these chemicals' combined effects in rat livers; xylene and formaldehyde in combination appeared to drastically decrease levels of GSH compared to exposure to each chemical individually, suggesting that they may interact in an additive manner [15]. In contrast, coexposure to formaldehyde and xylene has shown increases in oxidative stress in the liver and kidneys of rats; however these effects appear to be less than additive, therefore more research is needed to determine the toxicological significance of the coexposure to these chemicals.

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