Appendix B
Section T

XYLENE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research

New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

Xylene is produced in large amounts in the United States and is primarily used as a solvent. Releases of xylene into the environment are estimated to be nearly 410 million kilograms annually. Levels in New Jersey drinking water have been found to range from 0.2 to 3.0 ppb. In general, xylenes are acutely toxic to animals and humans only at higher concentrations; the liver and central nervous system being most notably affected by chronic exposure. Embryotoxic and developmental effects have been demonstrated in animals exposed to xylene at low doses either orally or by inhalation. Pregnant women and their fetuses should therefore be considered high risk subpopulations. A maximum concentration level of 44 micrograms of xylene per liter of drinking water has been calculated to protect these populations.

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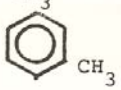
BACKGROUND INFORMATION AND PROPERTIES

m-XYLENE

Chemical Properties (U.S.EPA, 1984a, unless otherwise stated)

Synonyms: m-Dimethylbenzene, m-Xylol, and 1,3-Xylene (Sax, 1984)

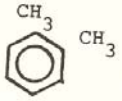
CAS #	108-38-3
Chemical formula	$C_6H_4(CH_3)_2$
Chemical structure	
Molecular weight	106.16
Physical state	colorless liquid (at room temperature)
Melting point	-48 °C
Boiling point	139.1 °C
Vapor pressure	6 mm Hg at 20 °C
Specific gravity	0.864 at 20 °C
Vapor density	3.7 (Toxicology Updates, 1982)
Water solubility	160 mg/L at 20 °C
Log octanol/water partition coefficient	3.20
Odor threshold, water	1.0 ppm
Odor threshold, air	Odor Index (at 20 °C)= 2100
Saturation concentration	35 g/m^3 at 20 °C (Verschueren, 1983)
Conversion factors	1 mg/m^3 = 0.23 ppm 1 ppm = 4.41 mg/m^3 (at 20 °C and 760 mm Hg)

BACKGROUND INFORMATION AND PROPERTIES

o-XYLENE

Chemical Properties (U.S.EPA, 1984a, unless otherwise stated)

Synonyms: o-Dimethylbenzene, o-Xylol, 1,2-Xylene (Sax, 1984)

CAS #	95-47-6
Chemical formula	$C_6 H_4 (CH_3)_2$
Chemical structure	
Molecular weight	106.17
Physical state	colorless liquid (at room temperature)
Melting point	-25 °C
Boiling point	144.4 °C
Vapor pressure	5 mm Hg at 20 °C
Specific gravity	0.88 at 20 °C
Vapor density	3.7 (Toxicology Updates,1982)
Water solubility	175 mg/L at 20 °C
Log octanol/water partition coefficient	2.77
Odor threshold, water	1.8 ppm
Odor threshold, air	0.73 mg/m^3 (0.17 ppm)
Saturation concentration	29 g/m^3 at 20 °C (Verschueren, 1983)
Conversion factors	1 mg/m^3 = 0.23 ppm 1 ppm = 4.41 mg/m^3 (at 20 °C and 760 mm Hg)

BACKGROUND INFORMATION AND PROPERTIES

p-Xylene

Chemical Properties (U.S.EPA, 1984a, unless otherwise stated)

Synonyms: p-Dimethylbenzene, p-Xylol; 1,4-Xylene (Sax, 1984)

CAS #	106-42-3
Chemical formula	$C_6H_4(CH_3)_2$
Chemical structure	
Molecular weight	106.17
Physical state	colorless crystalline solid (at room temperature)
Melting point	-13 °C
Boiling point	138.4 °C
Vapor pressure	6.5 mm Hg at 20 °C
Specific gravity	0.86 at 20 °C
Vapor density	3.7 (Toxicology Updates, 1982)
Water solubility	198 mg/L at 25 °C
Log octanol/water partition coefficient	3.15
Odor threshold, water	0.53 ppm
Odor threshold, air	Odor Index (at 20 °C) 18,200 (0.47 ppm)
Saturation concentration	38 g/m^3 at 20 °C (Verschueren, 1983)
Conversion factors	1 mg/m^3 = 0.23 ppm 1 ppm = 4.41 mg/m^3 (at 20 °C and 760 mm Hg)

Production and Use

Employed predominantly as a solvent, xylene is produced in very large quantities for a broad spectrum of applications. Its use is increasing as a "safe" replacement for benzene, and in gasoline as part of the benzene-toluene-xylene (BTX) component (Patty's Industrial Hygiene and Toxicology, 1982).

In 1983, the U.S. production of xylene was 5.57 billion pounds. It ranked 24th among the top 50 chemicals produced that year (Fishbein, 1985). The principal use of mixed xylenes is in the production of the p-xylene isomer, which amounted to 4.11 billion pounds in 1983; it ranked 29th among the top 50 chemicals produced in the U.S. that year (Fishbein, 1985).

The xylenes are widely used as solvents for inks, rubber, gums, resins, adhesives, and lacquers; as thinners and paint removers; in the paper coating industry; as a component of paint, varnishes, dyes, cements, cleaning fluids, and aviation fuels; as solvents and emulsifiers for agricultural products; in quartz crystal oscillators; in perfumes, insect repellants, pharmaceuticals, the production of hydrogen peroxide and in the leather industry (Sittig, 1981).

Guidelines, Regulations, and Standards

The National Academy of Sciences (NAS) has calculated a SNARL (Suggested No Adverse Response Level) for xylene of 21 mg/L for a 24-hour exposure period and 11.2 mg/L for a 7-day exposure period (NAS, 1980).

The U.S. Environmental Protection Agency (U.S.EPA) has issued a Health Advisory for xylenes which recommends longer-term Health Advisory numbers (HAs) for children (7.8 mg/L) and adults (27.3 mg/L). The lifetime HA for a 70-kg adult was calculated to be 0.44 mg/L with the assumption that 20% of the total exposure is contributed by drinking water (U.S.EPA, 1985).

The National Institute of Occupational Safety and Health (NIOSH) has established a time-weighted-average (TWA) of 100 ppm for a 10-hour/day, 40-hour work week, with a ceiling of 200 ppm (868 mg/m^3) as determined by a 10-minute sampling period (NIOSH, 1975).

The American Conference of Governmental Industrial Hygienists (ACGIH) specifies a TWA of 100 ppm (435 mg/m^3), and a short-term exposure limit (STEL) value of 150 ppm (655 mg/m^3) for exposure to xylene (ACGIH, 1983).

ENVIRONMENTAL EXPOSURE

Fate and Transport

Volatilization is the dominant process in the removal of xylene from water. Volatilization half-lives as predicted by the EXAMS mode range from 2.6 to 11.0 days (U.S.EPA, 1984a). Sorption will occur accounting for varying accumulations in the sediments (4.5 to 70% o the total xylene load from the EXAMS model). The rates are dependen on the type of environment, temperature, oxygen exchange rate, an amount of organic matter in the sediments (Burns et al., 1981).

Data are available that identify the xylenes in drinking water, a both the tap and the source. Biodegradation may be significant, bu appears to be highly variable (U.S.EPA, 1984a). The data indicate tha the xylenes are poorly to moderately degraded in water (U.S.EPA 1984a). Although the major reaction of volatile alkylated aromati hydrocarbons in the environment involves the oxidation of the sid chains, this does not appear to be a significant factor for xylen (Verschueren, 1983).

Ambient Levels

Xylenes have been detected in both air and water. No informatio is available concerning xylenes in food (U.S.EPA, 1984a). Releases o xylene into the environment each year are estimated to total nearly 41(million kg (NAS, 1980). Xylenes were ranked 13th in concentration i air out of 7,000 chemicals surveyed for occupational exposure; mor than 4 million workers are believed to be exposed (NAS, 1980).

The principal population at risk from xylene exposure is the occupational work force, which can be exposed to the emissions of mixe xylenes during both production and end-use, including its entensive us as an industrial solvent (Fishbein, 1985). Exposure of the genera public can also arise from automobile exhausts and the many consume products containing xylenes (Fishbein, 1985).

Levels of 0.05-0.15 mg/m^3 of xylenes have been reported in the atmosphere of some urban streets; while levels of 3 ug/L have bee found in some surface waters (Verschueren, 1983). In New Orleans, 0.2 mg/L of xylene (the isomers were unspecified) was found in the drinkin water (Verschueren, 1983).

In the 1982 U.S.EPA Ground Water Supply Survey (GWSS), 1.7% of the randomly sampled drinking water systems were found to have levels of xylene at or above the quantification limit of 0.2 ug/L. The median concentration was 0.3 ug/L for all isomers, with a maximum of 1.5 ug/L for m-xylene and 0.9 ug/L for o-, and p-xylene (U.S.EPA, 1984c).

During the period from 1978-1981, the New Jersey Department of Environmental Protection (N.J.DEP) collected approximately 500 water samples representing public water supplies statewide. o-Xylene was detected in 0.2% of the samples at a mean concentration of 0.4 ug/L (N.J.DEP, 1984).

From 1984 to 1985, the N.J.DEP found xylene contamination (all isomers) in 0.6% of the 635 drinking water samples analyzed during the initial round of testing under the Assembly Bill A-280 amendments to the N.J. Safe Drinking Water Act (N.J. SDWA). The mean xylene concentration was 1.0 ppb and ranged from a minimum of 0.2 ug/L to a maximum of 3.0 ug/L for the para-isomer (N.J.DEP, 1985).

METABOLISM AND PHARMACOKINETICS

Data on the pharmacokinetics of xylenes following oral ingestion are limited. Inhalation and dermal exposures to this common solvent have been more important industrially, and therefore more completely studied. The respiratory uptake and metabolism of the xylene isomers are not significantly different.

Absorption

Available metabolism and excretion studies appear to indicate that absorption of xylene from the gastrointestinal tract is complete. This conclusion is supported by a study using human volunteers by Bray et al. (1949) that reported 85 to 90% of the administered dose was accounted for in the urine and the remainder may have been accounted for in the expired air (U.S.EPA, 1984a). Pulmonary absorption of vapors amounts to approximately 60 to 65% of the quantity inhaled during light exertion and to about 50% of that inhaled during heavy physical labor (Sedivec and Flek, 1986).. Absorption of xylene vapor through the skin is much slower than pulmonary absorption and appears to represent 1.3 to 1.4% of that absorbed through the lungs (Riihimaki and Pfaffli, 1978).

Distribution

Like the other alkylbenzenes, xylene is rapidly distributed into all tissues, especially into the adrenal glands, bone marrow, brain, spleen, and adipose tissue (Fishbein, 1985).

Metabolism

The major pathway for the biotransformation of xylene isomers in man and animals is via the oxidation of one of the methyl groups to the corresponding toluic acid (methylbenzoic acids). In humans all isomers of toluic acid have been found to conjugate primarily with glycine to

form the corresponding methylhippuric acid (toluric acids). In animals it appears that o-toluic acid conjugates equally as well with glucuronide, resulting in both o-methylhippuric acid and o-toluyl glucuronide in the urine (Sedivec and Flek, 1976).

Excretion

In man, approximately 95% of the absorbed xylene is metabolized and excreted in the urine, while only 3 to 6% is eliminated unchanged in the expired air (Sedivec and Flek, 1976, U.S.EPA, 1984a, and Fishbein, 1985).

HEALTH EFFECTS

Overview

The acute toxicity of xylene in humans has been demonstrated in several inhalation studies which describe adverse effects on the central nervous system (CNS), and eye and upper respiratory irritation. Chronically exposed humans have developed CNS, cardiovascular, and pulmonary irregularities, as well as renal dysfunction. CNS effects are usually the first symptoms of acute xylene toxicity in animals. Adverse effects on the lungs and liver have also been reported. Chronic xylene exposure is reported to adversely affect the liver, CNS, lungs, and kidneys. The primary target organ in animals is the liver.

Genetic effects were not seen in all but one of the test systems used to evaluate xylene mutagenicity. Technical-grade xylene was weakly mutagenic in the Drosophila recessive lethal test. Xylene appears to be embryotoxic and may possibly cause increased malformations in mice and rats. Currently there is no evidence to indicate that xylene is a carcinogen.

Human

Acute. Recent studies have produced the most useful data on human health effects from acute exposures to xylenes. Hake et al. (1981) noted a decrease in coordination on performance tests in two of four male subjects exposed to p-xylene at 150 ppm for 7.5 hours per day on five consecutive days. In conclusion it was stated that 100 ppm appeared to be near a no-effect level in sedentary males, but the no-effect level may be lower in sensitive individuals, women, and men at work (Hake et al., 1981).

Psychophysiological performance was adversely affected in various tests conducted on eight male volunteers exposed to m-xylene concentrations varying between 90 to 188 ppm (TWA) for 6 hours per day on five consecutive days and for one day after the weekend (Savolainen

et al., 1980). These performance tests included reaction time, manual dexterity, body balance, and EEG.

CNS function was impaired in five behavioral tests conducted on eight males exposed to mixed xylenes via inhalation at 1,300 mg/m^3 (estimated uptake = 1,210 mg) for 70 minutes, with a 30 minute exercise period preceding each exposure (Gamberale et al., 1978). These tests included addition, simple and choice reaction time, short-term memory, and critical flicker fusion frequency.

Carpenter et al. (1975) exposed human volunteers to mixed xylenes at four different concentrations (110, 230, 460, and 690 ppm) for 15 minutes on four consecutive days and found that with the exception of the lowest dose group the predominant subjective complaints were of eye and throat irritation, and dizziness (Carpenter et al., 1975).

Chronic. Clinical case studies indicate that workers who are chronically exposed to xylene may develop symptoms of xylene toxicity: headache, cyanosis, thoracic pains, electrocardiogram abnormalities, decreased pulmonary function, leukopenia, dyspnea, nausea, and vertigo (Hipolito, 1980).

Epidemiological studies have shown that long-term exposure of workers to solvent mixtures containing various amounts of xylene can adversely affect renal function (Askergien et al., 1981a,b, Askergien, 1981 and 1982,, Mikulski et al., 1972, and Franchini et al., 1983). This was manifest in increased urinary excretion of xylene metabolites, and glucuronidase, albumin, creatinine, erythrocytes, and leukocytes. Glomerular damage has been suggested as possibly being responsible for these effects (Askergien, 1982).

Animal

Acute. Xylene has a low acute toxicity, of the same order of magnitude as that of toluene (NIOSH, 1975). Oral LD_{50} values in rats range from 3.6-6.75 g/kg for the specific isomers, and 4.3-6.1 g/kg for xylene (assumed to be a mixture of isomers) (U.S.EPA, 1984b). The LD_{50} for mixed xylene (assumed to contain xylene isomers and ethylbenzene) in rats was reported to be 8.8 g/kg (U.S.EPA, 1984b).

The target organs most notably affected by acute exposure to mixed xylene are the nervous system, lungs, and liver (U.S.EPA, 1984a). CNS effects are usually the first observable signs of acute toxicity. Prostration, depression of the nervous system, and neuromuscular disorders have been reported in rats inhaling high levels (5,800 to 26,000 mg/m^3) of xylene for short periods of time (up to four hours) (Carpenter et al., 1975). These and other narcotic effects are typically noted when such exposures cause particularly high blood and brain levels to develop.

The lungs and respiratory system are usually affected in acute studies when xylene is administered at high concentrations via inhalation (U.S.EPA, 1984a). Health effects, including congestion, edema, and hemorrhage have been attributed to irritation and disruption of the endothelium and alveolar epithelium (Carpenter, 1975).

Subchronic/Chronic. In animals, chronic xylene exposure has been reported to affect adversely the liver, CNS, lungs, and kidneys. Most of the currently available information suggests that the primary target organ in animals for chronic xylene toxicity is the liver (U.S.EPA, 1984a).

Tatrai et al. (1981) exposed male CFY rats to o-xylene via inhalation at 4,750 mg/m^3 for 8 hours per day, 7 days per week for one year. Decreased body weight gain, hepatomegaly, and hepatic enzyme induction were observed after the 6th and 12th months of exposure. Routine histological investigations showed no pathological alterations in the liver and other organs. However, ultrastructural examinations revealed moderate proliferation of smooth endoplasmic reticulum and glycogen depletion in the centrilobular hepatocytes. Occasional mitochondrial damage and an increase in the number of peroxisomes and autophagous bodies were also found in liver cells. Proliferation of the endoplasmic reticulum is consistent with increased enzymes of the mixed function oxidase system. In this study, o-xylene was regarded as an inducer of hepatic enzyme metabolism, and liver enlargement was due to functional hypertrophy during the chronic exposure.

Bowers et al. (1982) found ultrastructural changes in the hepatocytes of rats administered o-xylene in the diet for up to six months, at 200 mg/kg of feed. Rats exposed for at least one month had two types of vesicles not present in the hepatocytes of control animals. One vesicle was double membrane-bound and appeared to originate from the smooth endoplasmic reticulum (SER). The second type of vesicle was peripherally located and appeared to fuse to the plasmalemma as in exocytosis. The first vesicle may have been of an autophagous type derived from the SER and involved in the elimination of xylene. The second type was felt to be involved with increasing hepatocyte surface area and/or elimination of metabolites (Bowers et al., 1982).

Many studies indicate hepatic enzyme induction following exposure to xylene. In addition to the previously described study by Tatrai et al. (1981) there are two subchronic studies that seem particularly significant. Their combined findings reveal increased activity or content for many hepatic enzymes and cytochromes in rats exposed to xylene levels ranging from 600 ppm for four weeks to 1,035 ppm for six weeks (Ungvary et al., 1980 and Toftgaard and Nilsen, 1982).

Jenkins et al. (1970) exposed rats, guinea pigs, dogs, and monkeys

to o-xylene at 337 mg/m^3 (78 ppm) continuously for 90 days, and at 3,358 mg/m^3 (780 ppm) for 8 hours per day, 5 days per week over a six-week period. No significant effects were observed with respect to body weight, hematology, and histopathological examinations of heart, lung, liver, spleen, and kidney tissue sections for all species, and brain and spinal cord sections in dogs and monkeys. One rat died on day 56 at the lower dose level.

During the repeated exposure at the higher dose level, two rats died on the third day of exposure, and another rat and one monkey died on day seven; one of the dogs exhibited tremors of varying severity throughout the exposure period (Jenkins et al., 1970).

Behavioral and Central Nervous System

Behavioral and CNS effects have been reported in several studies on animals, and in human clinical case studies and laboratory experiments (U.S.EPA, 1984a).

In animals acutely exposed to high concentrations of xylene by inhalation, the initial signs of toxicity include prostration, CNS depression, and neuromuscular disorders. Longer-term studies have revealed CNS impairment in both behavioral and biochemical tests (U.S.EPA, 1984a).

In humans, the narcotic properties of xylene are generally noted at high atmospheric concentrations (5,000 ppm) (Fishbein, 1985). At lower concentrations (100 to 300 ppm), acute xylene exposures have resulted in: the impairment of CNS function on behavioral tests; disturbances in psychophysiological performance; decreased coordination; eye, nose, and throat irritation; and dizziness (Fishbein, 1985 and U.S.EPA,1984a).

Reproductive, Embryotoxic, and Teratogenic

Embryotoxicity and teratogenicity studies indicate that xylene is embryotoxic and teratogenic.

Marks et al. (1982) administered mixed xylene to pregnant CD-1 mice by gavage on days 6 to 15 of gestation in doses of 0.52, 1.03, 2.06, 2.58, 3.10, and 4.13 mg/kg per day. A significant increase resulted in the average percent of malformed fetuses and a significant decrease was observed in the average weight of fetuses from animals dosed at 2.06, 2.58, and 3.10 mg/kg per day. Cleft palate was the major malformation noted at all three dose levels. Decreased average weight gain during pregnancy and resorptions were significant at the 3.10 mg/kg per day dose but only resorptions increased in a dose related fashion. Mortality at this level was 12 of 38 in the dams. All the dams who received the 4.13 mg/kg per day dose died. Doses of 0.52 and

1.03 mg/kg per day had no effect on maternal or fetal toxicity (Marks et al., 1982).

Hudak and Ungvary (1978) found a significant increase in skeletal anomalies, including fused sternebrae and extra ribs, among fetuses of 20 CFY rats exposed via inhalation to mixed xylene at 1,000 mg/m^3 for 24 hours per day, on days 9 to 14 of pregnancy. There were both air chamber and non-chamber controls of 26 and 28 animals, respectively.

Ungvary et al. (1980) studied the embryotoxic effects of o-, m-, and p-xylene in groups of 20 pregnant CFY rats exposed to atmospheres of 150, 1,500, or 3,000 mg/m^3 for 24 hours per day from day 7 to day 14 of pregnancy. There were air chamber exposed control groups composed of 15, 25, and 20 rats for the ortho-, meta-, and para-isomers, respectively. All three isomers produced a significant decrease in the mean fetal weight and a significant increase in the percent of weight-retarded fetuses at 3,000 mg/m^3. o-Xylene also produced these effects at the 1,500 mg/m^3 concentration. At the dose of 3,000 mg/m^3, m-xylene exposure resulted in a significant decrease in both the maternal weight gain and the average number of implants/pregnant rat. The highest dose level of p-xylene caused a significant increase in fetal loss and a significant decrease in mean litter size. Signs of skeletal retardation increased significantly with exposure to o-xylene at 3,000 mg/m^3, and with p-xylene at all three doses. Skeletal anomalies (extra ribs) were significantly increased in fetuses of rats exposed to m- or p-xylene at a concentration of 3,000 mg/m^3 (Ungvary et al., 1980).

Shigeta et al. (1983) exposed pregnant ICR mice to 500, 1,000, 2,000, and 4,000 ppm of xylene for 6 hours per day, during days 6 to 12 of gestation. Significant decreases in fetal weight were seen in the 2,000 and 4,000 ppm xylene exposed groups when compared to controls. Decreased weight gains and delayed development of body hair and teeth were observed in the 4,000 ppm xylene exposed group. Dose-response relationships were observed for both the development of the 14th rib and delayed ossification of the sternebrae (Shigeta et al., 1983).

Mirkova et al. (1983) exposed 160 pregnant Wistar rats to mixed xylene via inhalation for the duration of gestation. The rats were exposed to concentrations of 10, 50, and 500 mg/m^3 of xylene for 6 hours per day, 5 days a week from day 1 to day 21 of gestation. There was a chamber control group of 46 animals. At the two highest dose levels, xylene was shown to elicit embryotoxic and teratogenic effects in fetal rats. Embryotoxic effects were characterized by a significant increase in both the number of postimplantation fetal losses and the incidence of fetal hemorrhages; significant decreases in fetal body weight were also noted.

Adverse effects were manifest in a significant increase in both the incidence of visceral anomalies and the number of induced defects

in the ossification of the fetal skeleton. The effects could be considered embryotoxic or developmental and could be due in part to maternal toxicity.

Xylene concentrations of 50 and 500 mg/m^3 induced metabolic changes in enzyme activity in tissues of the liver, brain, myocardium, and lung, and significantly decreased the mean body weights of the F_1 generation.

The authors cited the 50 mg/m^3 dose level as the threshold for embryotrophic effects from xylene exposure. No significant adverse effects were seen at the 10 mg/m^3 level (Mirkova et al., 1983).

Genetic

Mutagenicity of the xylenes has recently been reviewed by Fishbein (1985), Dean (1978), and U.S.EPA (1979, 1984a,b). Mixed xylene or its isomers were tested for mutagenicity in: (1) Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 by the Ames test; (2) human lymphocytes (by the Sister Chromatid Exchange or chromosome aberration techniques); (3) Drosophila (by the recessive lethal test); and (4) E. coli strains WP2, WP2uvrA, CM611, WP67, WP100, W3110 and p3478. The Ames Salmonella/microsome assay for reverse mutations can detect both base-pair substitutions and frameshift mutagens. Sister Chromatid Exchange (SCE) techniques are used to detect primary DNA damage. The Drosophila Recessive Lethal Test and the E. coli strains are both useful for detecting gene mutations. In these tests xylene was not found to be mutagenic in any of the biological systems that were studied except in the case of the Drosophila recessive lethal test that found technical-grade xylene to be weakly mutagenic (U.S.EPA, 1984a).

Carcinogenicity

There is no current evidence indicating that xylene is a carcinogen.

Maltoni et al. (1985) administered xylene in olive oil to 40 male and female Sprague-Dawley rats by ingestion (stomach tube) at a dose of 500 mg/kg body weight per day 4-5 days a week for 104 weeks. Hemolymphoreticular neoplasias were found in 5/34 (14.7%) of the treated males and 3/36 (8.3%) of the treated females. Only 3/45 (6.7%) of the control males and 1/49 (2.0%) of the control females were found to have these types of tumors.

The total number of malignant tumors found in treated males was 18/38 (47.4%) with 14 animals bearing tumors. Total malignant tumors in treated females was 26/40 (65.0%) with 22 animals bearing the

tumors. Control males had 12/45 (26.7%) total malignant tumors in 11 animals. Control females had 11/49 (22.4%) total malignant tumors in 10 animals (Maltoni et al., 1985).

Although these results appear to indicate the possibility of a xylene-related increase in total malignant tumor incidence, the data do not provide tumor type or site-specific information for the tumors. Furthermore, since the results of this study have not yet been adequately reviewed or statistically analyzed they must be considered preliminary and interpreted with caution.

The National Toxicology Program (NTP) has tested mixed xylenes for carcinogenicity in rats and mice. The test compound was a commercial preparation containing p-xylene (13.6%), m-xylene (60.2%), o-xylene (9.1%), and ethylbenzene (17%). The compound was administered 5 days per week for 104 weeks by gavage in corn oil at the following doses: 1,000 mg/kg and 500 mg/kg plus vehicle controls for mice; 500 mg/kg and 250 mg/kg plus vehicle controls for rats.

The NTP Pathology Working Group's (PWG) pathology evaluation report for xylene is currently being reviewed by the pathologist of record at the contract laboratory. A summary of the NTP/PWG report has been received by this office from the chemical manager for xylene at the NTP. This summary states that "Administration of xylenes by gavage for two years to male and female rats and mice does not appear to be associated with systemic toxic effects nor biologically significant elevations in tumor incidence at any site". This is a preliminary assessment based only on the NTP pathology review; a final NTP position on the effect of mixed xylenes in a chronic oral exposure to rats and mice has not been made. This study is scheduled for peer review in February, 1986 (Eastin, 1985).

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

Several studies of xylene toxicity in animals may be useful for the purpose of calculating a health-based maximum contaminant level for xylene in drinking water.

Bowers et al. (1982) identifies a NOAEL in rats fed o-xylene at 200 mg/kg in the diet for up to six months. This study may be useful for risk assessment because it uses the preferred route of exposure and is a chronic study. However, as stated by the U.S.EPA (1984a,b) certain major weaknesses of this study rule out its consideration in risk assessment.

Jenkins et al. (1970) exposed rats, guinea pigs, dogs, and monkeys

to 337 mg/m^3 o-xylene via inhalation continuously for 90 days. This study may be useful for risk assessment because it identifies one NOAEL for several different species of animals.

Mirkova et al. (1983) exposed pregnant rats to xylene via inhalation for the duration of the gestational period. Unlike the other candidate studies three different dose levels were used to provide dose-response data for NOAEL development. The LOAEL identified in this study is based on both embryotoxic and developmental endpoints of xylene toxicity. These endpoints appear to be the most sensitive indicators of toxicity in the rat. No other study identified adverse effects occurring at exposure levels lower than the NOAEL identified in this study. In addition, the LOAEL identified in this study is lower than the NOAEL reported by Jenkins et al. (1970). Therefore, this study is judged to be the most appropriate for MCL calculation because it supports a NOAEL which is protective for the most sensitive members of the population. No significant adverse effects were seen at the 10 mg/m^3 level.

Calculations of a Health-based Maximum Contaminant Level

The U.S.EPA (1984d) outlined a method to convert the inhalation dose to an absorbed dose in the mouse or rat. Route-to-route extrapolation is appropriate when pharmacokinetic data exist to convert the inhalation dose to the equivalent effective oral dose (also referred to as the absorbed dose). This method is outlined below, giving the equations used to estimate the respiratory rate and absorbed dose in the rat, the extrapolation to an absorbed dose (ADI) in the human followed with the calculation of the health-based MCL. Data from the study by Mirkova et al. (1983) is used in the calculations.

Estimation of Breathing Rate (BR):

In order to calculate the absorbed dose in the rat, its breathing rate needed to be estimated. Anderson et al. (1977) reported that the inhalation rate can be estimated based on the observation that 25 gram mice breathe 34.5 L/day and 113 gram rats breathe 105 L/day. To estimate the inhalation rate (I) for mice or rats of other body weights (BW), a surface area proportionality can be used:

For mice: $0.0345\ (BW/0.025)^{2/3}\ m^3/day$
For rats: $0.105\ (BW/0.113)^{2/3}\ m^3/day$

$I = 0.105\ (0.35/0.113)^{2/3}\ m^3/d$
$= 0.223\ m^3/d$

The hourly respiratory rate (BR) is:

$$BR = 0.223\ m^3/d \times 1\ d/24\ hrs$$
$$= 0.0093\ m^3/hr$$

Estimation of the Absorbed Dose in the Rat (AD):

$$AD = \frac{(Cr)\ (De)\ (d)\ (A)\ (BR)}{BW}$$

where:

AD = Absorbed Dose in the rat (mg/kg/day)
Cr = NOAEL (10 mg/m^3)
De = hours of exposure per Day (6 hrs/day)
d = number of days exposed per week (5/7)
A = pulmonary Absorption factor (estimated to be 0.64, U.S.EPA, 1985)
BR = Breathing Rate in the rat (0.0093 m^3/hr)
BW = average Body Weight of the rats at the end of the treatment period (0.35 kg)

$$AD = \frac{10\ mg/m^3\ (6\ hrs/day)\ (5\ d/7\ d)\ (0.64)\ (0.0093\ m^3/hr)}{0.35\ kg}$$

$$= 0.73\ mg/kg/day$$

Extrapolation to an Absorbed Dose in the Human (ADI):

$$ADI = \frac{AD}{(OAF)\ (SF)}$$

where:

ADI = Average Daily Intake in the Human (mg/kg/day)
OAF = Oral Absorption Factor, assumed to be 100%
SF = Safety Factor of 100 is assumed when using a teratogenic study in risk assessment.

$$ADI = \frac{0.73\ mg/kg/day}{(1)\ (100)}$$

$$= 0.0073\ mg/kg/day$$

Calculation of the Health-Based Maximum Contaminant Level (MCL):

$$MCL = \frac{ADI\ (AAW)\ (SC)}{WC}$$

where:

MCL = health-based Maximum Contaminant Level

AAW = Average Adult Weight of a pregnant female, assumed to be 60 kg.
SC = Source Contribution of 0.20 from drinking water
WC = average drinking Water Consumption of a 60 kg adult, assumed to be 2 liters per day

$$MCL = \frac{0.0073 \text{ mg/kg/day } (60 \text{ kg}) \ (0.20)}{2 \text{ L/day}}$$

$$= 0.0437 \text{ mg/L}$$
$$= 44 \text{ ug/L}$$

The health-based MCL for xylene is 44 ug/L.

The most appropriate method to convert an inhalation dose, NOAE or LOAEL, to an Adjusted Daily Intake (ADI) is the subject o discussion in the scientific community. The method used above in thi assessment converts the NOAEL to an absorbed dose in the laborator animal by a surface area adjustment. This absorbed dose is then use to extrapolate to an absorbed dose in the human (ADI). Another metho extrapolates directly from a NOAEL or LOAEL to the ADI for humans usin a standard average human daily respiratory rate (20 m^3/day). The former method, used here, results in a MCL of 44 ug/L after calculatin the absorbed dose in the rat of 0.73 mg/kg per day, an inhalation rate in the rat of 0.0093 m^3/hr, and an ADI of 0.0073 mg/kg per day. The U.S.EPA (1984d) outlined this method to convert the inhalation dose to an absorbed dose in the laboratory animal to an ADI. The former method uses experimental data to estimate the absorbed dose in the laboratory animal. On the other hand, the latter uses the assumption of an average human respiratory rate (20 m^3 per day) and a direct human-to-animal weight conversion. The MCLs obtained using the two methods are 44 ug/L and 23 ug/L, respectively.

Assumptions and Uncertainty

It has been assumed that: (1) pregnant women and specifically their fetuses are the most sensitive members of the population; (2) the rat fetus is at least as sensitive to a given dose of xylene as the human fetus; (3) an adult human consumes two liters of drinking water per day; (4) drinking water sources represent 20% of the total contribution to exposure; (5) the value of 0.64 is an accurate estimate of the pulmonary absorption of xylene (Astrand et al., 1978 and U.S.EPA, 1985); and 6) the average weight of a pregnant human female is 60 kg.

Uncertainty in applying dose-response data from animals to humans and the variability within the human species are addressed in the calculations by incorporating a safety factor of 100 into the equation.

Conclusions

Xylene is currently not classified as a carcinogen (Group D) according to the U.S.EPA proposed classification scheme for carcinogens. Preliminary results from NTP indicate that xylene does not appear to be associated with any increases in tumor incidence in exposed mice and rats. A maximum contaminant level of 44 micrograms of xylene per liter of drinking water has been calculated to protect the public from any toxic systemic effects, in paticular, the embryotoxic and teratogenic effects, of xylene.

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