XYLENES

Data were last evaluated in IARC (1989).

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

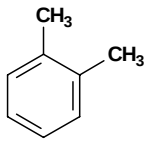
Chem. Abstr. Serv. Reg. No.: 1330-20-7
Chem. Abstr. Name: Dimethylbenzene
IUPAC Systematic Name: Xylene
Synonym: Xylol

Chem. Abstr. Serv. Reg. No.: 95-47-6
Chem. Abstr. Name: 1,2-Dimethylbenzene
IUPAC Systematic Name: *ortho*-Xylene
Synonym: *ortho*-Xylol

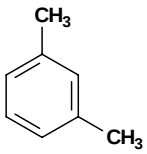
Chem. Abstr. Serv. Reg. No.: 108-38-3
Chem. Abstr. Name: 1,3-Dimethylbenzene
IUPAC Systematic Name: *meta*-Xylene
Synonym: *meta*-Xylol

Chem. Abstr. Serv. Reg. No.: 106-42-3
Chem. Abstr. Name: 1,4-Dimethylbenzene
IUPAC Systematic Name: *para*-Xylene
Synonym: *para*-Xylol

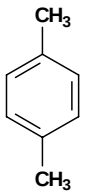
1.1.2 *Structural and molecular formulae and relative molecular mass*



o-Xylene



m-Xylene



p-Xylene

C_8H_{10} Relative molecular mass: 106.17

1.1.3 *Chemical and physical properties of the pure substances*

From American Conference of Governmental Industrial Hygienists (1992), unless otherwise noted.

(*a*) *Description*: Colourless liquids (Budavari, 1996)
(*b*) *Boiling-point*: 144.4°C (*ortho*); 139.1°C (*meta*); 138.3°C (*para*)
(*c*) *Melting-point*: –25.2°C (*ortho*); –47.9°C (*meta*); 13.3°C (*para*)
(*d*) *Solubility*: Insoluble in water; miscible with ethanol, diethyl ether and other organic solvents (*ortho*, *meta* and *para*)
(*e*) *Vapour pressure*: 904 Pa at 25°C (*ortho*); 1104 Pa at 25°C (*meta*); 1184 Pa at 25°C (*para*)
(*f*) *Flash point*: 17°C (*ortho*), closed cup; 25°C (*meta* and *para*), closed cup
(*g*) *Conversion factor*: $mg/m^3 = 4.34 \times ppm$

1.2 Production and use

World production of *para*-xylene in 1983 was 3900 thousand tonnes, of which the United States accounted for 48%, Europe 23% and Japan 16%; the world production of *ortho*-xylene in 1983 was 1300 thousand tonnes, of which western Europe produced 30% and the United States 18% (WHO, 1997). In 1993, United States production of *ortho*-xylene was reported to be about 377 thousand tonnes and of *para*-xylene was about 2600 thousand tonnes (United States International Trade Commission, 1994). United States production of mixed xylene and *para*-xylene in 1994 was approximately 4100 and 2800 thousand tonnes, respectively (WHO, 1997).

The major uses of mixed xylene are in aviation gasoline and protective coatings, and as a solvent for alkyd resins, lacquers, enamels and rubber cements. *meta*-Xylene is used as a solvent, as an intermediate for dyes and organic synthesis, especially isophthalic acid and insecticides, and in aviation fuel; *ortho*-xylene is used in manufacture of phthalic anhydride, vitamin and pharmaceutical synthesis, dyes, insecticides, motor fuels; *para*-xylene is used in synthesis of terephthalic acid for polyester resins and fibres, vitamin and pharmaceutical syntheses, and insecticides (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES) (1997), approximately 1 106 800 workers in the United States were potentially exposed to xylene (see General Remarks).

Data on levels of occupational exposure to xylene are presented in a previous monograph (IARC, 1989).

1.3.2 *Environmental occurrence*

Commercial xylene is a mixture of the three xylene isomers in the following percentage ranges: *ortho*-xylene, 10–25%; *meta*-xylene, 45–70%; and *para*-xylene, 6–15%. Xylene may enter the atmosphere primarily from fuel emissions and exhausts, due to its

use in gasoline. Its production and use in petroleum products, as a solvent, and as an intermediate in organic synthesis may result in its release to the environment through various waste streams. Natural sources of xylene such as petroleum, forest fires and volatile substances in plants may also contribute to its presence in the environment (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 434 mg/m^3 as the threshold limit value for occupational exposures to xylene in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

The World Health Organization has established an international drinking-water guideline for xylene of 500 μg/L (WHO, 1993).

2. Studies of Cancer in Humans

2.1 Industry-based studies

In a case–control study within a cohort of 6678 rubber workers in the United States (IARC, 1987) (Wilcosky *et al.*, 1984), one of the substances assessed was xylene, which was analysed as a potential risk factor in relation to each of five cancer types. There were somewhat increased odds ratios (OR) for prostate cancer (OR, 1.5; $n = 8$), lymphosarcoma (OR, 3.7; $n = 4$; $p < 0.05$) and lymphatic leukaemia (OR, 3.3; $n = 4$). [The Working Group noted that workers were typically exposed to multiple exposures.]

2.2 Community-based studies

Olsson and Brandt (1980) carried out a hospital-based case–control study of Hodgkin's disease and chemical exposures in Lund, Sweden. Twenty-five consecutive male cases aged 20–65 years were included. Two neighbourhood-matched controls were selected for each case from the Swedish population register. Interviews with study subjects focused on their detailed job history, and in particular exposure to solvents. Interview data were supplemented with visits to employers in some cases. Four of the cases and none of the controls had been exposed to xylene. All exposed cases were also exposed to other solvents. [The Working Group noted the opportunity for information bias, since the interviewer was not blind to disease status or to the study objectives.]

In the nested case–control study of Carpenter *et al*. (1988) (described in more detail in the monograph on toluene in this volume), there was a hint of excess risk of central nervous system cancer among workers exposed to toluene, xylene and methyl ethyl ketone (evaluated as one chemical group) at two nuclear facilities located in Tennessee (United States). The relative risk was 2.0 (95% confidence interval (CI), 0.7–5.5; $n = 28$) in comparison with unexposed workers. [The Working Group noted that no separate

analysis was reported for the three solvents, and that there were many concurrent exposures. Exposure levels were not quantified.]

Gérin *et al.* (1998) presented results concerning xylene from the population-based case–control study in Montreal, Canada (described in more detail in the monograph on toluene in this volume). Of the entire study population, 12.4% had been exposed to xylene at some time. Among the main occupations to which xylene exposure was attributed were vehicle mechanics and repairmen, painters (except construction) and shoemakers. For the following cancer sites, there was little indication of excess risk in relation to exposure to xylene (results for 'high' exposure): oesophagus (OR, 1.4; *n* = 5), stomach (OR, 1.8; *n* = 2), pancreas (OR, 1.1; *n* = 4), prostate (OR, 1.4; *n* = 6), urinary bladder (OR, 0.8; *n* = 3), kidney (OR, 1.0; *n* = 6), skin melanoma (ever exposed OR, 0.3; *n* = 3) and non-Hodgkin lymphoma (OR, 1.0; *n* = 6). For the following sites there was indication of excess risk: colon (OR, 5.8; 95% CI, 1.5–22.0; *n* = 8), rectum (OR, 2.7; 95% CI, 0.9–8.3; *n* = 5) and lung (OR, 1.6; 95% CI, 0.7–3.8; *n* = 16). [The Working Group noted that most workers exposed to xylene were also exposed to benzene, toluene and perhaps other substances. Exposure levels were not quantified.]

3. Studies of Cancer in Experimental Animals

Xylene (technical grade or mixed xylenes) was tested for carcinogenicity in one strain of mice and in two strains of rats by gavage. 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 administration of a technical-grade xylene. No data were available on the individual isomers (IARC, 1989).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

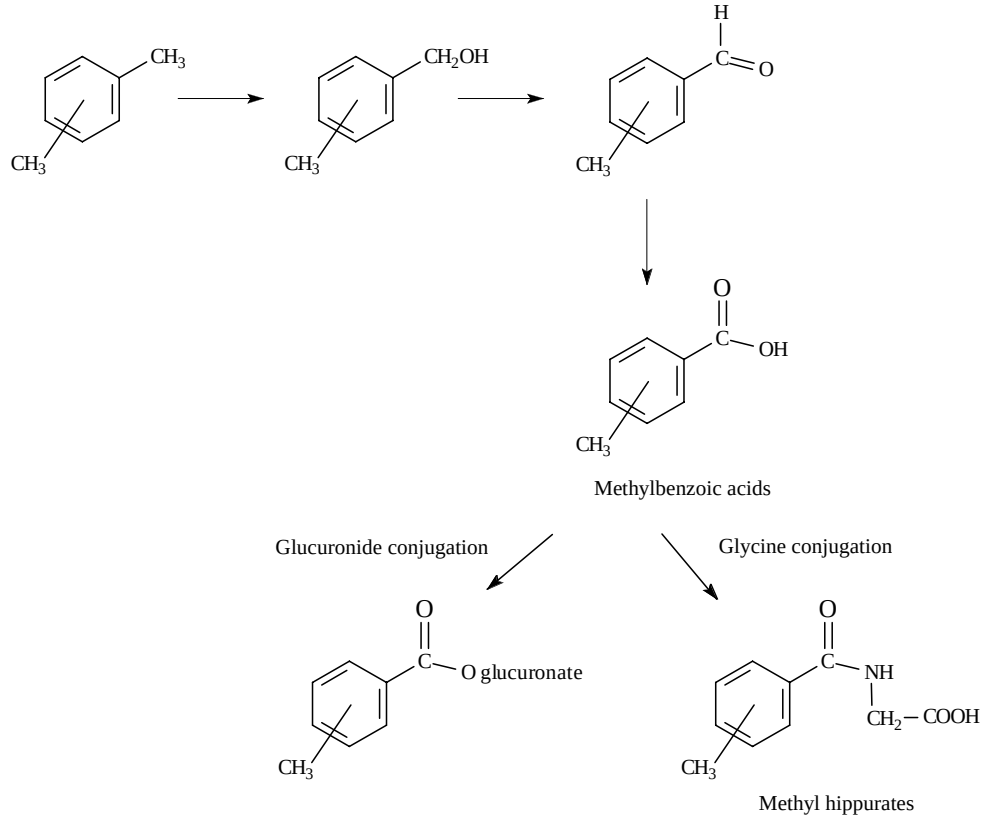
Xylenes are metabolized primarily by oxidation to the methylbenzyl alcohols, followed by further oxidation to the corresponding methylbenzoic acids (toluic acids). These can be conjugated with glycine to form methylhippurates, or with UDP-glucuronate to form acyl glucuronides (see Figure 1).

4.1.1 *Humans*

The pharmacokinetics and metabolism of the xylenes have been reviewed (Low *et al*., 1989; Langman, 1994).

In volunteers exposed by inhalation, lung retention of *meta*-xylene was about 60%. When volunteers immersed their hands in liquid *meta*-xylene, it was absorbed at 2 μg/cm^2

Figure 1. Metabolism of xylenes



Adapted from Low *et al.* (1989)

per min. 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 (IARC, 1989).

More than 70% of *meta*-xylene absorbed was excreted into the urine as metabolites. A minor portion was exhaled unchanged (IARC, 1989). Elimination 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. Removal of industrial xylene from subcutaneous adipose tissue, however, is slow, with a half-time of 25–128 h for the *meta* isomer (IARC, 1989).

Xylenes are metabolized in humans primarily to the corresponding methylhippuric acid (toluric acid); and glycine conjugation is considered to be a rate-limiting step. Only a small portion is excreted as dimethylphenol: 2,3-dimethylphenol and 3,4-dimethylphenol after exposure to *ortho*-xylene, 2,4-dimethylphenol after exposure to *meta*-xylene and 2,5-dimethylphenol after exposure to *para*-xylene (IARC, 1989).

When workers are exposed to xylenes at low exposure levels (up to 20 ppm [870 mg/m^3]), the end-of-shift urinary excretion of methylhippurates is a good indication of exposure because these methylhippurates are normally not present in urine (Jonai & Sato, 1988; Kawai *et al*., 1991).

4.1.2 *Experimental systems*

After inhalation exposure of mice to [^{14}C]-*para*-xylene, methylhippurate accumulated in nasal mucosa and the olfactory bulb, possibly due to axonal flow-mediated transport of the methylhippurate from the mucosa, where it is formed, to the olfactory lobe of the brain (Ghantous *et al*., 1990). Inhalation exposure of rats to *meta*-xylene with or without ethyl acetate showed that ethyl acetate caused a decrease in the blood concentration of *meta*-xylene (Freundt *et al*., 1989).

Tardif *et al*. (1997) developed a physiologically based pharmacokinetic model for *meta*-xylene in rats and humans. They also simulated interactions between *meta*-xylene, toluene and ethylbenzene, and showed that for exposures at air concentrations remaining within the permissible range for a mixture, biologically significant interactions at the pharmacokinetic level would not occur.

Exposure of Sprague-Dawley rats to 300 ppm [1300 mg/m^3] *meta*-xylene for 6 h inhibited several cytochrome P450 (CYP) isoenzymes in the lung (e.g., CYP2B1, 1A2, 2E1 and 4B1), but had little effect on the hepatic levels of these CYPs (Foy *et al*., 1996).

4.2 Toxic effects

The toxicity of xylene has been reviewed (Agency for Toxic Substances and Disease Registry, 1990).

4.2.1 *Humans*

Adverse effects on the kidney and liver have been observed in cases of accidental poisoning.

Local irritation and mild central nervous system symptoms were reported in a questionnaire survey, but no abnormalities were seen in a health examination, clinical chemistry, or haematological parameters among 175 xylene-exposed employees, whose exposure to xylene was on average 21 ppm [87 mg/m^3] (Uchida *et al*., 1993). Minor effects on body sway, reaction times or overnight sleep pattern were observed after experimental inhalation exposure to xylene (200 ppm [870 mg/m^3], 5 h per day for six days) (Laine *et al*., 1993).

4.2.2 *Experimental systems*

In experimental animals exposed to high doses of xylene, adverse effects have been observed in the kidney and liver (IARC, 1989).

Ninety-day gavage dosage of technical xylene (17.6% *ortho*-xylene, 62.3% *meta*- and *para*-xylene, 20% ethylbenzene; 150, 750 or 1500 mg/kg bw daily) induced no mortality in Sprague-Dawley rats (Condie *et al*., 1988). Slight increases in alanine aminotransferase

activity were observed in males (1500 mg/kg bw) and females (≥ 750 mg/kg bw), but not in other enzymes reflecting liver cell damage. No histological damage to the liver was noted, but liver weight was increased in males at all dose levels, and in females at levels ≥ 750 mg/kg bw per day. Minimal, but dose-dependent, nephropathy was observed in females.

Three-month inhalation exposure to *meta*-xylene (1000 ppm [4340 mg/m^3], 6 h per day on five days per week) of male Wistar rats had a very slight effect on the hepatocyte ultrastructure: limited proliferation of smooth endoplasmic reticulum and lysosomes was observed. Findings were similar after six months' exposure to 100 ppm [434 mg/m^3]. Simultaneous exposure to toluene made the proliferation of smooth endoplasmic reticulum more prominent (Rydzynski *et al*., 1992).

Exposure of male Fischer 344 rats to *para*-xylene (0–1600 ppm [0–6940 mg/m^3], 6 h per day for one or three days) had negligible effect on hepatic morphology and serum activities of alanine or aspartate aminotransferases, lactate dehydrogenase, ornithine carbamyl transferase, alkaline phosphatase or serum bilirubin concentration (Simmons *et al*., 1991). Liver size was increased and its cytochrome P450 content was elevated.

Treatment of male Charles-Foster rats with sublethal doses of xylene (0.2 mL of 5 mmol/L extra-pure xylene solution on alternate days for 30 days; isomeric composition not indicated) resulted in slight increases of serum aspartate and alanine aminotransferase and alkaline phosphatase activities and bilirubin concentration (Rana & Kumar, 1993). A slight increase in alanine aminotransferase activity was also observed after a 3.5-week treatment of male Wistar rats with *meta*-xylene (800 mg/kg bw per day on five days per week, by gavage) (Elovaara *et al*., 1989). Inhalation exposure of C3H/HeJ mice to *para*-xylene (1200 ppm [5200 mg/m^3], 6 h per day for four days) did not affect the serum alanine or aspartate aminotransferase or lactate dehydrogenase activities, or bilirubin level (Selgrade *et al*., 1993).

Inhalation and oral exposure to *meta*-xylene induced hepatic cytochrome P450 activities, notably that of CYP2B1, as well as the activities of UDP-glucuronosyltransferase, DT-diaphorase and glutathione *S*-transferase (Savolainen *et al*., 1978; Toftgård *et al*., 1983; Elovaara *et al*., 1989; Raunio *et al*., 1990; Gut *et al*., 1993). On the other hand, short-term inhalation exposure (≥ 75 ppm [325 mg/m^3], 24 h) led to a decrease in cytochrome P450 activity in rat lung (Elovaara *et al*., 1987). Inhalation exposure of C3H/HeJ mice to *para*-xylene (1200 ppm [5200 mg/m^3], 6 h per day for four days) slightly increased the hepatic cytochrome P450 content (Selgrade *et al*., 1993).

When *para*-xylene-exposed (1200 ppm [5200 mg/m^3], 6 h per day for four days) C3H/HeJ mice were infected intraperitoneally with murine cytomegalovirus (10^5 plaque-forming units after the first xylene exposure), 34% of the mice died, while none died after either exposure alone or after a similar exposure to xylene at 600 ppm [2600 mg/m^3], combined with exposure to the virus (Selgrade *et al*., 1993). Elevated mortality was not related to immune function or hepatic damage.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

In a case–control study of congenital malformations and spontaneous abortions within a cohort of workers who at some time of their career had had a biomonitoring measurement for occupational solvent exposure performed, data on medically diagnosed pregnancies were extracted from the hospital discharge registry, and data on abortions separately from polyclinics. Exposure of the father and mother of the cases and referents was collected by questionnaire (Taskinen *et al*., 1989; Lindbohm *et al*., 1990). An elevated odds ratio of spontaneous abortions for paternal exposure to xylene (37 cases; OR, 1.8; 95% CI, 1.1–3.2) was observed. However, most xylene-exposed fathers also had been exposed to other solvents; after adjustment for confounders, only paternal exposure to organic solvents as a group remained significant. Xylene exposure of women was not associated with spontaneous abortions; malformations were not associated with exposures of either men or women. In a similar case–control study on solvent exposure and pregnancy outcome among laboratory assistants (Taskinen *et al*., 1994), the odds ratio of spontaneous abortion was increased among the women who were exposed to xylene for at least three days per week during the first trimester of pregnancy (OR, 3.1; 95% CI, 1.3–7.5). Simultaneous exposure to other solvents was common; two cases (out of 36) and two controls (out of 105) were exposed to xylene only. No elevated odds ratio for congenital malformations was observed for any solvent, but the power of the study was limited.

4.3.2 *Experimental systems*

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 (IARC, 1989).

When female Wistar rats were exposed to technical xylene (200 ppm [870 mg/m^3], 6 h per day) on days 4 through 20 of gestation, no exposure-related embryo- or fetotoxicity or terata were observed, but the frequency of delayed ossification of maxillary bone was increased. Postnatal weight gain was faster in pups from exposed dams, and they also showed advanced development of some physical milestones (ear unfolding, eye opening) but a weaker performance on Rotarod (Hass & Jakobsen, 1993). Xylene did not induce malformations in explanted rat embryos at the highest concentrations tested (0.28–0.57 μL/mL), but retarded the growth and development of the embryos at the lowest concentration tested (0.15–0.45 μL/mL) (Brown-Woodman *et al*., 1991). Male Sprague-Dawley rats exposed to xylene (1009 ± 47 ppm [4380 ± 204 mg/m^3], 18 h per day on seven days per week for 61 days) showed no evidence of histological damage to the testes (percentage of intact spermatozoa or of normal head and tail, testis weight, ventral prostate weight, noradrenaline content of vas deferens) two weeks or 10 months after the cessation of exposure (Nylén *et al*., 1989).

4.4 Genetic and related effects

4.4.1 *Humans*

Sister chromatid exchanges were not induced in peripheral lymphocytes of workers in two studies (exposure to a variety of compounds) or in five healthy volunteers exposed for seven consecutive hours per day over three consecutive days to 40 ppm [174 mg/m^3] xylene either alone or in combination with 50 ppm [189 mg/m^3] toluene (Haglund *et al*., 1980; Pap & Varga, 1987; Richer *et al*., 1993).

4.4.2 *Experimental systems* (see Table 1 for references)

Technical grade xylene did not induce DNA damage in bacteria.

No gene mutations were induced by xylenes in *Salmonella typhimurium* strains or in *Escherichia coli* WP*uvr*A.

Xylene of unspecified grade did not induce morphological transformation in cultured Syrian hamster cells.

In vitro, mixtures of xylenes did not induce sister chromatid exchanges or chromosomal aberrations either in Chinese hamster ovary CHO cells or in human lymphocytes, in the absence of an exogenous metabolic system.

None of the three isomers of xylene induced micronuclei or chromosomal aberrations in mouse bone marrow *in vivo* (chromosomal aberrations were observed in mouse spleen lymphocytes *in vivo*).

5. Summary of Data Reported and Evaluation[1]

5.1 Exposure data

Exposure to xylenes may occur during their production and in the production of aviation gasoline and protective coatings, and during their use in petroleum products, e.g., solvents, and as intermediates in organic synthesis. Natural sources include petroleum, forest fires and volatile substances in plants.

5.2 Human carcinogenicity data

Xylene was mentioned as an exposure in four studies. Two were community-based case–control studies, one of which involved brain cancer and one involved several types of cancer. The two industry-based studies were configured as nested case–control studies, one of central nervous system tumours and one of several sites. In none of these studies was xylene the sole or predominant exposure. Cancers at most sites were not significantly associated with xylene exposure in any study. Incidence of colorectal cancer was significantly elevated in the Canadian case–control study, but no other study reported colorectal cancer results. Hodgkin's disease was elevated in one study; non-Hodgkin lymphoma was elevated in one study, but not in another. Most results were based on small numbers. In

[1] Summary (but not the evaluation) prepared by the Secretariat after the meeting.

Table 1. Genetic and related effects of xylenes

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
***meta*-Xylene**				
SA0, *Salmonella typhimurium* TA100, reverse mutation (spot test)	–	–	160	Florin *et al*. (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	250	Bos *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	16	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Connor *et al*. (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation (spot test)	–	–	160	Florin *et al*. (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	250	Bos *et al*. (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	16	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation (spot test)	–	–	160	Florin *et al*. (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	250	Bos *et al*. (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	16	Haworth *et al*. (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	250	Bos *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation (spot test)	–	–	160	Florin *et al*. (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250	Bos *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	16	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Connor *et al*. (1985)
SAS, *Salmonella typhimurium* UTH 8414 and UTH 8413, reverse mutation	–	–	500	Connor *et al*. (1985)
MVM, Micronucleus test, NMRI mice *in vivo*	–		650 ip × 2	Mohtashamipur *et al*. (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
***ortho*-Xylene**				
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	250	Bos *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	50	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Connor *et al*. (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	250	Bos *et al*. (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	250	Bos *et al*. (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	50	Haworth *et al*. (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	250	Bos *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250	Bos *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	50	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Connor *et al*. (1985)
SAS, *Salmonella typhimurium* UTH 8414 and UTH 8413, reverse mutation	–	–	500	Connor *et al*. (1985)
MVM, Micronucleus test, NMRI mice *in vivo*	–		435 ip × 2	Mohtashamipur *et al*. (1985)
SPR, Sperm morphology, Sprague-Dawley rats *in vivo*	(+)		435 ip × 2	Washington *et al*. (19
***para*-Xylene**				
SA0, *Salmonella typhimurium* TA100, reverse mutation (spot test)	–	–	160	Florin *et al*. (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	250	Bos *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	50	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Connor *et al*. (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	50	Shimizu *et al*. (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
***para*-Xylene (contd)**				
SA5, *Salmonella typhimurium* TA1535, reverse mutation (spot test)	–	–	160	Florin *et al*. (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	250	Bos *et al*. (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50	Haworth *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50	Shimizu *et al*. (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation (spot test)	–	–	160	Florin *et al*. (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	250	Bos *et al*. (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	50	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	50	Shimizu *et al*. (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	250	Bos *et al*. (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	50	Shimizu *et al*. (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation (spot test)	–	–	160	Florin *et al*. (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250	Bos *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	50	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Connor *et al*. (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	50	Shimizu *et al*. (1985)
SAS, *Salmonella typhimurium* UTH 8414 and UTH 8413, reverse mutation	–	–	500	Connor *et al*. (1985)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	–	50	Shimizu *et al*. (1985)
MVM, Micronucleus test, NMRI mice *in vivo*	–		650 ip × 2	Mohtashamipur *et al*. (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Mixtures of xylenes				
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links	–	–	36	Nakamura *et al*. (1987)
ECL, *Escherichia coli pol* A/W3110-P3478, differential toxicity (liquid suspension)	–	–	10000	McCarroll *et al*. (1981a)
ERD, *Escherichia coli rec* strains, differential toxicity	–	–	10000	McCarroll *et al*. (1981a)
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	–	100000	McCarroll *et al*. (1981b)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	250	Bos *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	16	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	100	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	166	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Connor *et al*. (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	50	Shimizu *et al*. (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	100	Zeiger *et al*. (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	250	Bos *et al*. (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	16	Haworth *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	100	Haworth *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	166	Haworth *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50	Shimizu *et al*. (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	100	Zeiger *et al*. (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	250	Bos *et al*. (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	16	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	100	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	166	Haworth *et al*. (1983)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Mixtures of xylenes (contd)				
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	50	Shimizu *et al*. (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	250	Bos *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250	Bos *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	16	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	100	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	166	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Connor *et al*. (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	50	Shimizu *et al*. (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	100	Zeiger *et al*. (1987)
SAS, *Salmonella typhimurium* 4HT 8414 and 4HT 8413, reverse mutation	–	–	500	Connor *et al*. (1985)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	100	Zeiger *et al*. (1987)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	–	50	Shimizu *et al*. (1985)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	50	Anderson *et al.* (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	100.5	Anderson *et al.* (1990)
T7S, Cell transformation, SA7/Syrian hamster embryo cells *in vitro*	–	NT	1000	Casto (1981)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	1500	Gerner-Smidt & Friedrich (1978)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	212	Richer *et al*. (1993)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	1500	Gerner-Smidt & Friedrich (1978)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Mixtures of xylenes (contd)				
MVM, Micronucleus test, NMRI mice *in vivo*	–		435 ip × 2	Mohtashamipur *et al*. (1985)
MVM, Micronucleus test, NMRI mice *in vivo*	–		650 ip × 2	Mohtashamipur *et al*. (1985)
SPR, Sperm morphology, Sprague-Dawley rats *in vivo*	(+)		435 ip × 2	Washington *et al*. (1983)
Mixtures of *para*-xylene, benzene, chloroprene and epichlorohydrin (2/2/2/1)				
SA0, *Salmonella typhimurium* TA100 (urine from treated mice), reverse mutation	–	–	9:10:11:5 ppm inh 6 wk	Au *et al*. (1988)
SA9, *Salmonella typhimurium* TA98 (urine from treated mice), reverse mutation	–	–	9:10:11:5 ppm inh 6 wk	Au *et al*. (1988)
MVM, Micronucleus test, CD-1 Swiss mouse bone marrow *in vivo*	–		9:10:11:5 ppm inh 6 wk	Au *et al*. (1988)
CBA, Chromosomal aberrations, CD-1 Swiss mouse bone marrow *in vivo*	–		9:10:11:5 ppm inh 6 w	Au *et al*. (1988)
CLA, Chromosomal aberrations, CD-1 Swiss mouse spleen lymphocytes *in vivo*	+		0.09:0.08:0.02:0.04 ppm inh 3 wk	Au *et al*. (1988)

[a] +, positive; (+), weak positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; ip, intraperitoneal; inh, inhalation

view of the multiple exposure circumstances in most studies, the multiple inference context of these studies, and the weak consistency of the findings, these results are not strong enough to establish whether there is an association with xylene exposure.

5.3 Animal carcinogenicity data

Xylene (technical grade or mixed xylenes) was tested for carcinogenicity in one strain of mice and in two strains of rats by gavage. 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 indidivual isomers.

5.4 Other relevant data

Xylenes are absorbed after inhalation and dermal exposure. Elimination after human exposure is rapid and mostly as urinary metabolites after oxidation to the methylbenzyl alcohols, methylbenzoic acids and their glycine and glucuronic acid conjugates. In mice inhaling *para*-xylene, methylhippurate accumulated in the nasal mucosa and olfactory bulb.

Renal and hepatic toxicity has been described following human accidental poisonings and experimental exposure of rats and mice. In rats, hepatic cytochrome P450 content, particularly of CYP2B1, and the activities of certain conjugation enzymes are increased upon inhalation exposure to *meta*-xylene. Although xylenes have been studied extensively, there is no confirmed evidence of genetic activity for any of the isomers.

5.5 Evaluation

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

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

Overall evaluation

Xylenes are *not classifiable as to their carcinogenicity to humans (Group 3)*.

6. References

Agency for Toxic Substances and Disease Registry (ATSDR) (1990) *Toxicological Profile for Total Xylenes*, Washington DC, US Public Health Service

American Conference of Governmental Industrial Hygienists (1992) *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 6th Ed., Vol. 3, Cincinnati, OH, pp. 1732–1740

American Conference of Governmental Industrial Hygienists (1997) *1997 TLVs® and BEIs®*, Cincinnati, OH, p. 40

Anderson, B.E., Zeiger, E., Shelby, M.D., Resnick, M.A., Gulati, D.K., Ivett, J.L. & Loveday, K.S. (1990) Chromosome aberration and sister chromatid exchange test results with 42 chemicals. *Environ. mol. Mutag.*, **16** (Suppl. 18), 55–137

Au, W.W., Ward, J.B., Jr, Ramanujam, V.M.S., Harper, B.L., Moslen, M.T. & Legator, M.S. (1988) Genetoxic effects of a sub-acute low-level inhalation exposure to a mixture of carcinogenic chemicals. *Mutat. Res.*, **203**, 103–115

Bos, R.P., Brouns, R.M.E., van Doorn, R., Theuws, J.L.G. & Henderson, P.T. (1981) Non-mutagenicity of toluene, *o*-, *m*- and *p*-xylene, *o*-methylbenzylalcohol and *o*-methylbenzylsulfate in the Ames assay. *Mutat. Res.*, **88**, 273–279

Brown-Woodman, P.D.C., Webster, W.S., Picker, K. & Ritchie, H.E. (1991) Embryotoxicity of xylene and toluene: an in vitro study. *Ind. Health*, **29**, 139–152

Budavari, S., ed. (1996) *The Merck Index*, 12th Ed., Whitehouse Station, NJ, Merck & Co., pp. 1722–1723

Carpenter, A.V., Flanders, W.D., Frome, E.L., Tankersley, W.G. & Frey, S.A. (1988) Chemical exposures and central nervous system cancers: a case–control study among workers at two nuclear facilities. *Am. J. ind. Med.*, **13**, 351–362

Casto, B.C. (1981) Detection of chemical carcinogens and mutagens in hamster cells by enhancement of adenovirus transformation. In: Mishra, N., Dunkel, V. & Mehlman, I., eds, *Advances in Modern Environmental Toxicology*, Vol. 1, Princeton, NJ, Senate Press, pp. 241–271

Condie, L.W., Hill, J.R. & Borzelleca, J.F. (1988) Oral toxicology studies with xylene isomers and mixed xylenes. *Drug chem. Toxicol.*, **11**, 329–354

Connor, T.C., Theiss, J.C., Hanna, H.A., Monteith, D.K. & Matney, T.S. (1985) Genotoxicity of organic chemicals frequently found in the air of mobile homes. *Toxicol. Lett.*, **25**, 33–40

Elovaara, E., Zitting, A., Nickels, J. & Aitio, A. (1987) *m*-Xylene inhalation destroys cytochrome P-450 in rat lung at low exposure levels both after single 1-day and intermittent 5-week treatments. *Arch. Toxicol.*, **61**, 21–26

Elovaara, E., Engström, K., Häyri, L., Hase, T. & Aitio, A. (1989) Metabolism of antipyrine and *m*-xylene in rats after prolonged pretreatment with xylene alone or xylene with ethanol, phenobarbital or 3-methylcholanthrene. *Xenobiotica*, **19**, 945–960

Florin, I., Rutberg, L., Curvall, M. & Enzell, C.R. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames' test. *Toxicology*, **18**, 219–232

Foy, J.W.-D., Silverman, D.M. & Schatz, R.A. (1996) Low-level *m*-xylene inhalation alters pulmonary and hepatic cytochrome P-450 activity in the rat. *J. Toxicol. environ. Health*, **47**, 135–144

Freundt, K.J., Römer, K.G. & Federsel, R.J. (1989) Decrease of inhaled toluene, ethyl benzene, *m*-xylene, or mesitylene in rat blood after combined exposure to ethyl acetate. *Bull. environ. Contam. Toxicol.*, **42**, 495–498

Gérin, M., Siemiatycki, J., Désy, M. & Drewski, D. (1998) Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene and styrene: results of a case–control study in Montreal. *Am. J. ind. Med.*, **34**, 144–156

Gerner-Smidt, P. & Friedrich, U. (1978) The mutagenic effect of benzene, toluene and xylene studied by the SCE technique. *Mutat. Res.*, **58**, 313–316

Ghantous, H., Dencker, L., Gabrielsson, J., Danielsson, B.R.G. & Bergman, K. (1990) Accumulation and turnover of metabolites of toluene and xylene in nasal mucosa and olfactory bulb in the mouse. *Pharmacol. Toxicol.*, **66**, 87–92

Gut, I., Terelius, Y., Frantík, E., Linhart, I., Soucek, P., Filipcová, B. & Klucková, H. (1993) Exposure to various benzene derivatives differently induces cytochromes P450 2B1 and P450 2E1 in rat liver. *Arch. Toxicol.*, **67**, 237–243

Haglund, U., Lundberg, I. & Zech, L. (1980) Chromosome aberrations and sister chromatid exchanges in Swedish paint industry workers. *Scand. J. Work Environ. Health*, **6**, 291–298

Hass, U. & Jakobsen, B.M. (1993) Prenatal toxicity of xylene inhalation in the rat: A teratogenicity and postnatal study. *Pharmacol. Toxicol.*, **73**, 20–23

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. & Zeiger, E. (1983) *Salmonella* mutagenicity test results for 250 chemicals. *Environ. Mutag.*, **Suppl. 1**, 3–142

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 332–334

IARC (1989) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 47, *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting*, Lyon, pp. 125–156

International Labour Office (1991) *Occupational Exposure Limits for Airborne Toxic Substances*, 3rd Ed. (Occupational Safety and Health Series No. 37), Geneva, pp. 420–421

Jonai, H. & Sato, M. (1988) Exposure indices for painters exposed to toluene and xylene at low concentrations. *Ind. Health*, **26**, 197–202

Kawai, T., Mizunuma, K. & Yasugi, T. (1991) Urinary methylhippuric acid isomer levels after occupational exposure to a xylene mixture. *Int. Arch. occup. environ. Health*, **63**, 69–75

Laine, A., Savolainen, K., Riihimäki, V., Matikainen, E., Salmi, T. & Juntunen, J. (1993) Acute effects of *m*-xylene inhalation on body sway, reaction times, and sleep in man. *Int. Arch. occup. environ. Health*, **65**, 179–188

Langman, J.M. (1994) Xylene: its toxicity, measurement of exposure levels, absorption, metabolism and clearance. *Pathology*, **26**, 301–309

Lewis, R.J., Jr (1993) *Hawley's Condensed Chemical Dictionary*, 12th Ed., New York, Van Nostrand Reinhold, p. 1235

Lindbohm, M.-L., Taskinen, H., Sallmén, M. & Hemminki, K. (1990) Spontaneous abortions among women exposed to organic solvents. *Am. J. ind. Med.*, **17**, 449–463

Low, L.K., Meeks, J.R. & Mackerer, C.R (1989) Health effects of the alkylbenzenes. II. Xylenes. *Toxicol. ind. Health*, **5**, 85–105

McCarroll, N.E., Piper, C.E. & Keech, B.H. (1981a) An *E. coli* microsuspension assay for the detection of DNA damage induced by direct-acting agents and promutagens. *Environ. Mutag.*, **3**, 429–444

McCarroll, N.E., Keech, B.H. & Piper, C.E. (1981b) A microsuspension adaptation of the *Bacillus subtilis* 'rec' assay. *Environ. Mutag.*, **3**, 607–616

Mohtashamipur, E., Norpoth, K., Woelke, U. & Huber, P. (1985) Effects of ethylbenzene, toluene, and xylene on the induction of micronuclei in bone marrow polychromatic erythrocytes of mice. *Arch. Toxicol*., **58**, 106–109

Nakamura, S., Oda, Y., Shimada, T., Oki, I. & Sugimoto, K. (1987) SOS-inducing activity of chemical carcinogens and mutagens in *Salmonella typhimurium* TA1535/pSk1002: examination with 151 chemicals. *Mutat. Res*., **192**, 239–246

NOES (1997) *National Occupational Exposure Survey 1981-83*, Unpublished data as of November 1997, Cincinnati, OH, United States Department of Health and Human Services, Public Health Service, National Institute for Occupational Safety and Health

Nylén, P., Ebendal, T., Eriksdotter-Nilsson, M., Hansson, T., Henschen, A., Johnson, A.-C., Kronevi, T., Kvist, U., Sjöstrand, N.O., Höglund, G. & Olson, L. (1989) Testicular atrophy and loss of nerve growth factor-immunoreactive germ cell line in rats exposed to *n*-hexane and a protective effect of simultaneous exposure to toluene or xylene. *Arch. Toxicol.*, **63**, 296–307

Olsson, H. & Brandt, L. (1980) Occupational exposure to organic solvents and Hodgkin's disease in men. A case–referent study. *Scand. J. Work Environ. Health*, **6**, 302–305

Pap, M. & Varga, C. (1987) Sister-chromatid exchanges in peripheral lymphocytes of workers occupationally exposed to xylenes. *Mutat. Res*., **187**, 223–225

Rana, S.V.S. & Kumar, S. (1993) Liver function in rats treated individually and with a combination of xylene, toluene and methanol. *Toxicol. ind. Health*, **9**, 479–484

Raunio, H., Liira, J., Elovaara, E., Riihimäki, V. & Pelkonen, O. (1990) Cytochrome P450 isozyme induction by methyl ethyl ketone and *m*-xylene in rat liver. *Toxicol. appl. Pharmacol.*, **103**, 175–179

Richer, C.-L., Chakrabarti, S., Senécal-Quevillion, M., Duhr, M.A., Zhang, X.X. & Tardif, R. (1993) Cytogenetic effects of low-level exposure to toluene, xylene, and their mixture on human blood lymphocytes. *Int. Arch. occup. environ. Health*, **64**, 581–585

Rydzinski, K., Korsak, Z., Jedlińska, U. & Sokal, J.A. (1992) The toxic effects of combined exposure to toluene and *m*-xylene in animals. IV. Liver ultrastructure after subchronic inhalatory exposure. *Pol. J. occup. Med. environ. Health*, **5**, 35–42

Savolainen, H., Vainio, H., Helojoki, M. & Elovaara, E. (1978) Biochemical and toxicological effects of short-term intermittent xylene inhalation exposure and combined ethanol intake. *Arch. Toxicol.*, **41**, 195–205

Selgrade, M.K., Daniels, M.J., Jaskot, R.H., Robinson, B.L. & Allis, J.W. (1993) Enhanced mortality and liver damage in virus-infected mice exposed to *p*-xylene. *J. Toxicol. environ. Health*, **40**, 129–144

Shimizu, H., Suzuki, Y., Takemura, N., Goto, S. & Matsuchima, H. (1985) The results of microbial mutation test for forty-three industrial chemicals. *Jpn. J. ind. Health*, **27**, 400–419

Simmons, J.E., Allis, J.W., Grose, E.C., Seely, J.C., Robinson, B.L. & Berman, E. (1991) Assessment of the hepatotoxicity of acute and short-term exposure to inhaled *p*-xylene in F-344 rats. *J. Toxicol. environ. Health*, **32**, 295–306

Tardif, R., Charest-Tardif, G., Brodeur, J. & Krishnan (1997) Physiologically based pharmacokinetic modelling of a ternary mixture of alkyl benzenes in rats and humans. *Toxicol. appl. Pharmacol*., **144**, 120–134

Taskinen, H., Anttila, A., Lindbohm, M.-L., Sallmén, M. & Hemminki, K. (1989) Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand. J. Work Environ. Health*, **15**, 345–352

Taskinen, H., Kyyrönen, P., Hemminki, K., Hoikkala, M., Lajunen, K. & Lindbohm, M.L. (1994) Laboratory work and pregnancy outcome. *J. occup. Med.*, **36**, 311–319

Toftgård, R., Halpert, J. & Gustafsson, J.-Å. (1983) Xylene induces a cytochrome P-450 isoenzyme in rat liver similar to the major isozyme induced by phenobarbital. *Mol. Pharmacol.*, **23**, 265–271

Uchida, Y., Nakatsuka, H., Ukai, H., Watanabe, T., Liu, Y.T., Huang, M.Y., Wang, Y.L., Zhu, F.Z., Yin, H. & Ikeda, M. (1993) Symptoms and signs in workers exposed predominantly to xylenes. *Int. Arch. occup. environ. Health*, **64**, 597–605

United States International Trade Commission (1994) *Synthetic Organic Chemicals: US Production and Sales, 1993* (USITC Publ. 2810), Washington DC, US Government Printing Office, p. 3–14

United States National Library of Medicine (1997*) Hazardous Substances Data Bank (HSDB)*, Bethesda, MD [Record No. 4500]

Washington, W.J., Murthy, R.C., Doye, A., Eugene, K., Brown, D. & Bradley, I. (1983) Induction of morphologically abnormal sperm in rats exposed to *o*-xylene. *Arch. Androl*., **11**, 233–237

WHO (1993) *Guidelines for Drinking-Water Quality,* 2nd Ed., Vol. 1, *Recommendations*, Geneva, p. 175

WHO (1997) *Xylenes* (Environmental Health Criteria No. 190), Geneva, International Programme on Chemical Safety

Wilcosky, T.C., Checkoway, H., Marshall, E.G. & Tyroler, H.A. (1984) Cancer mortality and solvent exposures in the rubber industry. *Am. ind. Hyg. Assoc. J*., **45**, 809–811

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K. & Speck, W. (1987) *Salmonella* mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ. Mutag*., **9** (Suppl. 9), 1–110