XYLENES

Major Uses and Sources of Emissions

Xylenes exist in ambient air as a mixture of ortho, meta and para isomers. Sources of xylenes include: petrol, motor vehicles, petroleum refineries and terminals, service stations, lawnmowers and other petrol-fuelled implements, chemical manufacture, polyester manufacture, manufacture and use of paints, dyes, and lacquers, wood burning stoves and fireplaces.

Critical health endpoint

The first signs of adverse effects on humans are irritation of the nose, throat and eyes. The irritation has been chosen as the critical end point because it occurs at a low levels after short exposures.

Californian Environmental Protection Agency, 1999 (CEPA 1999), Office of Environmental Health Hazard Assessment (OEHHA)

Short-term exposures in humans

OEHHA have concluded that respiratory and eye irritation were the principal effect(s) of xylenes following short term exposures in healthy human volunteers.

Hastings et al. (1984) exposed 50 healthy individuals to 100, 200, or 400 ppm mixed xylenes for 30 minutes to evaluate eye, nose, and throat irritation. The percent of subjects reporting eye irritation was 56% for controls (clean air), 60% at 100 ppm, 70% at 200 ppm, and 90% at 400 ppm. The authors concluded there was no effect on eye irritation at 100 ppm because the incidence of irritation was as low as the control group.

Carpenter et al. (1975) evaluated eye irritation in 6 human volunteers exposed for 15 minutes to 460, 1,000, 2,000, or 3,000 mg/m^3. One volunteer noted mild throat discomfort at 460 mg/m^3, but not at 2,000 mg/m^3. Four subjects reported eye irritation after exposure to 2000 or 3000 mg/m^3 (460 or 690 ppm) xylene for 15 min while one subject reported eye irritation at 1000 mg/m^3 (230 ppm) and none at 478 mg/m^3 (110 ppm)

Nelson et al. (1943) exposed 10 healthy human volunteers for periods of 3 to 5 minutes to estimated concentrations of 100 or 200 ppm technical grade xylene. The subjects reported eye, nose, and throat irritation at 200 ppm but not at 100 ppm. A significant area of uncertainty arising from the study is the use of estimated rather than measured exposure concentrations.

OEHHA considered that data from Hastings et al. (1984) and Carpenter et al. (1975) taken together are consistent with a human NOAEL for eye irritation of about 100 ppm for at least a 30-minute exposure.

Longer term exposures in Humans

Information on the toxicity of xylenes to humans is almost exclusively limited to case reports of acute exposures and studies of occupational exposures in which persons

often inhaled a mixture of hydrocarbon solvents 8 hours per day, 5-6 days per week. These studies often have incomplete information on the airborne concentrations of xylene and other hydrocarbons. One study examining chronic effects in humans from inhalation of predominantly mixed xylenes for up to 7 years was identified (Uchida et al., 1993) and one 4-week controlled exposure study examining the effects of p-xylene exclusively was identified (Hake et al., 1981). No studies examining the chronic effects of oral or dermal xylene exposure in humans were identified.

Xylene exposure has been associated with effects in a number of organ systems including the lungs, skin and eyes; neurological system; heart and gastrointestinal system; kidney; and possibly the reproductive system. Pulmonary effects have been documented in occupational exposures to undetermined concentrations of mixed xylenes (and other solvents) and include laboured breathing and impaired pulmonary function

Laboratory Animal Exposures

Animal data are consistent with human data in documenting respiratory effects from xylene exposure. Acute and subacute exposures in mice, rats, and guinea pigs have been associated with; decreased respiratory rate; labored breathing; irritation of the respiratory tract; pulmonary edema; and pulmonary inflammation by a number of studies.

Of the three chronic studies available (Tatrai et al., 1981; Jenkins et al., 1970; NTP 1986) none comprehensively examined systemic effects.

The study by Tatrai et al. (1981) exposed rats for one year, 7 days/week, 8 hours per day to 1096 ppm o-xylene. This exposure level was a LOAEL for body weight gain in males and a NOAEL for hepatic effects in male rats.

Jenkins et al. (1970) exposed rats, guinea pigs, squirrel monkeys, and beagle dogs for 90-127 days continuously to 78 ppm of o-xylene. The study examined body weight gain; haematological, serum and liver function. No effects were observed in any of the parameters examined in this study. This study found a NOAEL for all effects examined of 78 ppm o-xylene.

Reproductive and developmental toxicity in laboratory animals

Ungvary et al. (1980) tested by inhalation the individual ortho, meta, and para isomers of xylene in the rat. Pregnant rats were exposed 24 h/day on days 7 –14 of pregnancy up to 700 ppm of each isomer. An increased incidence of weight retarded foetuses was observed for each isomer at the 700 ppm level, and for the ortho isomer at the 350 ppm level. Embryotoxicity was increased only at the 700 ppm level in the para-xylene exposed group. Skeletal malformations were increased only at the 700 ppm level for the meta and para isomers of xylene.

Ungvary and Tatrai (1985) exposed mice by inhalation continuously to 120 ppm or 230 ppm xylenes for 24 h/day on days 7-15 of gestation. The LOAEL was 230 ppm (increased incidences of weight-retarded foetuses and increased skeletal retarded foetuses at 230 ppm) and the NOAEL was 120 ppm. Shigeta et al. (1983) reported

significant decreases in foetal weight in the 460 ppm and 920 ppm groups exposed to xylenes . There were no difference in the number of live or dead foetuses. Decreased weight gains and delayed foetal development were observed at the 920 ppm exposure level.

Hass et al. (1995) exposed pregnant rats to 500 ppm xylene 6 hr/day on gestation days 7-20 Xylene exposure caused no signs of maternal toxicity and no difference in the number of live or dead foetuses. The absolute brain weights in exposed litters were lower than for control litters. Exposed offspring showed impaired performance in tests for neuromotor abilities and for learning and memory. In a follow-up study under the same conditions, exposed offspring exhibited impaired performances for learning and memory for up to 28, weeks of age (Hass et al., 1997). These data indicate that xylene exposure during development may cause long-lasting deficits on learning and memory in offspring. It is not apparent if 500 ppm is a LOAEL concentration for these effects.

Carcinogenicity
The NTP (1986) study administered 0, 250, or 500 mg/kg/day doses of mixed xylene in corn oil by gavage 5 days/week for 103 weeks to groups of F344/N rats of both sexes, 50 animals per group. B6C3F1 mice were treated in a similar manner but given 0, 500 or 1000 mg/kg/day of mixed xylenes in corn oil by gavage. A complete histopathological examination of all tissues was made as well as determination of body weight gain. Based on histopathology of all organ systems, a NOAEL of 500 mg/kg/day was observed for rats and a NOAEL of 1000 mg/kg/day was observed for mice.

Summary

NOAEL of 78 ppm o-xylene obtained by Jenkins et al. (1970) in rats and guinea pigs continuously exposed for 90 days. Tatrai et al. (1981) reported a LOAEL of 1096 ppm o-xylene for body weight gain in male rats exposed every day for 8 hours. Ungvary and Tatrai (1985) exposed mice by inhalation continuously to 120 ppm or 230 ppm xylene for 24 h/day on days 7-15 of gestation. For developmental effects, the LOAEL was 230 ppm and the NOAEL was 120 ppm.

OEHHA concluded that the animal and human toxicity data suggest that mixed xylenes and the different xylene isomers produce similar effects, although different isomers are not equal in potency for producing a given effect. Therefore exposure of workers to a mix of xylenes in the Uchida *et al.* (1993) study would be expected to generate a similar spectrum of responses as exposure to single isomers, however the intensity of particular effects could be different. The use of a neurological endpoint for derivation of a chronic REL is supported by the large number of inhalation and oral studies, which associate neurological effects with xylene exposure.

US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, September 2000 (ATSDR 2000) Xylene

Acute Exposure in Humans

An acute-duration (14 days or less) inhalation exposure MRL has been derived for mixed xylene. This MRL is based on CNS effects in an acute inhalation exposure study by Dudek et al (1990), with supporting studies by Gamberale et al (1978) and Carpenter et al (1975).

Dudek et al.(1990) studied ten male volunteers who were exposed to 100 ppm xylene (purity not specified) or 100 ppm toluene or a mixture of 50 ppm of each. Exposure time was 4 h and each person participated in four exposure sessions. Changes in CNS functions were tested by nine psychological tests. Xylene had the most adverse effect on simple reaction time and choice reaction time, while the combined exposure gave weaker effects than xylene alone but stronger than toluene alone. This was considered to be a LOAEL by the investigators.

Gamberale et al (1978) confirmed that the 100 ppm is near the threshold for adverse effects as no effects on reaction times were seen in 15 volunteers exposed to xylenes at 100 and 299 ppm for 70 minutes. However when subjects exercised for the first 30 minutes of the 70 minute exposure to 299 ppm xylenes, reaction times were increased and short term memory was impaired.

Derivation of an acute MRL

The acute MRL of 1 ppm was derived from the LOAEL of 100 ppm, 4 hour exposure.

However, no information is provided in derivation of uncertainty factors for the use of a LOAEL, intraspecies variability, or exposure time conversion from 4 hours to 1 hour. A consolidated listing of acute MRLs does state that a cumulative uncertainty factor of 100 has been used in the acute inhalation MRL for total xylenes.

An intermediate-duration (15 to 364 days) inhalation exposure MRL has also been derived for total xylenes. This MRL is based on the observation of reduced rotarod performance of offspring (measured on the first 3 days after birth) from rats exposed to 200 ppm technical grade xylene 6 hours/day on gestation days 4-20 (Hass and Jakobsen 1993). No maternal toxicity (body weight, clinical signs) or effects on reproduction and litter end points (e.g., implantations, resorptions, foetal body weight) were observed.

A chronic exposure MRL (365 + days) has been derived for total xylenes. This MRL is based on a study in which xylene exposure was most well defined (Uchida et al. 1993). Workers in a Chinese factory exposed for an average of 7 years at a geometric mean TWA concentration of 14 ppm reported an increase in subjective symptoms of eye and nasal irritation, dizziness, and sore throats as well as an increased prevalence of anxiety, forgetfulness, inability to concentrate. Haematology, serum biochemistry and urinalysis measures did not show any effects.

Available case reports and occupational studies together provide suggestive evidence that acute and chronic inhalation exposure to xylene or solvent mixtures containing xylene may be associated with neurological effects, however, most studies are difficult to evaluate because the exposure conditions either have not been well

characterized or the subjects may have been exposed to other chemicals in addition to xylene.

Laboratory animal exposure
Exposure to concentrations of 2,440 ppm mixed xylene for 6 minutes (Korsak et al. 1988), to 1,467 ppm o-xylene for 5 minutes (De Ceaurriz et al. 1981), or to 1,361 ppm m-xylene for 6 minutes (Korsak et al. 1993) produced a 50% decrease in respiratory rate in mice.

Comparison of the individual xylene isomers showed that the irritant effects of m- and o-xylene as quantified by measurements of respiratory rate in mice are more pronounced than those of p-xylene, with o-xylene having the most prolonged effect (Korsak et al. 1990). In rats that died as a result of exposure to 9,900 ppm mixed xylene for 4 hours, lung collapse, haemorrhage, and edema of the lungs were observed (Carpenter et al. 1975).

No animal studies were located that evaluated the respiratory effects of mixed xylene or single xylene isomers following chronic inhalation exposure.

International Programme on Chemical Safety: Xylenes – Environmental Health Criteria 190 (1998)

Acute exposure to high concentrations of xylene can result in CNS effects and irritation in humans. The IPCS has concluded that there have been no long-term controlled human studies or epidemiological studies with exposure to xylenes alone.

Acute exposure in Humans

After exposure to about 700 ppm xylene (calculated) for up to one hour, headache, nausea, irritation of the eyes, nose and throat, dizziness, vertigo and vomiting have been reported (Klaucke et al., 1982).

Eye, nose and throat irritation, after acute exposures were noted by IPCS from studies of Carpenter et al (1975), Hastings et al 1986, Anshelm Olsen et al (1985) and Dudek et al (1990).

The odour threshold for xylene is about 1 ppm.

IPCS also noted the adverse effects of long term xylene exposures in occupational settings as increased prevalence of subjective symptoms related to depressant effects on the central nervous system and to local irritant effects on the eye, nose and throat from studies by Uchida et al., (1993), and Chen et al., (1994). No effects on haematology or serum biochemistry with respect to liver and kidney functions were observed in these two studies.

Laboratory Animal Studies

In mice (Swiss-Webster) exposed to 1300 ppm xylene for one minute, a decrease in respiratory rate as an indication of respiratory tract irritation was seen (Carpenter et al., 1975). This effect was not seen at an exposure level of 460 ppm.

On the basis of human volunteer studies (Anshelm Olson et al, 1985), one may conclude that the NOAEL for acute CNS effects in humans is about 304 mg/m^3 (70 ppm) for a 4-h exposure.

Laboratory animal reproductive studies

Effects on foetal weights and skeletal development were seen from rats exposed to o-xylene at 350 ppm and for m- and p-xylene at 700 ppm (Ungvary et al 1980). Similarly in mice, foetal skeletal development was decreased at 230 ppm concentrations of mixed xylenes. The rat LOAEL was 350 ppm, and the mouse NOAEL was 120 ppm for these effects. (Ungvary and Tatrai 1985)

Impaired performances were noted on neuromotor abilities and learning and memory lasting up to 28 weeks of age, were noted in offspring from pregnant rats exposed to xylenes at 500 ppm. It is not apparent if 500 ppm is a LOAEL concentration for these effects. (Hass et al. 1997)

On the basis of animal studies on developmental toxicity, IPCS concluded that the LOAEL for reduced foetal body weight is 500 mg/m^3 (115 ppm) (Ungvary and Tatrai, 1985) and that for developmental neurotoxicity is 870 mg/m^3 (200 ppm) (Hass & Jakobsen, 1993).

IPCS considered that the critical end-point for setting an exposure guidance value for the general population was developmental toxicity in laboratory animals.

Xylene appears not to be a mutagen or a carcinogen (IARC 1989).

The US EPA IRIS database on Xylenes does not at this time contain information regarding, Reference Concentration for Chronic Inhalation Exposure (RfC), or Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure.

Summaries of Pivotal Studies Identified in the above reviews.

Longer term exposures

The Uchida et al. (1993) study included a relatively large number of workers studied, exposure for an average of 7 years to xylenes predominately and a comprehensive set of medical examinations to document potential effects. A survey of 994 Chinese workers involved in the production of rubber boots, plastic coated wire and printing processes employing xylene solvents was carried out. The survey consisted of fitting individual workers with diffusive samplers for an 8 hour shift. At the end of the 8 hour shift the samplers were recovered for analysis of solvent exposure, and urine samples were collected for analysis of xylene metabolites.

The following day workers answered a questionnaire concerning subjective symptoms, and blood and urine were collected for analysis. Out of this group of xylene-exposed workers, 175 individuals (107 men and 68 women) were selected for further study and analysis based on completion of their health examinations and on results from diffusive samplers showing that xylene constituted 70% or more of that individual's exposure to solvents in the workplace. The control population consisted of 241 (116 men and 125 women) unexposed workers from the same factories or other factories in the same region, of similar age distribution, of similar time in this occupation (average of 7 years), and having a similar distribution of alcohol consumption and cigarette usage.

The xylene-exposed and unexposed groups were given health examinations which evaluated haematology, serum biochemistry, and subjective symptoms. Results of analysis of the diffusive samplers showed that workers were exposed to a geometric mean of 14.2 ± 2.6 ppm xylene (arithmetic mean of 21.3 ± 21.6 ppm). This was broken down into geometric means of 1.2 ppm o-xylene, 7.3 ppm m-xylene, 3.8 ppm p-xylene, 3.4 ppm ethyl benzene, and 1.2 ppm toluene. N-Hexane was rarely present and no benzene was detected. Analysis of data from the health examinations found no statistically significant difference ($p<0.10$) between haematology and serum biochemistry values for xylene-exposed and unexposed populations. The frequency of five symptoms experienced during work was significantly ($p<0.01$) elevated in either xylene-exposed men or women including: dimmed vision, unusual taste, dizziness, heavy feeling in the head, and headache. The frequency of four symptoms experienced during work were significantly ($p<0.01$) elevated in both men and women including irritation in the eyes, nasal irritation, sore throat, and floating sensation. Ten subjective symptoms occurring in the previous three months were significantly ($p<0.01$) elevated in exposed men and women including nausea, nightmare, anxiety, forgetfulness, inability to concentrate, fainting after suddenly standing up, poor appetite, reduced grasping power, reduced muscle power in the extremities, and rough skin. Dose dependency appeared to exist for 3 subjective symptoms noted during work: irritation in the eyes, sore throat, floating sensation, and for one symptom occurring in the last three months, poor appetite.

Gamberale et al., (1978) exposed 15 healthy male subjects to technical xylene, containing 40% ethylbenzene, for 70 minutes with or without a working load of 100 watts. The air concentration was 435 or 1300 mg/m^3. No noticeable changes in performance were seen in subjects without the exercise. During exercise (bicycle ergometer) at the higher exposure level, evidence of performance decrement was observed in three of the five performance tests: reaction time addition test ($p < 0.05$), short-term memory ($p < 0.05$) and choice reaction time ($p < 0.10$).

Hake et al. (1981) used groups of male volunteers (1 to 4 subjects/group) who exposed to p-xylene in a controlled-environment chamber for 7.5, 3, or 1 hr/day, 5 days/week for 4-weeks. The p-xylene concentration that were changed on a weekly basis starting at 100 ppm the first week, followed by 20 ppm, 150 ppm, and 100 ppm (average, with a range of 50 to 150 ppm) over subsequent weeks. In addition, groups of female volunteers (2 or 3/group) were exposed to 100 ppm p-xylene for 7.5, 3, or 1 hr/day for 5 days. The volunteers acted as their own controls, with exposure to 0 ppm p-xylene occurring for two days (males) or one day (females) the week before and the week after the xylene exposures. No serious subjective or objective health

responses, including neurological tests, cognitive tests and cardiopulmonary function tests were observed. Odour was noted, but the intensity decreased usually within the first hour of exposure. The authors concluded that p-xylene may have a weak irritating effect on the soft tissues starting at 100 ppm, but overall, the small sample size and high variability among the volunteers made all results difficult to interpret.

Laboratory animal studies

Ungvary and Tatrai. (1985) exposed CFY rats by inhalation to air concentrations of xylene (60 ppm, 440 ppm, 800 ppm) for 24 h/day on days 7-15 of gestation. Maternal toxicity was described as moderate and dose-dependent. They observed weight retarded foetuses at all air concentrations. However, there was no increase in malformations, and an increase in minor anomalies and resorbed foetuses occurred only at the highest concentration. In a separate study investigating the interactions between solvents and other agents,

Ungvary et al. (1980) tested by inhalation, the individual ortho, meta, and para isomers of xylene in the CFY rat. Pregnant rats were exposed 24 h/day on days 7 –14 of pregnancy to 35, 350, or 700 ppm of each isomer. An increased incidence of weight retarded foetuses was observed for each isomer at the 700 ppm level, and for the ortho isomer at the 350 ppm level. Post implantation losses were increased only at the 700 ppm level in the para-xylene exposed group. Skeletal anomalies were increased only at the 700 ppm level for the meta and para isomers of xylene.

Hudak and Ungvary (1978) have examined the effect of 230 ppm xylene (24 h/day, days 9-14 of pregnancy) in the CFY rat and reported effects on skeletal development (e.g., fused sternebrae).

With respect to mice, Ungvary and Tatrai (1985) exposed CFLP mice by inhalation to air concentrations of xylene (120 ppm, 230 ppm) for 24 h/day on days 7-15 of gestation. In the mouse, they observed increased incidences of weight-retarded foetuses and increased skeletal retarded foetuses at 230 ppm.

Ungvary and Tatrai (1985) also tested the individual ortho, meta, and para isomers of xylene at 120 ppm in the CFLP mouse. Each isomer of xylene also increased the incidence of weight-retarded foetuses and skeletal retarded foetuses at 120 ppm. There was no increase in malformations.

Hass and Jakobsen (1993) exposed groups of 36 pregnant Wistar rats to clean air or 200 ppm of xylene for 6 h/day on days 4-20 of gestation. There was no sign of maternal toxicity and no decrease in foetal weights and no increase in soft-tissue or skeletal malformations. A large increase in the incidence of delayed ossification of the *os maxillare* of the skull, however, was observed (53% of experimental foetuses as opposed to 2% of the controls). Potential neurological/muscular changes measured as performance on a rotorod were also noted upon testing of 2-day-old rat pups.

Hass et al. (1995) examined postnatal development and neurobehavioral effects in rats following prenatal exposure to 0 or 500 ppm technical xylene 6 hr/day on gestation days 7-20 of pregnancy. Xylene exposure caused no signs of maternal toxicity and no

difference in the number of live or dead foetuses. The mean birth weight in exposed litters was about 5% lower compared to control litters but the difference was notstatistically significant. Body weights were similar between groups during the pre-weaning and post-weaning period but lower absolute brain weights were observed in exposed animals. Exposed offspring showed a delay in the ontogeny of the air righting reflex and exhibited impaired performance in behavioural tests for neuromotor abilities (Rotorod) and for learning and memory (Morris water maze). In a follow-up study under the same exposure conditions, exposed offspring exhibited impaired performances in the Morris water maze at 16, 28, and 55 weeks of age, although the difference was not statistically significant at 55 weeks (Hass *et a*l., 1997). These data indicate that xylene exposure during development may cause long-lasting deficits on learning and memory in offspring.

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