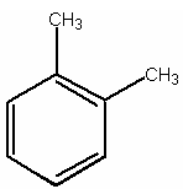
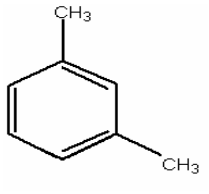
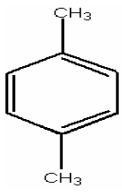
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-47-6 106-42-3 108-38-3 1330-20-7
Chemical Name	Xylenes Category: o-xylene, m-xylene, p-xylene, and xylene (mixed isomers)
Structural Formula	  

SUMMARY CONCLUSIONS OF THE SIAR

Evaluation Criteria

The data presented below are based on data presented in the IPCS (1997) Environmental Health Criteria 190 "Xylenes" as well as any further data that are relevant to the assessment of xylenes. Literature searches were performed on publicly available and company consortia data. The last literature search was conducted in January 2003.

Category Rationale

Ortho- meta- and para-xylene are chemical isomers, with the only difference being the position of the methyl group on the benzene ring. Mixed xylene is a mixture of the three isomers and in addition, typically contains 15-20% ethylbenzene. The xylene isomers have similar physicochemical properties with the exception perhaps of the higher melting point of p-xylene. In addition, the toxicity of the three individual isomers and mixed xylene is qualitatively similar.

Human Health

The human health effects of xylene by inhalation have been studied to the greatest extent because this is the most likely route of exposure, though under certain circumstances absorption through skin may contribute to exposure. Approximately 64 % of xylene is absorbed after inhalation. Xylene readily passes the placenta and is secreted into maternal milk. Approximately 72% to 95% of absorbed xylene is biotransformed and excreted in the urine within 18 hours. Around 4-6 % of retained xylene is eliminated via the expired air.

The primary metabolic pathway of xylene is the cytochrome P450-dependent monooxygenase system. Xylene is metabolised by oxidation of a methyl group to the corresponding o-, m-, or p-toluic acid, which are then excreted in the form of a glycine conjugate as o-, m-, or p-methyl hippuric acid in the urine.

Results from acute oral, dermal or inhalation toxicity studies in rats and mice indicate that the acute toxicity of xylene isomers and mixed xylenes is very low. Acute toxicity was typically characterized by central nervous system

depression. Animals exposed to xylene became uncoordinated, prostrate and comatose at doses that produced mortality within the dose group. The reported 6-hour LC50 values for xylene isomers ranged from 18.8 to 25.9 mg/L (4,330-5,984 ppm) in rats and from 16.9 to 22.8 mg/L (3,907-5,267 ppm) in the mouse. The reported 4-hour LC50 for mixed xylenes ranged from 27.5 to 47.4 mg/L (6,350-10,950 ppm) in rats. In o-, m- and p-xylene, rat oral LD50s of 3580, 5010 and 4020 mg/kg were reported. In mixed xylenes rat oral LD50 values of 3500, 5,779 and 8,600 mg/kg were reported. While a dermal LD50 of 12,180 mg/kg (rabbit) was reported for m-xylene and LD50 values of 3200 mg/kg and 4300 mg/kg were reported for the mixed xylenes. Mixed xylenes and xylene isomers are irritating to the skin and eyes.

In repeated dose studies, the principle effects of xylenes were adaptive changes in the liver, body weight changes, organ weight changes and altered motor coordination. Oral administration of 200 mg/kg o-xylene for up to 6 months resulted in formation of vacuolar structures in hepatocytes visible via electron microscopy. Inhalation exposure of male rats to m-xylene at 1000 ppm (4330 mg/m^3) for 3 months or 100 ppm (433 mg/m^3) for 6 months resulted in slight changes in liver ultrastructure primarily limited to proliferation of the smooth endoplasmic reticulum. Several studies with mixed xylenes show similar adaptive changes on the liver and liver metabolising enzymes. A 13-week oral gavage study in rats to m-xylene resulted in a dose related significant decrease in body weight gain (NOEL females 200 mg/kg, males 100 mg/kg) A similar study using p-xylene reported a slight decrease in body weight for both males and females at 800mg/kg, the highest dose tested (NOEL 200mg/kg). Oral administration of mixed xylenes orally to mice at 2000mg/kg/day for 13 weeks resulted in mortality [2F], clinical signs lasting up to 1hr after dosing, and reduced body wt gain. [particularly in females] but did not cause overt signs of toxicity or pathological changes. A NOAEL and LOAEL of 1000 and 2000 mg/kg/day respectively, could be derived from this study. This study, in conjunction with an earlier 14-day study was used to establish doses for a 2-year cancer bioassay. . In rats, administration of mixed xylenes orally at 1000 mg/kg/day for 13 weeks resulted in reduced body wt gain [particularly males] but did not cause overt signs of toxicity or pathological changes. A NOAEL and LOAEL of 500 and 1000 mg/kg/day respectively could be derived from this study. This study, in conjunction with an earlier 14-day study was used to establish doses for a 2-year cancer bioassay. Rats exposed to inhalation concentrations (600, 1500 or 4000 mg/m^3 ; 139, 346, 923 ppm) of mixed xylenes for 8h/day for up to 6 months had a NOEL of 346 ppm and a LOEL of 923 ppm. Increased liver weights; hypertrophy of the centrilobular zone in the liver including a change of the smooth and rough endoplasmic reticulum; and an increase in liver enzymatic activity (first six weeks of the study) were noted.

Rats exposed via inhalation to m-xylene 6 hour/day, 5 days/week for 1,2 or 3 months at 0, 50 of 100 ppm (0, 217, 433 mg/m^3) resulted in motor coordination disturbances (rotorod performance) and increased sensitivity to pain (NOEL 50 ppm based on rotorod performance). In addition, three repeated-dose ototoxicity studies in rats have been conducted with mixed xylenes. These studies reported an increase in auditory response thresholds at certain frequencies at inhalation concentrations of 800 ppm (3464 mg/m^3) and 1000 ppm (4330 mg/m^3) using prolonged dosing regiments (14hr/day for 6 weeks and 18hr/day for 61 days, respectively) for two of the studies and at 2,500 ppm (10825 mg/m^3), 6hr/day for 5 days, in the third study. One of these studies also reported a slight impairment of auditory response at 1,200 ppm (5196 mg/m^3), 14hr/day for 6 weeks.

Available data from both *in vitro* and *in vivo* studies suggest that xylenes are not genotoxic. Furthermore, rats exposed up to 500 mg/kg and mice exposed up to 1000 mg/kg body weight mixed xylenes for 103 weeks showed no treatment related increases in any tumor type for either sex.

Inhalation exposure of rats from gestation day 6-20 for 6h/day to o-, m-, p-, or mixed-xylene resulted in maternal toxicity at 1000 (4330 mg/m^3) and 2000 ppm (8660 mg/m^3). All test materials produced fetal toxicity effects at 1000 and 2000 ppm, in the presence of maternal toxicity. With o- and mixed-xylene, fetal toxicity also occurred at 500 ppm (2165 mg/m^3), in the absence of maternal toxic effects. However, the only indication of a treatment related effect was a slight decrease in fetal weights. No teratogenic effects were reported. The NOAEL for maternal and developmental effects was 500 ppm for m-, and p-xylene. For o- and mixed-xylene, the NOAEL for maternal and developmental toxicity were 500 and 100 ppm, respectively. In a developmental neurotoxicity study impaired performance in a motor ability test was reported in rats exposed to mixed xylene on days 4-20 of gestation (LOAEL 200 ppm; 866 mg/m^3) 200 ppm). In a follow-up developmental neurotoxicity study in rats exposed to mixed xylenes on days 7-20 gestation additional effects on learning and memory were observed at 500 ppm. In a one-generation reproductive study no dose related effects on mating indices, mean duration of gestation, mean litter size, or pup survival were reported at exposures of mixed xylenes up to 500 ppm. Mean pup weight was significantly lower in the group where

both parents had been exposed to 500 ppm (NOAEL reproductive effects 500 ppm).

Available case reports, occupational studies, and studies on human volunteers suggest that both short- and long-term exposures result in a variety of adverse nervous system effects that include headache, mental confusion, narcosis, equilibrium, impaired short-term memory, dizziness and tremors. In addition to the CNS effects xylene is irritating to the eye and skin and to the respiratory tract. Single exposure human studies were conducted with concentrations ranging from 70 to 300 ppm for up to 4 hours. No CNS symptoms were experienced when subjects were exposed to pure xylene and no deficits in performance in neurobehavioral test applied only increases in reaction time were observed at 200 ppm TWA that included peak exposures of 400 ppm. A single repeated-dose human exposure study, at similar levels, also showed an increase in reaction time.

Environment

Xylene isomers have melting points of –25.2˚, -47.9˚and 13.3˚C, boiling points of 144.4˚, 139.1˚ and 138.3˚C vapor pressures of 665Pa, 798Pa, and 865Pa at 20˚C, Log Kows of 3.12, 3.2 and 3.15 and water solubilities of 178, 161, 162 mg/L at 25˚C for o-, m-, and p-xylene, respectively. Based on the above Log Kows, the estimated BCFs for o-, m- and p- xylene are 50, 58 and 53, respectively. The Kow values in addition results from bioaccumulation studies suggest that the relative bioaccumulation potential for xylenes is low.

The half-life in air is estimated to be 19.7, 9.47, 19.7 hours for o-, m-, and p-xylene, respectively due to direct reactions with photochemically generated hydroxyl radicals. Experiments using xylenes adsorbed on silica gel have shown that the photomineralization rates for all three isomers are low using radiation with a wavelength longer than 290 nm. As xylenes are volatile organic chemicals (VOCs), they have the potential to form ozone (smog). The calculated POCPs (Photochemical Ozone Creation Potentials) for o-, m- and p- xylenes are 41, 78 and 63. Based on the physical chemical properties xylenes are likely to partition primarily to the air compartment. The m-, p- and mixed xylenes are readily biodegradable under aerobic conditions in sewage sludge and are expected to biodegrade in soil and water as well. The o-xylene isomer is considered to be inherently biodegradable under aerobic conditions.

The 96-hour LC50s for *Oncorhynchus mykiss* were 7.6 mg/L, 8.4 mg/L, 2.6 mg/L, and 13.5 mg/L for o-, m-, p-, and mixed-xylenes, respectively. The 96-hour LC50s for *Pimephales promelas* were 16.4 mg/L, 28 mg/L, and 26.7 mg/L for o-, m-, and mixed-xylenes, respectively. The 48-hour EC50s for *Daphnia magna* were 3.2 mg/L, 9.56 mg/L, and 8.5 mg/L for o-, m-, and p-xylene, respectively. The 96-hour EC50s for *Crangon franciscorum* were 1.3 mg/L, 3.7 mg/L, and 2 mg/L for o-, m-, and p-xylene, respectively. The 72-hour EC50s for *Selenastrum capricornutum* were 4.7 mg/L, 4.9 mg/L, and 3.2 mg/L for o-, m-, and p-xylene, respectively. Algal data for mixed-xylenes included a 72-hour EC50 of 10 mg/L for *Skeletonema costatum*. A chronic fish study on mixed-xylenes using *Oncorhynchus mykiss* reported a NOEC ≥ 1.3 mg/L.

Exposure

The principal population at risk of exposure is the occupational workforce, which can be exposed to the emissions of mixed xylenes during its production and end-use, as well as during its wide use as an industrial solvent. Exposure to the general public can arise from automobile exhausts and many consumer products (degreasing cleaners, lacquers, paints removers and pesticides but also from tobacco smoke).

Worldwide production of mixed xylenes is 1999 was estimated at 24,027,000 metric tonnes (SRI International, 2001). The US production of the xylene isomers in 1999: p-xylene was 2,850,000 metric tonnes; o-xylene was 500,000 metric tonnes, and m-xylene was 125,000-150,000 metric tonnes. In Hungary, mixed xylenes production decreased from 60,000 tonnes in 1996 to 40,000 tonnes in 2001.

The primary use of the individual xylene isomers is as chemical intermediates. Almost all o-xylene produced in the U.S. is consumed in the manufacture of phthalic anhydride. Other minor uses include the use of o-xylene as a feedstock in the production of bactericides, soybean herbicides and dyes. Most m-xylene is used as a chemical intermediate in the production of isophthalic acid. Small amounts of m-xylene are also consumed in the production of meta-toluic acid, isophthalonitrile, and other compounds. Almost all U.S. production of p-xylene is consumed in

the manufacture of dimethyl terephthalate (DMT) and terephthalic acid (TPA), which are used in production of polyester fiber and plastics.

The main use of mixed-xylenes is as a component of gasoline (approximately 92% of mixed-xylenes produced is blended into fuel gasoline). It is also used as solvent in paints, and paint-related products (varnishes, lacquers, dyes, cleaning fluids, thinners, paint removers), printing inks, coatings, cements and adhesives, as a component of Canada balsam in the oil-immersion microscopy in medical laboratories, and it is further applied as a cleaning agent in histology specimen preparation.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

These chemicals possess properties indicating a hazard for human health and the environment. In addition, based on data presented by the Sponsor countries, exposure to humans and the environment is anticipated. It is known that risk management measures are being applied within OECD countries. Countries may desire to check their own risk management measures to find out whether there is a need for measures beyond those which are being applied.

An IPCS Environmental Health Criteria assessment document (EHC 190) exists for this category of chemicals.