XYLENE

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. Nos: 1330–20–7 (xylene)
95–47–6 (*ortho*–xylene)
108–38–3 (*meta*–xylene)
106–42–3 (*para*–xylene)

Chem. Abstr. Names: 1,2–Dimethylbenzene
1,3–Dimethylbenzene
1,4–Dimethylbenzene

IUPAC Systematic Name: Xylene (*ortho*–, *meta*–, *para*–)

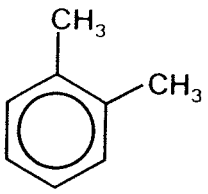
Synonyms: *ortho*–Xylene: *ortho*–Dimethylbenzene; *ortho*–methyltoluene; 2–methyltoluene; 1,2–xylene; *ortho*–xylol

meta–Xylene: *meta*–Dimethylbenzene; *meta*–methyltoluene; 3–methyltoluene; 1,3–xylene; *meta*–xylol

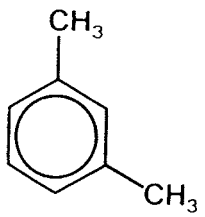
para–Xylene: *para*–Dimethylbenzene, *para*–methyltoluene; 4–methyltoluene; 1,4–xylene; *para*–xylol

1.2 Structural and molecular formulae and molecular weight

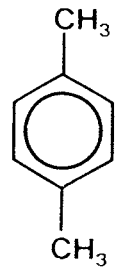
C_8H_{10}



ortho–xylene



meta–xylene



para–xylene

Mol. wt: 106.18

1.3 Chemical and physical properties of the pure substances

Table 1. Chemical and physical properties of the pure isomers

Property	*ortho*-Xylene	*meta*-Xylene	*para*-Xylene	Reference
Description	Clear, colorless liquid		Crystalline solid	Windholz (1983)
Boiling point (°C)	144.4 32 at 10 mm Hg	139.1 28.1 at 10 mm Hg	138.3 27.2 at 10 mm Hg	Weast (1985)
Melting-point (°C)	-25.2	-47.9	13.3	Weast (1985)
Density	0.8802 at 20°/4°C	0.8642 at 20°/4°C	0.8611 at 20°/4°C	Weast (1985)
Refractive index	1.5055 at 20°C	1.4972 at 20°C	1.4958 at 20°C	Weast (1985)
Spectroscopy data	Infrared, ultraviolet and nuclear magnetic resonance spectral data have been reported			Sadtler Research Laboratories (1980); Pouchert (1981, 1983, 1985)
Solubility	Soluble in ethanol, diethyl ether, acetone, benzene; insoluble in water			Weast (1985)
Volatility (vapour pressure, mm)	6.8 at 25°C	8.3 at 25°C	8.9 at 25°C	Sandmeyer (1981)
Flash-point (°C)	32	29	27	Sandmeyer (1981)
Octanol/water partition coefficient (log P)	2.77-3.12	3.2	3.15	Hansch & Leo (1979)
Conversion factor	$mg/m^3 = 4.34 \times ppm^a$			
Reactivity	Highly inflammable			Hansch & Leo (1979)

[a]Calculated from mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg)

1.4 Technical products and impurities

Trade Names: Chromar; Dilan; Scintillar

Xylene is marketed principally as a mixture of *ortho*, *meta* and *para* isomers, generally referred to as 'mixed xylenes'. The individual isomers are also available commercially. Most mixed xylenes contain ethylbenzene, except for a small volume produced by toluene disproportionation (Ransley, 1984). Commercial-grade (mixed) xylene typically is composed of approximately 20% *ortho*-xylene, 40% *meta*-xylene and 20% *para*-xylene, with about 15% ethylbenzene and smaller amounts of toluene, trimethylbenzene (pseudocumene), phenol, thiophene, pyridine and non-aromatic hydrocarbons (National Institute for Occupational Safety and Health, 1975; Clement Associates, 1977). A product of higher purity is reported to contain a minimum of 97% xylene isomer with maximum impurities of 3% ethylbenzene, 0.1% benzene, 0.1% toluene and 0.01% water (Riedel-de Haën, 1984).

Typical *para*-xylene products (99.5% pure) contain 0.3% ethylbenzene, 0.1% *meta*-xylene and 0.1% *ortho*-xylene (Ransley, 1984). All three isomers are available at 99.9% minimal high purity, spectrophotometric grade as well as in 'chemically pure' grades, as follows: *ortho*-xylene, 98% pure; *para*-xylene, 99%; and *meta*-xylene, 99% (Riedel-de Haën, 1984).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Xylene occurs in petroleum stock, but in very small quantities. It is produced primarily by the catalytic reforming of naphtha streams, which are rich in alicyclic hydrocarbons. The aromatic reformate fractions consist mainly of benzene, toluene and mixed xylenes, xylenes representing the largest fraction. The xylene isomers are separated from the reformate by extraction and distillation on the basis of differences in boiling-point. *ortho*-Xylene, which has the highest boiling point, is separated as the bottom distillate; *para*-xylene is separated by continuous crystallization or adsorption from the mixed xylenes or isomerized from the *meta*-xylene/*para*-xylene distillate; and *meta*-xylene is obtained by selective crystallization or solvent extraction of *meta-para* mixtures (Mannsville Chemical Products Corp., 1981; Ransley, 1984).

Another source of mixed xylenes is pyrolysis gasoline, a by-product that results from cracking of hydrocarbon feeds during olefin manufacture (Fishbein, 1985). The mixed xylene content of pyrolysis gasoline varies, depending upon the feed and the severity of the cracking process. Pyrolysis gasoline is a less efficient source for recovery of mixed xylene than catalytic reformate because it contains large amounts of ethylbenzene.

Mixed xylenes may also be produced from petroleum refining operations by the Toyo Rayon and Atlantic-Richfield processes, in which toluene is transalkylated or disproportionated. Benzene and toluene are the principal products (Fishbein, 1985). Xylenes obtained from this source are 'ethylbenzene free', provided the transalkylation feed stocks are limited to toluene and (polymethyl)benzene (Ransley, 1984).

Less than 1% of the mixed xylenes in the USA are derived from coal. Coal subjected to high-pressure carbonization (coke manufacture) yields crude light oil containing 3–6% mixed xylenes. Every tonne of coal yields 2–3 gallons (7.6–11.4 l) of crude light oil (Ransley, 1984), which may be used as a supplementary source of aromatic compounds in petroleum refining, processed for recovery of light naphtha containing mixed xylenes and styrene, or burned as fuel.

The Mitsubishi Gas Chemical Company (MGCC) process is another commercial method for separating the *meta* isomer from mixed xylenes using a hydrofluoric acid-borofluoride separation technique. It is also a straightforward means of separating the other C_8 aromatic isomers (Ransley, 1984).

The total quantities of mixed xylenes (and the percentages isolated as xylene) produced in the USA in 1978 in the ways described above were as follows: catalytic reformate, 34.9

million tonnes (10%); pyrolysis gasoline, 375 thousand tonnes (52%); toluene disproportionation, 90 thousand tonnes (54%); and coal–derived, 15 thousand tonnes (88%). Of the total 35.44 million tonnes produced in 1978, about 11% was isolated (Fishbein, 1985).

Mixed xylenes are also produced in large quantities in Europe and Japan. Data on production of xylenes in a number of areas are presented in Table 2.

Table 2. Annual production of xylenes (thousands of tonnes)[a]

Country or region	1981	1982	1983	1984	1985	1986	1987
Brazil[b]	86	83	80	84	79	NA[c]	NA
Bulgaria	32	32	29	32	31	NA	NA
Canada	409	431	426	406	415	356	345
China	86	100	104	128	257	NA	NA
Czechoslovakia	99	107	119	119	117	108	NA
France	114	51	90	85	126	113	129
Germany, Federal Republic of	486	459	511	455	495	540	501
Hungary	76	79	93	94	95	94	NA
India	NA	14[b]	18[b]	NA	NA	NA	28
Italy	256	269	365	395	432	405	491
Japan	1202	1225	1264	1401	1523	1570	1767
Korea, Republic of	244	249	300	304	330	490	552
Mexico	104	115	236	268	291	273	381
Portugal	NA	84	110	104	106	NA	NA
Romania	224	254	269	254	225	NA	NA
Spain	40	49	58	53	53	60	NA
Taiwan	241	200	239	291	270	237	NA
Turkey	0.4	0.3	0.2	0.2	0.2	NA	NA
USA	2477	1905	2225	2251	2479	2647	2772
USSR	468	409	556	849	937	962	NA
Yugoslavia	16	NA	11	17	8	NA	NA

[a]From US International Trade Commission (1982, 1983, 1984); Anon. (1985); US International Trade Commission (1985, 1986); Anon. (1987); US International Trade Commission (1987); Anon. (1988a,b)
[b]*ortho*–Xylene
[c]NA, not available

(*b*) *Use*

Mixed xylenes recovered from all sources (petroleum refineries, pyrolysis gasoline, coal–tar) are used in the chemical and solvent industries (Ransley, 1984). Although isolated xylenes are also blended into gasoline to improve octane rating, the reformate without isolation of mixed xylenes or other aromatics is primarily used for gasoline blending. Unleaded premium gasoline has been reported to contain 10–22% xylenes (Korte & Boedefeld, 1978; Ikeda *et al.*, 1984).

Mixed xylenes are also used in the manufacture of perfumes (Sittig, 1985), insecticides, pharmaceuticals and adhesives and in painting, printing, rubber, plastics (Sandmeyer, 1981) and leather industries (IARC, 1981).

In the USA, most of the production of isolated mixed xylenes is separated into the individual isomers for use as chemical intermediates or as solvents (Mannsville Chemical Products Corp., 1981). The approximate distributions of the production of mixed xylenes in the USA are as follows: *para*–xylene, 50–60%; gasoline blending, 10–25%; *ortho*–xylene, 10–15%; solvents, 10%; ethylbenzene, 3%; and *meta*–xylene, 1% (Ransley, 1984). *para*–Xylene is used principally to manufacture terephthalic acid and dimethylterephthalate, used in the production of saturated polyester resins and fibres (Mannsville Chemical Products Corp., 1981). The remaining small amount of *para*–xylene produced is used as a pharmaceutical or pesticide intermediate and in solvents for adhesives and coatings (Hawley, 1981; Anon., 1986). *ortho*–Xylene is used primarily as a feedstock for the manufacture of phthalic anhydride: almost 60% of the *ortho*–xylene produced in the USA in 1978 was used in this way (Fishbein, 1985). It is also used as a chemical intermediate in synthesis of dyes, pharmaceuticals and insecticides (Hawley, 1981; Ransley, 1984). *meta*–Xylene is used in the manufacture of isophthalic acid for polyester resins (Mannsville Chemical Products Corp., 1981) and as a chemical intermediate for dyes and insecticides (Hawley, 1981).

(*c*) *Regulatory status and guidelines*

Occupational exposure limits for xylenes in 32 countries or regions are presented in Table 3.

Table 3. Occupational exposure limits for xylenes (all isomers)[a]

Country or region	Year	Concentration[b] (mg/m^3)	Interpretation[c]
Austria	1985	435	TWA
Belgium	1985	S 435	TWA
Brazil	1985	S 340	TWA
Bulgaria	1985	50	TWA
Commission of the European Communities	1986	435 2175	Average Maximum
Chile	1985	S 348	TWA
China	1985	100	TWA

Table 3 (contd)

Country or region	Year	Concentration[b] (mg/m^3)	Interpretation[c]
Czechoslovakia	1985	200	Average
		1000	Maximum
Denmark	1988	S 217	TWA
Finland	1987	S 435	TWA
		S 655	STEL
France	1986	435	TWA
		650	STEL (15 min)
German Democratic Republic	1985	200	TWA
		600	STEL
Germany, Federal Republic of	1988	440	TWA
Hungary	1985	50	TWA
		100	STEL
India	1985	S 435	TWA
		655	STEL
Indonesia	1985	435	TWA
Italy	1985	S 400	STEL
Japan	1988	435	TWA
Korea, Republic of	1985	435	TWA
		655	STEL
Mexico	1985	S 435	TWA
Netherlands	1986	S 435	TWA
Norway	1981	435	TWA
Poland	1985	100	TWA
Romania	1985	S 300	TWA
		S 400	Maximum
Sweden	1987	S 200	TWA
		S 450	STEL (15 min)
Switzerland	1985	S 435	TWA
Taiwan	1985	435	TWA
UK	1987	S 435	TWA
		S 650	STEL (10 min)
USA[d]			
OSHA	1988	200	TWA
		300	Ceiling
NIOSH	1986	434	TWA
		868	Ceiling (10 min)
ACGIH	1988	435	TWA
		655	STEL (15 min)
USSR	1985	50	Ceiling

Table 3 (contd)

Country or region	Year	Concentration[b] (mg/m^3)	Interpretation[c]
Venezuela	1985	S 435 S 655	TWA Ceiling
Yugoslavia	1985	50	TWA

[a]From Direktoratet for Arbeidstilsynet (1981); National Swedish Board of Occupational Safety and Health (1984); Arbeidsinspectie (1986); Commission of the European Communities (1986); Institut National de Recherche et de Sécurité (1986); National Institute for Occupational Safety and Health (1986); Cook (1987); Health and Safety Executive (1987); Työsuojeluhallitus (1987); American Conference of Governmental Industrial Hygienists (1988); Arbejdstilsynet (1988); Deutsche Forschungsgemeinschaft (1988); US Occupational Safety and Health Administration (1988)

[b]S, skin notation

[c]TWA, 8-h time-weighted average; STEL, short-term exposure limit

[d]OSHA, Occupational Safety and Health Administration; NIOSH, National Institute for Occupational Safety and Health; ACGIH, American Conference of Governmental Industrial Hygienists

2.2 Occurrence

(a) *Natural occurrence*

Mixed xylenes are present in coal-tar, petroleum stocks (Fishbein, 1985) and natural gas (Hillard, 1980) in small quantities.

(b) *Occupational exposure*

On the basis of a US National Occupational Exposure Survey, the National Institute for Occupational Safety and Health (1983) estimated that 1 106 800 workers were potentially exposed to xylene in the USA in 1981–83.

Levels of xylene to which workers have been exposed are summarized in Table 4. Levels determined during the manufacture and application of paints are described in the monograph on occupational exposures in paint manufacture and painting (see p. 329). Levels of exposure to xylene in petroleum refining and in the manufacture and use of petroleum fuels are reported in Volume 45 of the *Monographs* (IARC, 1989).

Pre- and post-shift concentrations of methyl hippuric acid in the urine of workers in a shipbuilding yard were 0.2–7.1 mg/ml. The workers were using a thinner in spray-painting operations that contained 32.8% *meta*- or *para*-xylene (Ogata *et al.*, 1971). Mean urinary concentrations of methyl hippuric acid in workers in a photograph album manufacturing plant who used a cleaning solvent (complex mixture of 90% C_7–C_9 aliphatic hydrocarbons, 5% toluene and 5% xylene) to remove excess glue were 0.07 g/g creatinine before a shift and 0.48 g/g creatinine afterwards (Baker & Fannick, 1983).

(c) *Air*

Mixed xylenes are emitted to the ambient air during their production and use from reactor, distillation and crystallization vents. Emissions may also occur during storage, loading and handling. Total emissions of mixed xylenes in the USA in 1978 were estimated to be

4100 tonnes from catalytic reformate, 150 tonnes from pyrolysis gasoline, 18 tonnes from toluene disproportionation and 19 tonnes from coal-derived production. Emissions of total individual isomers were estimated to be 1180 tonnes of *ortho*-xylene, 2900 tonnes of *para*-xylene and 80 tonnes of *meta*-xylene (Fishbein, 1985). Merian (1982) reported that worldwide losses of xylenes into air from refineries, evaporation of gasoline, automobile exhaust and solvent losses are approximately 3 million tonnes.

Table 4. Occupational exposure to xylene

Environment	Sampling[a]	Concentration in air[b]	Reference
Laboratories			
Histology laboratory (USA)	4-h personal	3.2–102 ppm (14–443 mg/m^3)	Kilburn *et al.* (1985)
Histology laboratory [FRG]	8-h TWA personal	(*m*+*p*)-xylene, 56–68 ppm (243–295 mg/m^3) *o*-xylene, 10–13 ppm (43–56 mg/m^3)	Angerer & Lehnert (1979)
Histology laboratory (USA)	8-h TWA personal	2.5–72.6 ppm (11–315 mg/m^3)	Roper (1980)
	8-h TWA area	18.3–28.3 ppm (79–123 mg/m^3)	
Cytopathology laboratory (USA)	8-h TWA personal	1.6–12.8 ppm (7–55 mg/m^3)	Roper (1980)
	8-h TWA area	15–32 ppm (65–139 mg/m^3	
Hospital laboratory (USA)	Point	0.6–400 ppm (2.6–1700 mg/m^3)	Klaucke *et al.* (1982)
Chemical plant (Hungary)		Mean, 47–56 mg/m^3	Pap & Varga (1987)
Extraction plant producing xylene from gasoline (USSR)	Air	75–200 mg/m^3 in 35–40% of samples	Sukhanova *et al.* (1969)
Lithography (Poland)			Moszczyński & Lisiewicz (1985)
1968		32–450 mg/m^3; mean, 119 mg/m^3	
1970		110–130 mg/m^3	
1971		ND–360 mg/m^3; mean, 102 mg/m^3	
1974		ND–150 mg/m^3	
1977		15–30 mg/m^3; mean, 17 mg/m^3	
1978		10–506 mg/m^3; mean, 130 mg/m^3	
Manufacture of photograph albums (USA)	Personal TWA	1–56 mg/m^3	Baker & Fannick (1983)
Golf club and baseball bat manufacturing plant (USA)	8-h TWA personal	2–14 ppm (9–61 mg/m^3	Rivera & Rostand (1975)

[a]TWA, time-weighted average

[b]ND, not detected

Mixed xylene are also lost during use, as in the processing of chemicals and solvents, evaporation during transportation, distribution, storage and use of gasoline, in motor vehicle emissions and from agricultural spraying (Fishbein, 1985).

Atmospheric concentrations of total mixed xylenes have been determined at various locations around the world. Mean values and ranges measured between 1961 and 1980 are as follows: (in mg/m^3): France (0.003–0.01), Federal Republic of Germany (rural, 0.001–0.04; urban, 0.15), Japan (0.06–0.39), the Netherlands (urban, 0.07), South Africa (0.02–0.03) and Switzerland (urban, 0.02–0.05). In the USA, mean concentrations of atmospheric xylene at urban sites in California, Texas and New York/New Jersey in 1961–74 were 0.08–0.12, 0.04–0.07 and 0.15 mg/m^3, respectively (Merian & Zander, 1982). Xylene levels of 116–684 mg/m^3 have been reported in smoke from forest fires (Merian & Zander, 1982), and xylene has been detected in cigarette smoke (Holzer *et al.*, 1976). Concentrations of *meta*-xylene in outdoor air in the USA have been reported to range from 0.016 to 0.061 ppm (0.069–0.265 mg/m^3; Fishbein, 1985).

Xylene has been detected in indoor environments as a consequence of cooking, fuel burning and tobacco smoking. The mean concentrations of combined *meta*- and *para*-xylenes in indoor air were 0.029, 0.021 and 0.014 mg/m^3 in kitchens, other rooms and bedrooms, respectively (Seifert & Abraham, 1982; Wallace *et al.*, 1983). Holzer *et al.* (1976) found approximately 50 ppb (0.2 mg/m^3) *meta*- plus *para*-xylene in nonventilated cigarette smoke-filled room air and 18 ppb (0.08 mg/m^3) in the air of a room where no cigarettes had been smoked.

Outdoor air next to dwellings contained 0.009–0.028 mg/m^3 combined *meta*- and *para*-xylenes and that in backyards, 0.0011 mg/m^3 (Seifert & Abraham, 1982; Wallace *et al.*, 1983); 0.0042 mg/m^3 *ortho*-xylene was measured in backyards (Wallace *et al.*, 1983), and 0.1 mg/m^3 *meta*- and *para*-xylenes was measured at traffic intersections (Seifert & Abraham, 1982).

Krotoszynski *et al.* (1979) reported mean levels of 0.001, 0.0003 and 0.0031 mg/m^3 *ortho*-, *meta*- and *para*-xylene, respectively, in expired air of 54 normal, healthy volunteers from an urban population in Chicago, IL, USA. Xylene was also found in breath samples from urban residents of two New Jersey cities in the USA; mean values were 0.0034 mg/m^3 for *ortho*-xylene and 0.009 mg/m^3 for combined *meta*- and *para*-xylene. Levels were higher in persons who pumped their own gasoline or were exposed to auto and truck exhaust (Wallace *et al.*, 1984).

(*d*) *Water*

Xylenes have been identified in surface and drinking-waters, for example in the river Glatt, a tributary of the Rhine. In the USA, levels of 2–8 µg/l were reported in surface water from the Florida Bay and 3–8 µg/l in drinking- and tap-water in New Orleans, LA (Merian & Zander, 1982).

(*e*) *Animal tissues*

Ogata and Miyake (1973) measured mean concentrations of 21.7, 30.1 and 25.0 mg/kg *meta*-, *para*- and *ortho*-xylene in the muscles and 5.2, 26.6 and 6.1 mg/kg of the three isomers, respectively, in the liver of eels (*Aguilla japonica*) exposed to sea water containing 14.1 mg/kg *meta*-xylene and 13.1 mg/kg *ortho*-xylene.

2.3 Analysis

Selected methods for the analysis of xylene in various matrices are listed in Table 5. Methods for the analysis of xylene have recently been reviewed and compiled (Fishbein & O'Neill, 1988).

Colorimetric detection systems have been developed for xylenes in air (The Foxboro Co., 1983; Sensidyne, 1985; National Draeger, Inc., 1987; SKC, 1988; ENMET Corp., undated; Matheson Gas Products, undated; Roxan, Inc., undated).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F1 mice, eight weeks of age, received 0, 500 or 1000 mg/kg bw technical-grade xylene (comprising 60.2% *meta*-, 13.6% *para*- and 9.1% *ortho*-xylene with 17% ethylbenzene; purity, 99.7% with 2.8 ppm (0.00028%) benzene as contaminant) in corn oil by stomach tube on five days per week for 103 weeks. The animals were killed in weeks 104–105. No significant difference in mean body weights or survival was observed between control and treated mice. Survival at termination of the experiment was: males – 27 controls, 35 low-dose and 36 high-dose; and females – 36 controls, 35 low-dose and 31 high-dose. No treatment-related increase in the incidence of any tumour was seen in animals of either sex (National Toxicology Program, 1986; Huff *et al.*, 1988).

Rat: Groups of 40 male and 40 female Sprague–Dawley rats, seven weeks of age, were administered 500 mg/kg bw mixed xylenes (*ortho*-, *meta*- and *para*-; purities, >99% [source and percentage composition unspecified]) in olive oil by stomach tube on four to five days per week for 104 weeks. A group of 50 males and 50 females received olive oil only. Rats were maintained until natural death; all rats had died by week 141. At that time, thymomas were reported in 1/34 treated males and 0/36 treated females, compared to 0/45 and 0/49 in the control groups. Other haemolymphoreticular tumours [histology unspecified] were reported in 4/34 treated males and 3/36 treated females, compared to 3/45 and 1/49 controls. (The denominators are numbers of rats alive in each group at 58 weeks when the first haemolymphoreticular tumour was observed.) The authors reported an increase in the total number of animals with malignant tumours [type unspecified] at 141 weeks: in 14/38 treated males and 22/40 treated females compared to 11/45 and 10/49 controls. (The denominators are the number of rats alive in each group at 33 weeks when the first malignant tumour was observed.) (Maltoni *et al.*, 1983, 1985). [The Working Group noted the incomplete reporting of the composition of the test material and of tumour pathology, and that combining different types of tumours is not usually the most appropriate method for evaluating carcinogenicity (IARC, 1980; Montesano *et al.*, 1986).]

Table 5. Analytical methods for the determination of xylene and its metabolites in various matrices

Sample matrix	Sample collection	Sample preparation	Assay procedure	Detection limits	Reference
Air	Passive sampler with charcoal	Desorb (carbon disulfide); inject aliquot; analyse using glass capillary column	GC	0.3 mg/m^3 per h	Seifert & Abraham (1983)
	Charcoal tube	Desorb (carbon disulfide); inject aliquot; analyse on packed column	GC–FID	0.001–0.01 mg/sample	Eller (1984)
Water		Extract with hexane; inject aliquot	GC–FID	5 μg/l	Otson & Williams (1981)
		Heat samples in water bath at 25 °C for 1 h; inject headspace aliquots	GC–MS	1 μg/l	Otson *et al.* (1982)
Automotive exhaust gas	Tenax GC polymer adsorbant cartridge	Desorb thermally into liquid nitrogen-cooled capillary trap	GC–MS	Not given	Hampton *et al.* (1982)
Breath (air)	Specially designed spirometer containing Tenax–GC cartridge	Dry cartridge over calcium sulfate; desorb thermally in a fused silica capillary column	GC–MS	Not given	Wallace *et al.* (1983, 1984, 1986)
Blood	Heparinize or antifoam emulsion B	Purge (nitrogen) at room temperature; trap (Tenax TA); desorb thermally; analyse volatiles on column	GC–MS	10 ppt (μg/l)	Cramer *et al.* (1988)
Tissue (muscle, liver)	Mince tissue	Heat with ethanol and potassium hydroxide; extract with *n*-hexane; apply extract to silica gel/-aluminium trioxide column; elute with *n*-hexane; concentrate eluate; inject aliquot into GC	GC–FID	Not given	Ogata & Miyake (1973, 1978)
Urine (methylhippuric acid)		After alkaline hydrolysis, extract with diethyl ether at acidic pH; silylate and inject onto GC	GC–FID	Not given	Engström & Riihimäki (1988)

[a]Abbreviations: GC, gas chromatography; FID, flame-ionization detection; MS, mass spectrometry

Groups of 50 male and 50 female Fischer 344/N rats, seven weeks of age, received 0, 250 or 500 mg/kg bw technical-grade xylene (containing 60.2% *meta*-, 13.6% *para*- and 9.1% *ortho*-xylene with 17% ethylbenzene; purity, 99.7% with 2.8 ppm (0.00028%) benzene as contaminant) in corn oil by stomach tube on five days per week for 103 weeks. The animals were killed in weeks 104–105. High-dose males had lower mean body weights from week 59 onwards; body weights of low-dose males and treated females were comparable to those of controls. At termination of the experiment, 36 male controls and 25 males at the low dose and 20 at the high dose were still alive; the differences were due in part to accidental killing of animals. Survival in control and treated females was similar at termination (38 controls, 33 low-dose and 35 high-dose). The incidences of tumours in treated animals of either sex were not significantly higher than that in the control group (National Toxicology Program, 1986; Huff *et al.*, 1988).

3.2 Other relevant data

The toxicology of xylenes has been reviewed (Riihimäki & Engström, 1979; World Health Organization, 1981; Fishbein, 1985; European Chemical Industry Ecology and Toxicology Centre, 1986).

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

ortho-Xylene was found to penetrate rat skin excised three days after clipping and depilation with cream at a rate that was 1/10 that of toluene and 1/100 that of benzene (Tsuruta, 1982).

In rats exposed to 208 mg/m^3 [methyl-^{14}C]*para*-xylene for 1 h, distribution of radioactivity immediately after termination of the exposure was highest in the kidneys, followed by subcutaneous fat, ischiatic nerve, blood, liver and lungs. Activity was 1/5 to 1/30 of these levels 6 h after the end of exposure (Carlsson, 1981).

Xylenes are metabolized both in the liver and lungs (Carlone & Fouts, 1974; Smith *et al.*, 1982; Toftgård *et al.*, 1986), primarily at a side-chain, to form methylhippuric acid and toluic acid (methylbenzoic acid) glucuronide as major metabolites and methylbenzyl mercapturic acid as a minor metabolite (Carlone & Fouts, 1974; Ogata *et al.*, 1980; van Doorn *et al.*, 1980). They are metabolized to a lesser extent at the aromatic ring to form dimethylphenol (e.g., Toftgård *et al.*, 1986). The ratio among the metabolites varies depending on the isomer (Bray *et al.*, 1949; Bakke & Scheline, 1970) and the species of animal (e.g., Ogata *et al.*, 1980).

Most of the xylene that is absorbed is excreted rapidly into the urine as metabolites. When rabbits were given oral doses of up to 1.8 g each of the three isomers, separately, well over 50% of the radioactivity was recovered in urine within 24 h (Bray *et al.*, 1949).

When 3 mmol/kg *ortho*-, *meta*- or *para*-xylene were given intraperitoneally to rats, urinary excretion of thiocompounds was highest with *ortho*-xylene and much lower with *meta*-xylene and *para*-xylene (van Doorn *et al.*, 1980).

In male rats exposed to *meta*-xylene vapour at concentrations of 200, 1700 or 3200 mg/m^3 for 6 h per day on five days per week for two weeks, xylene concentrations in brain and

perirenal fat were increased during the second week of exposure (Savolainen & Pfäffli, 1980).

Pregnant mice were exposed by inhalation to ^{14}C-*para*-xylene [theoretical concentration, 2000 ppm (8680 mg/m^3)] for 10 min on days 11, 14 or 17 of gestation, and distribution of the label was determined 0, 0.5, 1 and 4 h after exposure. The label quickly entered the embryo, but uptake was low relative to maternal tissues. All fetal activity was extractable, indicating that no firmly bound metabolite was present (Ghantous & Danielsson, 1986).

(ii) *Toxic effects*

Oral LD_{50} values for *ortho*-xylene, *meta*-xylene, *para*-xylene and the isomer mixture in rats range between 3600 and 5800 mg/kg bw (Wolf *et al.*, 1956; European Chemical Industry Ecology and Toxicology Centre, 1986). The intraperitoneal LD_{50}s of the pure isomers in male mice ranged from 1360 to 2100 mg/kg bw (Mohtashampur *et al.*, 1985). An inhalation LC_{50} (4 h) for the isomer mixture in male rats has been determined as 6700 ppm (29 078 mg/m^3; Carpenter *et al.*, 1975). The 6 h-inhalation LC_{50}s of the pure isomers in female mice were 3900–5300 ppm (17 000–23 000 mg/m^3; Bonnet *et al.*, 1979).

A 4-h percutaneous administration of 4400 mg/kg bw of mixed xylenes to three male rabbits resulted in the death of one rabbit on the fifth day after exposure. At dose levels of 1700 mg/kg bw, none of three rabbits died (Hine & Zuidema, 1970).

Ten to 20 applications of undiluted mixed xylenes on the ears or shaved abdomen of rabbits for two or four weeks resulted in moderate to marked erythema and oedema, with superficial necrosis at both sites. After introduction of two drops of mixed xylenes into the rabbit eye, slight conjunctival irritation and transient corneal injury were observed (Wolf *et al.*, 1956). Application of undiluted xylene to the eye caused corneal lesions in cats (Schmid, 1956).

Rats were exposed by inhalation for 4 h to 2500, 5800, 12 000, 26 000 and 43 000 mg/m^3 mixed xylenes. All rats at the highest concentration and 4/10 at 26 000 mg/m^3 died; xylene-induced pneumonitis was noted in two of the rats that died. Prostration was noted with 43 000 and 12 000 mg/m^3 and poor coordination with 5800 mg/m^3; no such sign was observed at the lowest exposure concentration. Exposure of four male cats to 41 000 mg/m^3 mixed xylene vapour for 2 h resulted in ataxia, spasms and anaesthesia, followed by death (Carpenter *et al.*, 1975).

Exposure of rats by inhalation to *meta*-xylene at concentrations of 200, 1700 or 3200 mg/m^3 for 6 h per day on five days per week for two weeks resulted in changes in the activities of brain enzymes (NADPH-diaphorase, azoreductase and superoxide dismutase), which were reversible two weeks after cessation of exposure (Savolainen & Pfäffli, 1980). Changes in open-field behaviour were observed in rats exposed by inhalation to 300 ppm (1300 mg/m^3) for 6 h per day for five to 18 weeks (Savolainen *et al.*, 1979).

Intraperitoneal administration of 1 g/kg bw xylene resulted in an increase in serum ornithine carbamyl transferase activity and lipid accumulation in the liver of rabbits and guinea-pigs, indicating liver damage (DiVincenzo & Krasavage, 1974). Similarly, increases in liver enzyme activities in the serum of rats exposed by inhalation to 1500 ppm (6510 mg/m^3) *para*-xylene for 4 h (Patel *et al.*, 1979) and to 400 ppm (1730 mg/m^3) *meta*-xylene for 6 h per

day on five days per week for two weeks (Elovaara, 1982) are indicative of xylene-induced liver damage. Exposure of rats to 600 ppm (2600 mg/m^3) xylene during the light period of the day for four weeks (Toftgård *et al.*, 1981) or to 2000 ppm (8680 mg/m^3) *ortho*–, *para*– or *meta*–xylene for 6 h per day for three days (Toftgård & Nielsen, 1982) induced microsomal cytochrome P450. Repeated oral administration (1 g/kg per day) of *ortho*–, *meta*– or *para*–xylene to rats for three days (Pyykkö, 1980) or intermittent exposure of rats by inhalation to 300 ppm (1300 mg/m^3) xylene on 6 h per day for two weeks (Savolainen *et al.*, 1978) also increased the activities of drug metabolizing enzymes in the liver and kidney. Inhalation exposure of groups of rats to 3000 mg/m^3 *para*–xylene on day 10 or on days 9 and 10 of gestation [daily duration was presumably for 24 h] reduced concentrations of progesterone and 17β–oestradiol in the maternal circulation (Ungváry *et al.*, 1981).

In some rats exposed to 3000 mg/m^3 mixed xylenes for 8 h per day on six days per week for 110–130 days, exposure resulted in paralysis of the hind legs, weight loss, a slight decrease in leukocytes, increases in blood urea, urinary blood and albumin, and hyperplasia of the bone marrow. Slight congestion of kidney, liver, heart, adrenal, lung and spleen were observed. Cellular desquamation of glomeruli and necrosis of the convoluted tubules were also reported (Fabre *et al.*, 1960).

Rats, guinea–pigs, monkeys and dogs were exposed either to 780 ppm (3368 mg/m^3) *ortho*–xylene for 8 h per day on five days per week for six weeks or to 78 ppm (337 mg/m^3) continuously for 90 days. No significant change in body weight or in haematological parameters and no significant toxicity were observed after histopathological examination of all major organs (Jenkins *et al.*, 1970).

Groups of four male rats and four male dogs were exposed for 6 h per day on five days per week for 13 weeks to 180, 460 or 810 ppm (770, 200 or 3500 mg/m^3) mixed xylenes. No significant effect was reported on body weight, haematology, blood chemistry, urine chemistry, organ weight or macroscopic and microscopic pathology at any concentration tested (Carpenter *et al.*, 1975).

Groups of 15 male rats were exposed by inhalation to 3500 ppm (15 200 mg/m^3) *ortho*–xylene for 8 h per day for one or six weeks. Slight decreases in body weight gain and increased liver weight were observed in both groups (Tátrai & Ungváry, 1980).

(iii) *Effects on reproduction and prenatal toxicity*

The teratogenic and developmental effects of xylene have been reviewed (Hood & Otley, 1985).

Groups of 30 Mallard eggs were exposed by immersion for 30 sec in a 1 or 10% aqueous suspension of xylene on day 3 or 8 of incubation; control eggs were immersed in distilled water. No significant effect was observed on the growth, survival or development of embryos examined at day 18 of incubation (Hoffman & Eastin, 1981).

In one study reported in an abstract (Nawrot & Staples, 1980), exposure of CD–1 mice to 0.75 or 1.0 ml/kg bw of any of the three isomers on days 6–15 of gestation was reported to cause maternal toxicity and fetal death; cleft palates were also reported in fetuses exposed to the *ortho*– and *para*–isomers. When the experiment was repeated with *meta*–xylene, a low but statistically significant incidence of cleft palates occurred after repeated exposures to 1.0

ml/kg bw in the absence of overt maternal effects. [The Working Group noted that the doses were incorrectly expressed as mg, rather than ml, in the abstract.] Marks *et al.* (1982) exposed CD-1 mice to 0.52–4.13 g/kg bw mixed xylenes on days 6–15 of gestation. All dams and fetuses at the highest dose died, and dams died at 3.1 g/kg bw. Fetal viability was reduced at this dose, and growth at 2.06 g/kg bw. Cleft palate and wavy ribs were seen with 2.06 g/kg bw and above. [The Working Group noted an error in the paper in converting the dose from volume per kilogram to mass per kilogram.] In ICR/SIM mice given *meta*-xylene at 2000 mg/kg bw on days 8–12 of gestation, no significant effect was seen on maternal toxicity or postnatal growth or on viability of the offspring (Seidenberg *et al.*, 1986).

In one study reported as an abstract, ICR mice were exposed to 0, 500, 1000 and 2000 ppm (2170, 4340 and 8680 mg/m^3) xylene on days 6–12 of gestation. It was stated that fetal growth was retarded at the two highest dose levels and that there was a dose-related increase in the frequency of supernumerary ribs and delayed ossification of the sternebrae. At the high dose, growth retardation persisted into the postnatal period (Shigeta *et al.*, 1983). [The Working Group noted that the reporting of the experimental design and results were insufficient to evaluate many of the parameters.] CFLP mice were exposed to 0, 500 or 1000 mg/m^3 xylene or to 500 mg/m^3 *ortho*-, *meta*- or *para*-xylene for 24 h per day on days 6–15 of gestation. Fetal growth and skeletal retardation were reported at the highest doses (Ungváry & Tátrai, 1985). [The Working Group noted that this paper is a compendium of data on rats, mice and rabbits from one laboratory and presents few details of experimental results.]

In CFY rats, fused sternebrae and extra ribs were observed in fetuses of dams exposed to 1000 mg/m^3 xylene for 24 h per day on days 9–14 of pregnancy, in the absence of maternal effects (Hudák & Ungváry, 1978). In another study in CFY rats using levels of 0, 250, 1900 or 3400 mg/m^3 xylene given on days 7–15 of gestation, it was stated that maternal effects were moderate and dose-dependent; the highest dose resulted in decreased embryonic viability and fetal growth as well as an increased incidence of extra ribs; skeletal retardation was seen with all three doses (Ungváry & Tátrai, 1985). [The Working Group had the same reservations about this paper as expressed above.] Mirkova *et al.* (1983) reported fetal growth retardation following exposure of Wistar rats to 50 and 500 mg/m^3 xylene on days 1–21 of gestation; these effects were not seen with 10 mg/m^3. The growth retardation persisted through postnatal day 21. [The Working Group noted that the reporting of the experimental design and results were insufficient to evaluate many of the parameters.]

CFY rats were exposed *via* inhalation to *ortho*-, *meta*- or *para*-xylene (analytical purity) at concentrations of 0, 150, 1500 and 3000 mg/m^3 for 24 h per day on days 7–14 of gestation. Food consumption was reduced at the two higher concentrations of *ortho*-xylene and in the groups exposed to the highest level of *meta*- and of *para*-xylene. Exposure to 3000 mg/m^3 *meta*-xylene killed 4/30 dams and reduced weight gain in the surviving dams; 2/20 and 7/20 of the females receiving the high doses of *ortho*- and *para*-xylene, respectively, resorbed their entire litters. Increased maternal liver weight:body weight ratios were observed in all groups exposed to *ortho*-xylene. Fetal body weights were reduced by the two highest levels of *ortho*-xylene and by the highest level of *meta*- and of *para*-xylene; fetal viability was affected only by the highest dose level of *para*-xylene. There was no indication that any xylene isomer caused visceral abnormalities in fetuses in a dose-related manner, but skeletal development was

retarded by the high concentration of *ortho*-xylene and by all concentrations of *para*-xylene. Extra ribs were seen in significantly more fetuses in the groups exposed to the high doses of *meta*- and *para*-xylene (Tátrai *et al.*, 1979; Hudák *et al.*, 1980; Ungváry *et al.*, 1980). [The Working Group noted that the analysis supporting this observation is based on data on fetuses, rather than on data on litters, the customary unit of comparison.]

Groups of 25 Sprague–Dawley rats were exposed by inhalation to 0, 3500 or 7000 mg/m^3 *para*-xylene (purity, 99%) for 6 h per day on days 7–16 of gestation, and the offspring were evaluated for growth, viability and neurobehavioural development. The high dose level reduced maternal weight gain during the exposure period, but growth, viability, locomotor activity and the acoustic startle response of the offspring were not affected (Rosen *et al.*, 1986).

Groups of New Zealand white rabbits were exposed to 0 (60 animals in a pooled control group), 500 or 1000 mg/m^3 of *ortho*-xylene, *meta*-xylene, *para*-xylene or xylene [composition unspecified] for 24 h per day on days 7–20 of gestation. Fetuses were examined by routine teratological techniques on day 30 of gestation. It was stated that for each solvent the high-dose level produced mild maternal toxicity [no data were presented for the 1000-mg/m^3 *ortho*- and *meta*-xylene group]. Maternal death and abortion were noted with both xylene and *para*-xylene at 1000 mg/m^3. The body weights of female fetuses exposed to 500 mg/m^3 xylene were significantly reduced, but no other effect on fetuses was reported (Ungváry & Tátrai, 1985). [The Working Group noted that this paper is a compendium of data on rats, mice and rabbits from one laboratory and presents few details on experimental results.]

(iv) *Genetic and related effects*

The genetic and related effects of xylene have been reviewed (Dean, 1978, 1985; Fishbein, 1985).

Technical-grade xylene did not produce differential killing in DNA repair-proficient compared to repair-deficient strains of *Bacillus subtilis rec*$^{+/-}$ (McCarroll *et al.*, 1981a) or *Escherichia coli* (McCarroll *et al.*, 1981b). Xylene [grade unspecified] did not induce SOS activity in *Salmonella typhimurium* TA1535/pSK 1002 (Nakamura *et al.*, 1987). *para*-Xylene was not mutagenic to *E. coli* WP2*uvr*A in the presence or absence of an exogenous metabolic system from Aroclor-induced rat liver (Shimizu *et al.*, 1985). *ortho*-, *meta*- and *para*-Xylene, xylene [grade unspecified] and mixed xylenes were not mutagenic to *S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100, UTH8413 or UTH8414 in the presence or absence of an exogenous metabolic system from uninduced or Aroclor-induced rat and Syrian hamster livers (Lebowitz *et al.*, 1979 (abstract); Bos *et al.*, 1981; Haworth *et al.*, 1983; Connor *et al.*, 1985; Shimizu *et al.*, 1985; Zeiger *et al.*, 1987).

As reported in an abstract, exposure to technical-grade xylene (contaminated with 18.3% ethylbenzene), but not exposure to *meta*- or *ortho*-xylene, caused recessive lethal mutations in *Drosophila melanogaster* (Donner *et al.*, 1980).

As reported in an abstract, xylene [grade unspecified] did not induce mutation in mouse lymphoma L5178Y TK$^{+/-}$ cells or chromosomal aberrations in rat bone marrow (Lebowitz *et al.*, 1979). Xylene [grade unspecified] did not induce sister chromatid exchange or chromosomal aberrations in human lymphocytes *in vitro* (Gerner-Smidt & Friedrich, 1978).

[The Working Group noted that the study of human lymphocytes was performed without an exogenous metabolic system.]

None of the three isomers induced micronuclei in the bone marrow of male NMRI mice after two intraperitoneal administrations of 0.12–0.75 ml/kg bw (0.11–0.65 mg/kg bw) at a 24-h interval (Mohtashamipur *et al.*, 1985); however, they enhanced the induction of micronuclei by toluene (Mohtashamipur *et al.*, 1987).

As reported in an abstract, exposure of rats to mixed isomers (300 ppm; 1300 mg/m^3) for 6 h per day on five days per week for nine, 14 and 18 weeks did not induce chromosomal aberrations in bone-marrow cells (Donner *et al.*, 1980).

As reported in an abstract, xylene did not inhibit intercellular communication (as measured by metabolic cooperation) in Chinese hamster V79 cells (Awogi *et al.*, 1986).

Xylene [grade unspecified] did not enhance morphological transformation of Syrian hamster embryo cells by the SA7 adenovirus (Casto, 1981).

Rats injected intraperitoneally with 0.5 and 1.5 ml/kg bw (0.44 and 1.32 mg/kg bw) *ortho*-xylene showed a significant increase in the percentage of abnormal sperm when housed at temperatures of 24–30 °C (control: 2.94±1.36; treated: 4.17±1.41) but not at 20–24 °C (Washington *et al.*, 1983). The authors interpreted this as a synergistic effect between xylene and temperature.

(*b*) *Humans*

(i) *Absorption, distribution, excretion and metabolism*

Most of the available information on xylene metabolism in humans deals with *meta*-xylene.

In volunteers exposed by inhalation, lung retention was practically identical (64%) for the three isomers (Šedivec & Flek, 1976a). In other studies with volunteers, lung retention of *meta*-xylene was about 60% (Riihimäki *et al.*, 1979) to 75% (Senczuk & Orłowski, 1978). When volunteers immersed their hands in liquid *meta*-xylene, it was absorbed at 2 μg/cm^2 per min (Engström *et al.*, 1977). A nine-fold interindividual variation in skin absorption rate was observed among volunteers (Lauwerys *et al.*, 1978). The amount of *meta*-xylene absorbed after whole-body exposure of volunteers to 600 ppm (2600 mg/m^3) vapour, excluding inhalation, for 3.5 h was equivalent to the amount absorbed after inhalation exposure to 20 ppm (87 mg/m^3) for the same duration (Riihimäki & Pfäffli, 1978).

More than 70% of *meta*-xylene absorbed was excreted into the urine as metabolites (Ogata *et al.*, 1970; Engström *et al.*, 1984). A minor portion (~5%, apparently irrespective of the isomer) was exhaled unchanged (Šedivec & Flek, 1976a; Riihimäki *et al.*, 1979; Åstrand *et al.*, 1978).

Elimination of *meta*-xylene from the body *via* excretion and inhalation is rapid, with a biological half-time of 1 h for a rapid phase after 6–16 h of exposure and of about 20 h for a slow phase (Riihimäki *et al.*, 1979). About 72% of total urinary metabolites was excreted in the urine within 24 h after termination of exposure to the three isomers (Šedivec & Flek, 1976a). Removal of industrial xylene from subcutaneous adipose tissue, however, is slow (Engström & Bjurström, 1978), with a half-time of 25–128 h for the *meta* isomer (Engström & Riihimäki, 1979).

Xylenes are primarily metabolized in humans to the corresponding methylhippuric acid (toluric acid); and glycine conjugation is considered to be a rate-limiting step (Riihimäki, 1979). When volunteers were exposed to *ortho*-, *meta*- or *para*-xylene vapour, more than 95% of the absorbed compound was excreted as methylhippuric acid, and only a small portion was excreted as dimethylphenol: 0.86% as 2,3-dimethylphenol and 3,4-dimethylphenol, after exposure to *ortho*-xylene (the ratio between the two dimethylphenols varied depending on individuals), 1.98% as 2,4-dimethylphenol after exposure to *meta*-xylene and 0.05% as 2,5-dimethylphenol after exposure to *para*-xylene (Šedivec & Flek, 1976a). In other experiments in which volunteers were exposed to *meta*-xylene, *meta*-methylhippuric acid in the urine accounted for 72% (Ogata *et al.*, 1970) to 97% (Engström *et al.*, 1984) of the *meta*-xylene absorbed, whereas 2,4-dimethylphenol and 3-methylbenzyl alcohol accounted for 2.5 and 0.05%, respectively (Engström *et al.*, 1984). Similar results were found for *para*-xylene (Ogata *et al.*, 1970). *ortho*-Xylene was metabolized almost exclusively to *ortho*-methylhippuric acid; only trace amounts of *ortho*-toluic acid (*ortho*-methylbenzoic acid) glucuronide were detected in the urine of volunteers exposed to *ortho*-xylene vapour (Ogata *et al.*, 1980).

Methylhippuric acid has therefore been proposed as a marker urinary metabolite for the biological monitoring of factory workers exposed to xylene, and urine collected in the latter half of a shift is recommended for analysis (Lundberg & Sollenberg, 1986; for reviews, see Šedivec & Flek, 1976b; Riihimäki, 1979).

(ii) *Toxic effects*

Some of the information on the adverse effects of xylene on the central and peripheral nervous systems originates from studies of workers exposed occupationally (mainly painters); such workers are generally also exposed to other organic solvents (Seppäläinen *et al.*, 1978; Elofsson *et al.*, 1980; Ekberg *et al.*, 1986). For further information, see the monograph on occupational exposures in paint manufacture and painting.

Most volunteer subjects exposed to 2000 mg/m^3 technical xylene for 15 min had eye irritation (Carpenter *et al.*, 1975); workers exposed to a mixture of solvents, including xylene, displayed corneal vacuoles (Schmid, 1956). Similar effects have been described in spray painters exposed to almost pure xylene as a lacquer-diluting agent (Matthäus, 1964).

Exposure of volunteers to technical xylene by inhalation caused irritation of the airways (Carpenter *et al.*, 1975); very high accidental exposure caused pneumonitis (Morley *et al.*, 1970). Ingestion of xylene caused irritation of the gastrointestinal tract (Gosselin *et al.*, 1976).

Skin contact caused a burning sensation and reversible erythema (Lauwerys *et al.*, 1978). Prolonged exposure may cause contact dermatitis (European Chemical Industry Ecology and Toxicology Centre, 1986).

In studies of volunteers exposed to 200 ppm (870 mg/m^3) xylene for 8 h, simple reaction time was slowed (Ogata & Nagao, 1970). Heavy accidental exposure may cause narcosis (Bakinson & Jones, 1985) and death (Morley *et al.*, 1970). Goldie (1960) suggested that occupational exposure to xylene in paints provoked epileptic seizures in one case.

In volunteers exposed to 390 mg/m^3 or more technical xylene or *meta*-xylene, with or without physical exercise, reaction time, manual coordination, body equilibrium and

electroencephalogram were affected (Gamberale *et al.*, 1978; Savolainen & Linnavuo, 1979; Savolainen, 1980; Savolainen *et al.*, 1980a,b; Savolainen & Riihimäki, 1981a,b; Seppäläinen *et al.*, 1981; Savolainen *et al.*, 1984, 1985a,b). In particular, concentration peaks affected performance. Tolerance developed after exposure for a week and disappeared during the weekend.

Transient kidney damage has occasionally been reported in cases of severe, acute xylene poisoning (Morley *et al.*, 1970; Bakinson & Jones, 1985). Furthermore, indications of slight adverse effects on the kidney (Askergren, 1981; Askergren *et al.*, 1981a,b,c; Franchini *et al.*, 1983) have been reported in workers exposed mainly to xylene and toluene (see also the monograph on occupational exposures in paint manufacture and painting).

In cases of severe, acute poisoning, signs of liver damage have been reported (Morley *et al.*, 1970; Bakinson & Jones, 1985).

Aplastic anaemia was reported in one laboratory worker and decreased platelet counts in 12/27 other laboratory workers exposed to technical xylene (containing 0.2% benzene). When exposure to xylene was interrupted, platelet counts returned to normal (Forde, 1973). [The Working Group noted several early reports of effects on blood and blood forming organs, which might have been due to benzene contamination of xylene.]

(iii) *Effects on fertility and on pregnancy outcome*

In their study of female pharmaceutical workers in Finland, Taskinen *et al.* (1986; see the monograph on toluene) also assessed exposure to xylene. Exposure during the first trimester of pregnancy was reported by three of 38 (8%) women who had had a spontaneous abortion compared to four of 199 (3%) control women who had had live births. The corresponding relative risk (RR) was 2.0 (95% confidence interval (CI), 0.4–10.6). Cases and controls had been exposed to many solvents and other substances.

In the study of Swedish female laboratory workers (Axelsson *et al.*, 1984; see the monograph on toluene), 160 women reported having worked in a laboratory with exposure to xylene during the first trimester of pregnancy. The miscarriage rate of 10.3% compares with that of 11.5% among women who had not worked in a laboratory during the first trimester and that of 9.0% among women who had worked in a laboratory but not with solvents during the first trimester. Cases and controls had been exposed to many solvents and other substances.

Ericson *et al.* (1984; see the monograph on toluene) reported that exposure to xylene had been similar for Swedish laboratory workers who had given birth to children who died in early infancy or were malformed (8%) and for women who had had normal births (8%). Cases and controls were exposed to many solvents and other substances.

In the study of Holmberg (1979; described in the monograph on some petroleum solvents), the mother of one child with central nervous system defects and one control mother reported having worked with xylene during the first trimester of pregnancy. Both mothers had also been exposed to other solvents. In the study of Holmberg *et al.* (1982), described in the monograph on some petroleum solvents, three mothers of children with oral clefts but no control mother were reported to have worked with xylenes during the first trimester of pregnancy. The mothers had also been exposed to other solvents.

(iv) *Genetic and related effects*

No increase in the frequency of sister chromatid exchange was observed in ten workers in the Swedish paint industry exposed to various solvents, including more than 100 mg/m^3 xylene (Haglund *et al.*, 1980; see also the monograph on occupational exposures in paint manufacture and painting). [The Working Group noted the small number of workers observed.] No increase in sister chromatid exchange was observed in 46 workers at a Hungarian chemical plant exposed to technical xylene (*ortho*–, *meta*– and *para*–xylene, 6–15% ethylbenzene) with an average exposure of nine years to an average of 50 mg/m^3, compared with 34 clerical workers from the factory who were used as controls (Pap & Varga, 1987).

3.3 Epidemiological studies of carcinogenicity in humans

In each of the studies described below, exposures were mixed and overlapping, and these studies are cited in several monographs.

Olsson and Brandt (1980) performed a study on exposure to organic solvents among 25 cases of Hodgkin's disease and 50 controls in Sweden (see the monograph on some petroleum solvents). Exposure to xylene was mentioned by four cases but no referent. All exposed cases and referents were exposed to other solvents.

Wilcosky *et al.* (1984) performed a case–control study of rubber workers in the USA (see the monograph on some petroleum solvents). Exposure to xylene was associated with increased risks for prostatic cancer (relative risk (RR), 1.5, eight cases), lymphosarcoma (3.7, four cases) and lymphatic leukaemia (3.3, four cases). [The Working Group noted that the number of cases in each category is small and that multiple exposures were evaluated independently of other exposures. Although the risk for lymphosarcoma in xylene–exposed workers was significantly raised, four significant associations were reported out of the 20 substances, and these associations are based on larger numbers of exposed cases. It was therefore impossible to determine whether a single substance was associated with the risk.]

Carpenter *et al.* (1988) evaluated the possible association with exposure to 26 chemicals or chemical groups in 89 cases of primary cancers of the central nervous system and 356 matched controls in cohorts of workers at two US nuclear facilities. Toluene (see monograph, p. 79), xylene and methyl ethyl ketone were evaluated as one chemical group; the matched RR was 2.0 (28 cases; 95% confidence interval, 0.7–5.5) in comparison with nonexposed workers. Almost all cases had had low exposure according to the classification used. The authors reported that the RRs were adjusted for internal and external exposure to radiation. [The Working Group noted that no separate analysis was performed for the three solvents, nor were exposure levels quantified, and that there were many concurrent exposures.]

4. Summary of Data Reported and Evaluation

4.1 Exposures

Xylene is a major industrial chemical derived mainly from petroleum refining. It occurs in three isomeric forms (*ortho*, *meta* and *para*) and is produced and used both as 'mixed xylenes' (usually containing 10–15% ethylbenzene) and as the individual isomers. Xylene is used as a solvent in paints, inks, adhesives and insecticides. Xylene-containing petroleum distillates are used extensively and increasingly in gasoline blending.

The individual isomers are used mainly as chemical intermediates in the manufacture of derivatives of phthalic anhydride (from *ortho*-xylene), isophthalic acid (from *meta*-xylene) and terephthalic acid (from *para*-xylene).

Xylene is ubiquitous in the environment. Occupational exposure has been reported in petroleum refining, in the production of xylene and in the use of xylene and its end products.

4.2 Experimental carcinogenicity data

Xylene (technical grade or mixed xylenes) was tested for carcinogenicity in one strain of mice and in two strains of rats by gastric intubation. One study in rats with mixed xylenes was considered inadequate for evaluation. No increase in the incidence of tumours was observed in either mice or rats following the administration of a technical-grade xylene.

No data were available on the individual isomers.

4.3 Human carcinogenicity data

Exposure to xylene has been associated with increased risks for haematopoietic malignancies in two case–control studies, but the number of cases was limited and exposure was to a variety of compounds.

4.4 Other relevant data

In humans, exposure to xylene causes irritant and central nervous system effects. Adverse effects have been observed on the kidney and liver in cases of accidental poisoning. Similar effects have been seen in experimental animals after exposure to xylene at high levels.

In some studies of the reproductive outcome of women exposed to xylene during the first trimester of pregnancy, small excess risks for spontaneous abortion and for congenital malformation were reported. In all of these studies, the numbers of cases were small and the mothers had also been exposed to other substances.

Maternally toxic or near-toxic amounts of xylene have been associated with malformations in mice after oral administration and with embryotoxicity in rabbits, rats and mice after exposure by inhalation.

Sister chromatid exchange was not induced in peripheral lymphocytes of workers in two studies; however, exposure was to a variety of compounds.

None of the three isomers of xylene induced micronuclei in mice *in vivo*. Sister chromatid exchange and chromosomal aberrations were not induced in cultured human lymphocytes, in the absence of an exogenous metabolic system. Xylene of unspecified grade did not induce morphological transformation in cultured animal cells. None of the three isomers or xylene, either alone or in combination, induced mutation in bacteria. Technical-grade xylene did not induce DNA damage in bacteria. (See Appendix 1.)

4.5 Evaluation[1]

There is *inadequate evidence* for the carcinogenicity of xylene in humans.

There is *inadequate evidence* for the carcinogenicity of xylene in experimental animals.

Overall evaluation

Xylene *is not classifiable as to its carcinogenicity to humans (Group 3).*

5. References

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[1]For definitions of the italicized terms, see Preamble, pp. 27–30.

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