Health Hazards of Xylene: A Literature Review

ABSTRACT
Xylene, an aromatic hydrocarbon is widely used in industry and medical laboratory as a solvent. It is a flammable liquid that requires utmost care during its usage. On exposure the vapours are rapidly absorbed through the lungs and the slowly through the skin. Prolonged exposure to xylene leads to significant amount of solvent accumulation in the adipose and muscle tissue. This article reviews the various acute and chronic health effects of xylene through various routes of exposure.

INTRODUCTION
Xylene is one of the top 30 chemicals produced in the United States in terms of volume. It is used extensively as a solvent in the rubber, printing and leather industries. It is also used as a thinner for paints, cleaning agent and in varnishes. A small amount of xylene is also found in airplane fuel and gasoline [1]. In the field of histopathology xylene is used as a clearing agent that gives translucency to the tissues. Technical grade xylene is a combination of the three isomers: Ortho, Para and Meta. This mixture is referred to as ‘Xylol’ [2].

Xylene is released primarily from industrial sources. One can also come in contact with xylene through automobile exhaust and a variety of consumer products such as cigarette smoke, paints, varnish, rust preventives and shellac. Skin contact with xylene-containing products is also a likelihood of exposure to xylene. Workers in certain occupation are likely to get exposed to xylene. They include distillers of xylene, metal workers, wood processing plant workers, furniture refinishers and biomedical laboratory workers [1].

Studies have shown that xylene is well-absorbed by the inhalational, oral and to some extent by the dermal route. According to a study by Rihimaki and Savolainen exercise increased the amount of xylene absorbed that was directly reflected by the amount of methylhippuric acid excreted in the urine. Once absorbed, xylene enters into the blood and gets distributed throughout the body. The biotransformation of xylene regardless of the isomer/route of administration proceeds through the oxidation of a side chain methyl group by mixed function oxidases in the liver to form methyl benzoic acids that conjugate with glycine to yield methyl hippuric acid which is excreted in the urine. Most of the xylene that enters the body leaves within 18 hours after the end of the exposure [3].

Following prolonged exposure especially by occupational means it is likely to get accumulated chiefly in the muscle and adipose tissues. The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended Biological Exposure Index (BEI) for various chemicals including xylene [1]. The BEIs are not to be used for the diagnosis of an occupational illness but as an indicator of exposure to significant concentrations of the chemical substances if the workers show values of the analyte at/ above the value of its BEI [4]. The amount of biomarker of xylene exposure in urine can be analysed using techniques such as High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) [1].

In 1986 Abu Al Ragheb et al., reported the occurrence of pulmonary congestion and oedema in the post-mortem examination of a

INHALATIONAL EXPOSURE
Acute inhalational exposure to mixed xylene at 200 ppm for 3-5 minutes resulted in irritation of the nose and throat [9]. Morley et al., has reported an autopsy of a worker who died owing to several hours of exposure to xylene fumes while painting. Focal areas of intra-alveolar haemorrhage and pulmonary oedema with severe lung congestion were seen at the acute exposure of 100 ppm [10]. Uchida et al., has done an extensive study and reported the signs and symptoms of workers who have been chronically exposed to mixed xylene. A significant increase in throat and nasal irritation has been found in workers chronically exposed to xylene fumes [11]. Decreased pulmonary function and dyspnoea was reported by Hipolito RN among histology technicians chronically exposed to xylene in the laboratory.

In the same study cardiovascular effects such as flushing, palpitations and chest pains were seen among the histology technicians [12]. Several authors have reported various gastrointestinal symptoms such as gastric discomfort, nausea and vomiting in workers chronically exposed to xylene vapours. The authors have also specified that there was a cessation of such symptoms on terminating the exposure. Uchida et al., in his review of 175 workers chronically exposed to mixed xylene at 14 ppm has observed a reduction in the grasping power in the extremities. No adverse hepatic and renal effects were observed in the same study [11]. In the study by Hipolito RN and Uchida et al., several subjective neurological symptoms such as anxiety, dizziness, inability to concentrate and forgetfulness have been observed among subjects chronically exposed to vapours of xylene [11,12]. Taskinen et al., observed spontaneous abortions in female pathology technicians exposed to formalin and xylene although the study could not conclusively conclude that xylene was the direct cause of this effect [13].

ORAL EXPOSURE
In 1986 Abu Al Ragheb et al., reported the occurrence of pulmonary congestion and oedema in the post-mortem examination of a
person who had committed suicide by the consumption of xylene. He also observed no other adverse effects to the cardiovascular or gastrointestinal systems. He concluded that the death of the person was due to a centrally mediated depression of the respiratory system [14].

Condie et al., in his animal study of oral exposure to mixed xylene had observed an increase in hyaline droplet change in the male rats and early chronic nephropathic changes in the female rats exposed to mixed xylene for 90 days. It was therefore concluded that such continuous change could result in renal cell damage [15].

In the report of an accidental ingestion of xylene in a person by Recchia et al., it was found that it resulted in a persistent coma for more than 26 hours [16]. Condie et al., in his animal study reported signs of convulsions, hyperactivity, epistaxis and hypersalivation along with increased aggressiveness in rats given mixed xylene for 90 days [15].

**DERMAL EXPOSURE**

In acute dermal exposure of xylene by hand immersion technique in humans by Engstrom et al., and Riihimaki and Pfaffli, it was reported that it was associated with vasodilation of the skin of the hand, dryness and scaling of the area and skin erythema of the hand. It was also found that in patients with a history of atopic dermatitis who were symptom-free, it resulted in the development of toxic eczema of the hands of such subjects on exposure to xylene. It was also found that in such patients a three time greater absorption rate of xylene was observed compared to the other subjects in the study [17,18].

Palmer and Rycroft in 1993 also reported the occurrence of urticaria in a female technician of cytology laboratory who was predominantly exposed to vapours of xylene in the occupational environment. It was effectively proved that it was as a result of direct exposure to xylene by the performance of a closed patch test which elicited severe erythema and whealing of the skin [19].

**OCULAR EXPOSURE**

Several studies such as Nelson et al., Uchida et al., and Hake et al., have observed irritation of the eye on exposure to xylene vapours [9,11,20]. Hine and Zuidema in their animal study of instillation of 0.1 ml of mixed xylene directly to the eyes of rabbits resulted in moderate irritation of the eyes [21].

The various literatures on the health effects of xylene are tabulated according to the different routes of exposure [Table/Fig-1-3].

**DISCUSSION**

Xylene, a synthetic hydrocarbon produced from coal tar is a widely used as a universal solvent. Various health effects due to xylene exposure have been documented in the literature. A number of theories exist for the mechanisms by which xylene exerts its toxic effects on the various systems of the body. The pulmonary, gastric and ocular effects of xylene are attributed to the irritant nature of the chemical [1]. Some authors have suggested that certain metabolic intermediates such as methylibenzaldehyde may be responsible for the toxic effects of xylene. Inhibition of pulmonary microsomal enzymes by the binding of such toxic metabolites thereby inactivating the enzymes also might contribute to the toxic nature of xylene [22].

The mechanism of nephrotoxicity of xylene may be related to the reactive metabolite formation which subsequently causes irritation of the renal tissues or direct membrane fluidization [1,22,23]. According to Franchini et al., the urinary β-glucuronidase levels in humans exposed to xylene are high thereby indicating a faster turnover of the renal cells due to toxicity of the toxic metabolites of the chemical [24].

Padilla and Leyerly in their study have demonstrated a decrease in the axonal transport of stimuli following xylene exposure [25]. A decreased hypothalamic catecholamine levels following exposure to xylene has been observed by Andersson et al., [26]. The toxic symptoms of the central nervous system such as dizziness could be attributed to the liposolubility of xylene in the neuronal membrane according to Savolainen and Pfaffli. He has also suggested that xylene disturbs the activity of the proteins that are essential for normal neuronal function [27].

<table>
<thead>
<tr>
<th>System</th>
<th>Type</th>
<th>Dose</th>
<th>Time</th>
<th>Signs &amp; symptoms</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Mixed</td>
<td>200 ppm</td>
<td>3-5 min</td>
<td>Nose &amp; throat irritation</td>
<td>Nelson et al., 1943 [9]</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Mixed</td>
<td>10,000 ppm</td>
<td>Acute exposure (autopsy)</td>
<td>Death, severe lung congestion with focal interalveolar hemorrhage, pulmonary edema</td>
<td>Morley et al., 1970 [10]</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Mixed</td>
<td>Unspecified</td>
<td>Chronic occupational exposure</td>
<td>Labored breathing, impaired pulmonary function</td>
<td>Hipolito 1980 [12]</td>
</tr>
<tr>
<td>Respiratory</td>
<td>p-xylene</td>
<td>100 ppm</td>
<td>1-7.5 hrs/ day for 5 days</td>
<td>Nose &amp; throat irritation</td>
<td>Hake et al., 1981 [20]</td>
</tr>
<tr>
<td>Respiratory</td>
<td>mixed</td>
<td>14 ppm</td>
<td>7 yrs</td>
<td>Nose &amp; throat irritation</td>
<td>Uchida et al., 1993 [11]</td>
</tr>
<tr>
<td>GI</td>
<td>mixed</td>
<td>Unspecified</td>
<td></td>
<td>Nausea, vomiting, gastric discomfort</td>
<td>Hipolito 1980 [12]</td>
</tr>
<tr>
<td>Hematology</td>
<td>mixed</td>
<td>14 ppm</td>
<td>7 yrs</td>
<td>No effects</td>
<td>Uchida et al.,1993 [11]</td>
</tr>
<tr>
<td>Muscle</td>
<td>mixed</td>
<td>14 ppm</td>
<td>7 yrs</td>
<td>Decreased grasping power &amp; muscle power in extremities</td>
<td>Uchida et al.,1993 [11]</td>
</tr>
<tr>
<td>Hepatic</td>
<td>mixed</td>
<td>14 ppm</td>
<td>7 yrs</td>
<td>No change in serum biochemical values</td>
<td>Uchida et al.,1993 [11]</td>
</tr>
<tr>
<td>Renal</td>
<td>mixed</td>
<td>10,000 ppm</td>
<td>Acute exposure</td>
<td>Increased blood urea, distal tube academia, decreased urinary clearance of endogenous creatinine, increased β-glucuronidase increased albumin, RBC and WBC excretion</td>
<td>Morley et al., 1970 [10]</td>
</tr>
<tr>
<td>Neuro</td>
<td>mixed</td>
<td>14 ppm</td>
<td>7 yrs</td>
<td>Increased anxiety, forgetfulness inability to concentrate, dizziness</td>
<td>Uchida et al., 1993 [11]</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Along with formalin</td>
<td>14 ppm</td>
<td>7 yrs</td>
<td>Spontaneous abortions</td>
<td>Taskinen et al.,1989 [13]</td>
</tr>
</tbody>
</table>

**Table/Fig-1**: Inhalational route

<table>
<thead>
<tr>
<th>System</th>
<th>Type</th>
<th>Dose</th>
<th>Time</th>
<th>Signs</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS</td>
<td>unspecified</td>
<td>suicide</td>
<td></td>
<td>Pulmonary congestion &amp; edema</td>
<td>Abu Al Ragheb et al., 1980 [14]</td>
</tr>
<tr>
<td>Neuro</td>
<td>mixed</td>
<td>Accidental ingestion</td>
<td>Coma for 26 hrs</td>
<td></td>
<td>Recchia et al., 1985 [16]</td>
</tr>
</tbody>
</table>

**Table/Fig-2**: Oral route
### Table/Fig-3: Dermal and ocular route

<table>
<thead>
<tr>
<th>System</th>
<th>Type</th>
<th>Dose</th>
<th>Time</th>
<th>Signs</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermal</td>
<td>m-xylene</td>
<td>unspecified</td>
<td>unspecified</td>
<td>Skin erythema, vasoconstriction, dryness, scaling of skin</td>
<td>Engstrom et al., 1977 [17]</td>
</tr>
<tr>
<td>Dermal</td>
<td>unspecified</td>
<td>unspecified</td>
<td>unspecified</td>
<td>Urticaria</td>
<td>Palmer and Rycroft 1993 [19]</td>
</tr>
<tr>
<td>Ocular</td>
<td>Mixed</td>
<td>200 ppm</td>
<td>3-5 min</td>
<td>Eye irritation</td>
<td>Nelson et al., 1943 [8]</td>
</tr>
<tr>
<td>Ocular</td>
<td>p-xylene</td>
<td>100 ppm</td>
<td>1-7.5 hrs for 5 days</td>
<td>Eye irritation</td>
<td>Hale et al., 1981 [20]</td>
</tr>
<tr>
<td>Ocular</td>
<td>Mixed</td>
<td>14 ppm</td>
<td>7 yrs</td>
<td>Eye irritation</td>
<td>Uchida et al., 1993 [11]</td>
</tr>
</tbody>
</table>

Dermal absorption is also a major route of xylene exposure especially among the laboratory workers. Hino et al., has stated that workers with eczema of the hands had higher urinary methyl hippuric acids (xylene metabolite). He has attributed the removal of ceramide of the corneal layer of the skin epithelium thereby leading to the disruption of epithelial barrier to this exaggerated percutaneous absorption of xylene in such atopic individuals [28]. Gunasekar et al., has performed a histopathological study of the rodent skin epithelium exposed to xylene. Separation at the epithelial-connective tissue interface with infiltration of granulocytes was observed. At a molecular level, increased levels of interleukin and inducible nitric oxide synthase protein was observed serving as indicators of skin irritation [29].

Methods to reduce absorption of xylene following its acute exposure have been highlighted in literature. The first step is to immediately remove the person from the source of exposure. Dermal and ocular exposure can be dealt by decontaminating the area by thoroughly washing with tepid water or normal saline and mild soap. In case of oral exposure emesis with ipecac syrup could be done only when one is certain that there is no likelihood of aspiration thereby leading to aspiration pneumonitis [1,30]. Ellenhorn and Barceloux have suggested the usage of diluted dish washing oils and limonene based substitutes as clearing agents in the place of xylene [38,39]. The introduction of such substitutes can help in circumventing the toxic effects of xylene [38-40].

**REFERENCES**

5. Mao RF, Chang FK and Chen ML. Delayed and competitively inhibited excretion of urinary hippuric acid in field workers co-exposed to toluene, ethyl benzene and xylene. Arch Env Contam Toxicol. 2007; 53: 675-83.
Sharada T. Rajan and N. Malathi, Health Hazards of Xylene


274

1. Senior lecturer, Department of Oral Pathology, Faculty of Dental Sciences, Sri Ramachandra University, Chennai, India.
2. Professor and Head, Department of Oral Pathology, Faculty of Dental Sciences, Sri Ramachandra University, Chennai, India.

Dr. Sharada T. Rajan,
Old No: 4, New No: 6, North avenue, Srinagar Colony, Saidapet, Chennai-600015, India.
Phone: 9840082472, E-mail: dr.sharadaganesh@yahoo.co.in

FINANCIAL OR OTHER COMPETING INTERESTS: None.