JACC Report

No 6

Xylenes

CAS: 95-47-9 (o)
108-38-3 (m)
106-42-3 (p)
1330-20-7 (mixture)

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Joint Assessment of Commodity Chemicals

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European Chemical Industry
Ecology & Toxicology Centre

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THE ECETOC SCHEME FOR THE "JOINT ASSESSMENT OF COMMODITY CHEMICALS" (JACC)

This report has been produced as part of a programme for making critical reviews of the toxicology, including ecotoxicology, of selected industrial chemicals.

A number of organisations, world-wide, have produced and are continuing to produce such reviews with the aim of ensuring that, based on an up-to-date knowledge of the toxicological and other relevant information regarding existing chemicals, they can continue to be produced and used safely. ECETOC is contributing to this activity with its JACC reviews.

In general, commodity chemicals, i.e. those produced in large tonnage by several companies and having widespread and multiple uses, are reviewed jointly by experts from a number of the companies concerned. Before it is decided to review a chemical, every effort is made to discover whether an adequate review exists already, in which case no work is necessary.

It should be noted that in a JACC review only the uses of the chemical as such are considered, i.e. its occurrence as an impurity in other products is not normally taken into account. It should also be emphasised that in a JACC review only that scientific information is considered which can be fully assessed.

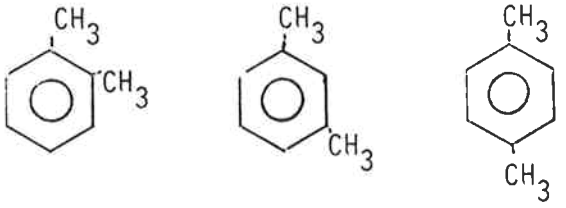
In this document a critical assessment of the toxicology and ecotoxicology of xylenes is presented. Whenever good scientific reviews on certain toxicological or ecotoxicological aspects exist, their conclusions are summarised and in these cases only the subsequent literature was assessed.

CONTENTS

A. CHEMICAL IDENTITY

Commercial xylenes consist of three main products : mixed or technical xylenes (ortho-, meta- and para-), ortho-xylene and para-xylene. Small quantities of meta-xylene are also sold. The Chem. Abstr. Service Reg. Nos. of these four materials are respectively 1330-20-7; 95-47-6; 106-42-3 and 108-38-3.

Formula : $C_6H_4(CH_3)_2$;



(o) (m) (p)

The following impurities occur in mixed xylenes :

ethylbenzene : up to 30% in "partially-depleted" mixed xylenes

other hydrocarbons : traces.

B. PRODUCTION, TRANSPORT, USES AND DISPOSAL

Most of the mixed xylenes currently used are produced by catalytic reforming of petroleum and as a by-product of olefin manufacture during the cracking of hydrocarbons. Small amounts are also obtained from coal-derived coke oven light oil and from the disproportionation of toluene (Ring, 1979).

The approximate world production of o-, p- and mixed xylenes in 1984 was 15,431,000 tonnes in 1984 (Dewitt, 1984).

Approximately 92% of the mixed xylenes produced are blended into gasoline. The remainder are used to produce the individual xylene isomers by extraction, and also in a variety of solvent applications (SAI, 1981). o-Xylene is used almost exclusively to produce phthalic anhydride for phthalate plasticizers. p-Xylene is used to produce terephthalic acid and dimethyl terephthalate, intermediates in the production of polyester fiber. m-Xylene is used for the production of isophthalic acid, an intermediate in the manufacture of polyester resins.

C. PHYSICO-CHEMICAL PROPERTIES*

	o-xylene	m-xylene	p-xylene
Physical form		colourless liquid	
Odour		typical aromatic	
Molecular weight	106.16	106.16	106.16
Boiling point, °C	144.4	139.1	138.3
Melting point, °C	-25.2	-47.9	13.3
Relative density 25°/4°	0.876	0.860	0.857
Refractive index (25°C)	1.503	1.494	1.493
Relative vapour density (air=1)	3.7	3.7	3.7
Vapour pressure, mbar(kPa) at 20°C	6.65 (0.66)	7.98 (0.79)	8.65 (0.86)
Solubility in water, mg/l	142	146	185
Solubility in organic solvents	soluble	soluble	soluble
Odour threshold, ppm	approx. 1	approx. 1	approx. 1
Flash point °C (closed cup)	30	25	25
Explosive limits, vol % in air	1.0-6	1.1-7	1.1-9
Autoignition temp. °C	465	525	525
Conversion factors (25°C, 1 atm) 1 ppm	4.35 mg/m³	4.35 mg/m³	4.35 mg/m³
1 mg/m³	0.23 ppm	0.23 ppm	0.23 ppm
CAS No.	95-47-6	108-38-3	106-42-3

* e.g. Gerarde, 1963; Verschueren, 1977.

D. ANALYTICAL METHODS

1. Environmental Media

1.1. In air

The presence of xylenes in air can be determined by gas chromatography (GC) in combination with flame ionisation or mass spectrometric (MS) detection (Grob and Grob, 1971). These authors sampled the air of Zürich with a portable captor filled with active carbon and reported hydrocarbon levels down to less than one ppb. Parsons and Mitzner (1975) found that the

detection limit could be reduced to 0.3 ppb by the use of a synthetic adsorber and a photo-ionisation detector. Detection tubes, such as Dräger-polytest with a detection limit at the ppm level, can also be used. Industrial-hygiene monitoring methods applicable to xylenes have been described by White et al.(1970), NIOSH (1977), and the UK Health and Safety Executive (HSE, 1984). The latter described a method for toluene which is also applicable to xylenes. These methods employ pumped sampling tubes, thermal or solvent desorption, and GC.

1.2. In water

Grob (1973) has reviewed and described the various analytical techniques. Drozd et al.(1978) determined xylenes in water using a head space technique coupled to HPLC, the detection limit being at the ppb level. These detection limits could be lowered if the xylenes were extracted from the water by an air stream and condensed in a refrigerated column, this enrichment permitting an increase of sensitivity to a fraction of ppb. A modified technique has been proposed by Grob and Zürcher (1976).

1.3. In various products

Crawford and Kretsch (1976) identified xylene in the vapours of roasted turkeys using a combination of GC and MS. Using the same technique Luskus et al.(1977) and Labows et al.(1979) detected xylene in human tissues and axillary volatiles.

2. Urine

Within the body xylene is metabolized principally to methylhippuric acids (Sedivec and Flek, 1976-a; Engström et al.,1984), which are not normally present in the urine of non-exposed subjects (Lauwerijs et al.,1978). Therefore the determination of these acids in the urine has been suggested as an appropriate method for routine monitoring of xylene exposure (Ogata et al.,1970; Sedivec and Flek, 1976-b; Senczuk and Orlowski, 1978). The excretion of methylhippuric acids in urine was found to be proportional to the product of the concentration of xylene in the air and duration of exposure. Because of the rapid excretion of methylhippuric acids it was necessary to use all-shift or 24-hour urine samples (Ogata et al.,1970; Sedivec and Flek, 1976-b).

Urinary methylhippuric acids have been measured by gas chromatography (Engström and Bjurström, 1978), colourimetry (Ogata and Hobara, 1979), HPLC (Ogata et al., 1977, 1980) or thin-layer chromatography (Bieniek and Wilczok, 1981). The correlation between xylene exposure and methylhippuric acids excretion was found to be best when the latter was expressed in mg/kgbw, mg/g creatinine or corrected for urine density (Ogata et al.,1970; Sedivec and Flek, 1976-b). Biological monitoring for xylene has also been suggested as a suitable procedure even when the subjects are exposed to a mixture of aromatic organic solvents (Ogata et al.,1977; Engström et al.,1984).

E. ENVIRONMENTAL DISTRIBUTION AND FATE

1. Environmental Distribution

SAI (1981) gives a comprehensive description of the emissions of xylene in the US from different sources. Total US emissions were estimated to be 480,000 tonnes in 1978. Approximately 92% of all mixed xylenes are incorporated into gasoline which may contain up to 15% of xylenes (DGMK, 1984), and gasoline is thus one of the largest sources of emission. The other major source is from its use as a solvent.

Daniels et al.(1982) calculated the partition coefficients and environmental equilibrium distribution from the vapour pressure and the estimated average water solubility. The calculated distribution percentages were : air: 99.1; water: 0.7; soil : 0.1; sediment : 0.1 and fish << 0.01. This theoretical distribution was confirmed by measurements taken following the Murban crude oil spill in the Gulf of Mexico (Cox et al.,1979). Between 5 and 35 min. after the spill, 88-94 percent of the maximum possible amount of xylene was in surface water. The concentrations of m- and p-xylene totaled 1,825 $\mu g.l^{-1}$ and that of o-xylene was 890 $\mu g.l^{-1}$. Two and a half hours after the spill there was a total of 12 $\mu g.l^{-1}$ xylene in the surface water, demonstrating its rapid disappearance from the water under natural conditions.

2. Persistence in the Environment

2.1. Breakdown in the atmosphere

The phototransformation of xylenes with OH radicals and ozone has been extensively studied (Atkinson et al.,1979; Cox et al.,1980; Mill et al.,1981). The reactivity constants, k_{OH}. and k_{O_3} and half lives, $t_{1/2}$ are summarised in Table 1.

TABLE 1
Phototransformation of Xylenes
with OH Radicals and O_3

	$10^{12}.k_{OH\cdot}$ ($cm^3.molec..s^{-1}$)	$t^{OH}_{1/2}$ (days)	$10^{25}.k_{O_3}$ ($cm^3.molec..s^{-1}$)	$10^{-3}.t^{O_3}_{1/2}$ (days)
o-xylene	13	0.6	1.6	5
m-xylene	20	0.4	1.3	6.2
p-xylene	10	0.8	1.6	5

From these results it can be concluded that xylenes are likely to disappear rapidly in the air by phototransformation with OH· but will react only slowly with ozone. The photoreaction products with OH· are formic and acetic acid (Kobayashi and Watanabe, 1980) which, after absorption in the hydrosphere, are further degraded to CO_2 and H_2O (Malaney and Gerhold, 1969; Guisti et al.,1974).

2.2. Breakdown in the hydrosphere

Bridié et al.(1979-b) using the standard dilution method with acclimatised sludge found BOD*(5) values of 52 and 57% of the ThOD* for o-, 80% for m-, and 44 and 74% for p-xylene.

The biodegradation of o-, m- and p-xylenes was also studied by Kappeler and Wührmann (1978). m- and p-Xylene were shown to be more rapidly degraded than was o-xylene, complete elimination being observed after respectively 7 and 11-12 days. In each case the corresponding methyl-benzylalcohol was detected as an intermediate. These results show that xylenes are readily biodegradable.

*BOD = Biological oxygen demand.
ThOD = Theoretical oxygen demand.

There was no effect on activated sludge at concentrations of up to 300 mg xylene/kg sludge/d (Gruenwald, 1979). However, a concentration of 500 $mg.l^{-1}$, o-, m- or p-xylene were toxic to unacclimatised activated sludge during the first 24h of aeration (Marion and Malaney, 1963).

Pseudomonas putida, Flavobacterium sp and Pseudomonas aeruginosa bacteria have been shown to be capable of utilizing xylene in the growth medium (Nozaka and Kusunose, 1968; Gibson et al.,1974; McKenna, 1976). Pseudomonas aeruginosa was able to use m- and p-xylene as the sole carbon source (Davey and Gibson, 1974). Other Pseudomonas sp., as well as Vibrio sp., Bacillus sp., and Arthrobacter sp., also utilised xylene as a carbon source (Bhosle and Mavinkurve, 1980-81). These investigations confirm that selected flora in aquatic systems are capable of degrading xylenes.

2.3. Breakdown in soil

No specific investigations on the breakdown of xylenes in soil are at present available. However, certain microorganisms known to be present in soil have been shown to be capable of oxidising xylenes. Norcadia salmonicolor, N. caralillina and N. minima have been shown to be capable of oxidising p-xylene (Gibson et al.,1974).

3. Bioaccumulation

The measured octanol/water partition coefficients (as log P_{OW}) are respectively 3.12, 3.20 and 3.15 for the o-, m- and p-isomers (Hansch and Leo, 1979; Yoshida et al.,1983). Chiou et al.(1982) found, for the same isomers, values of 2.77, 3.15 and 3.20 respectively. The theoretical bioconcentration factor calculated from these partition coefficients is about 80, which is rather low (Veith et al.,1979).

A 7 d exposure of shrimp (Pandalus platyceros) to the water-soluble fraction of Prudhoe Bay crude oil containing 37 ng/g of xylene in water resulted in tissue accumulation in the thorax (320 ng xylene/g tissue) and the abdomen (350 ng xylene/g tissue) (Sanborn and Malins, 1980). Funasoka et al.(1975) reported xylene levels in fish to be 0.02 mg/kgbw. As no depuration data were presented these studies are of limited value.

When manila clams (Tapes semidecussata) were exposed to o-, m-, and p-xylene for 8 d the tissue concentration of the compound approximated to the xylene

concentration in the water phase throughout the exposure (bioaccumulation factor: 6). There was a rapid elimination of the xylene in the first seven days following termination of the exposure and then a more gradual loss to below the detection limit in the next 7 days (Nunes and Benville, 1979).

When eels (Anguilla japonica) were exposed to 50 ppm of o,-, m- and p-xylene, tissue accumulation reached a steady state after 10 d (bioaccumulation factors 21.4, 23.6, 23.6 respectively). The tissue half-life of xylene in the eel was 2.6 d for m-xylene and 2 d for o- and p-xylene (Ogata and Miyake, 1978).

F. EXPOSURE LEVELS AND STANDARDS

1. Hygiene Standards - Occupational Exposure Levels

A Treshold Limit Value skin (8h time weighted average) of 100 ppm (435 mg/m^3) with a Short-term Exposure Limit of 150 ppm (655 mg/m^3) has been adopted by ACGIH (1985-86). The ACGIH concluded that irritant effects will be minimal and that no significant degree of narcosis or chronic injuries will result from continued occupational exposure at such levels. The German MAK value (DFG-1985) is also 100 ppm and many other countries have adopted this value.

The ACGIH (1985-86) has proposed two biological exposure indices for methylhippuric acids in urine: 1,500 mg/g creatinine (end of shift) and 2 mg/min (last 4 hours of shift).

2. Presence in Air

Levels in the air are variable, ranging from barely detectable in a measurement in Leningrad (Ioffe et al., 1978) to 266 ppb measured in Hamburg (Halket and Angerer, 1980). Concentrations in the air are considered to be primarily dependent on levels of urbanisation, since the largest source of xylene is auto emissions. A comparison between rural and urban locations in the UK showed a range from 16 ppb (rural) up to 49 ppb (motorway) (Thorburn and Colenutt, 1979). Louw and Richards (1977) reported o-xylene levels of 1.3 to 1.8 ppb in South African cities.

Using a passive sampler with a charcoal pad of known surface area (Bamberger et al., 1978) and gas chromatographic analysis, Seifert and Abraham (1982)

determined levels of m- and p-xylene ranging from 4.8-6.7 ppb indoors to 23 ppb outdoors.

3. Presence in Water

In petroleum refinery effluents, xylene levels varying from 6 µg/l (US) to 1 mg/l (Netherlands) have been found (CEC, 1976). More recent water monitoring data (Stuermer et al.,1982) indicated that surface waters contain very low levels (<25 ng/l(ppt)) of xylenes except in areas where there were fuel processing activities (e.g. up to 830 µg/l (ppb) in Hoe Creek, Wyoming, USA). Xylenes were detected in some rivers but the measurements could not be accurately quantified. Surface samples in the Gulf of Mexico contained levels of xylenes ranging from 0.3-24.4 ng/l(ppt) (Sauer et al.,1978). Kawamura and Kaplan (1983) found 2 and 9 ng/l of m- and p-xylene in the rainwater of Los Angeles.

4. Presence in Soil

Very little is known about the ability of soil particles to adsorb xylene (Gibson et al.,1970). However, in view of the rapid volatilisation of xylenes, their presence in the upper layer of soil is unlikely to be significant (Buikema and Hendricks, 1980).

G. TOXICOLOGICAL DATA

1. Acute

1.1. Human

The most frequent symptoms following exposure to high levels of xylenes have been reported to be headache, fatigue, lassitude, mental confusion, temporary exhilaration, narcosis, and gastro-intestinal disturbances such as nausea, anorexia and flatulence (Gerarde, 1960). More severe cases of acute poisoning have resulted in unconsciousness (ILO, 1982) and death. During the period 1961-1980, 38 cases of xylene intoxication were reported in the United Kingdom, the effects most frequently reported being narcosis, respiratory irritation and gastrointestinal disturbances (Bakinson and Jones, 1985).

Dreisbach (1980) has stated that xylene is "toxic" to man at a dose of 0.5-1.0 g/kgbw. No scientific justification for this statement is given. Gerarde (1960) concluded that xylene, like many hydrocarbons, may cause

pneumonitis following aspiration of the liquid, however, no human case reports are however available.

A 17 year-old worker overcome by xylene vapour remained unconscious for 3 hours and thereafter disturbances of heart function were reported (NIOSH, 1975). A Russian study, mentioned by NIOSH (1975), on four subjects with a low olfactory threshold to xylenes, showed a marked inhibition of the electrical activity of the cerebral cortex when they had been exposed to concentrations higher than 0.07 ppm. NIOSH (1975) reported that further investigations are necessary to validate these findings.

As a result of an exposure to xylenes, estimated to be at 10,000 ppm, three painters working in a confined space became unconscious and were discovered after 18.5 hours. One man died shortly after, and autopsy revealed severe lung congestion with focal intra-alveolar haemorrhage, and acute pulmonary oedema. The brain showed microscopical petechial haemorrhages and anoxic neuronal damage with swelling and loss of Nissl substance. The liver showed congestion with swelling and vacuolation of centrilobular cells. On recovering consciousness, the other two men remained confused for some time, suffered from amnesia, and showed evidence of liver damage. After two days they recovered. Severe impairment of the renal function was reported in one man, but was, however, reversible after two weeks (Morley et al.,1970).

Impairment of balance has been reported in volunteers exposed for a short-time (hours) to m-xylene at 100-400 ppm. The same concentrations also influenced reaction time and manual coordination. No dose-response relationship was found between blood xylene levels and these effects, (Savolainen and Linnavuo, 1979; Savolainen et al., 1979-a; Riihimäki and Savolainen, 1980; Savolainen and Riihimaki, 1981; Savolainen et al.,1984). Slight exercise seemed to antagonise the effects of m-xylene (Savolainen et al., 1980, 1984).

Browning (1965) reported two cases where xylenes induced convulsions in subjects suffering from latent epilepsy. Carpenter et al.(1975) investigated the sensory threshold in 7 volunteers exposed to mixed xylenes for 15 minutes a day. The exposure levels were 110, 230, 460 and 690 ppm on days 1, 2, 3 and 4 respectively. All exposures resulted in some degree of

irritation of the throat and/or eyes, the effects being minimal at 110 ppm. Dizziness was reported in one volunteer at 230 and 460 ppm, and in four at 690 ppm. No effects remained 1h after exposure.

The odour threshold for xylenes has been estimated to be 1 ppm (Carpenter et al.,1975).

In a recent case report, ingestion of food probably contaminated with technical xylene induced deep coma, acute pulmonary oedema, hepatic impairment, and haematemesis. o-, m-, and p-Xylenes and ethylbenzene were detected in the blood and in the exhaled vapours. Charcoal haemoperfusion treatment was started after 26 hours of coma, and within two hours the man recovered (Recchia et al.,1985).

Since, in practice, workers are usually exposed to more than one solvent, a number of studies have been performed to assess the effects of the combined exposure to xylene with other solvents. m-Xylene did not influence changes induced by 1,1,1-trichloroethane in body sway, reaction time and visual-evoked potentials of male volunteers exposed by inhalation (Savolainen et al., 1982). A mixture of 200 ppm of toluene and 100 ppm of p-xylene did not effect simple and choice reaction-times and short term memory in men exposed for four hours (Anshelm Olsen et al., 1985).

The possibility that alcohol intake could modify the biological effects of xylene has also been examined. It has been concluded from experimental studies in rats that alcohol can potentiate the biochemical and behavioural effects induced by technical xylene (Savolainen et al.,1978, 1979-b; Elovaara et al.,1980). It has also been found that alcohol may potentiate CNS effects induced by m-xylene in male volunteers (Savolainen, 1980). The ingestion of alcohol (0.8 g/kgbw) before or after the inhalation of 250-300 ppm of m-xylene for four hours has been reported to cause dizziness, nausea or red flush in susceptible individuals (Riihimäki et al.,1982).

Serum enzyme estimations in 102 car painters (Kurppa and Husman, 1982) and in patients with suspected organic solvent poisoning (Pedersen and Rasmussen, 1982), where exposures to a variety of solvents including xylene were identified or suspected, showed no clear or consistent differences from control values.

1.2. Experimental

In Table 2 are summarised the presently available LD_{50}-LC_{50} values.

TABLE 2

LD_{50}-LC_{50} Values for Xylenes

Route	Species	LD_{50}-LC_{50}	Reference
Oral (LD_{50})			
Isomer Mixture	rat (M)*	4300 mg/kgbw	Wolf et al. (1956)
Isomer Mixture	rat (F)*	(5950 mg/kgbw) (minimal lethal dose)	Muralidhara and Krishnakumari (1980)
o-Xylene	rat (**)	3600 mg/kgbw	Ungváry et al.(1979)
m-Xylene	rat (**)	5000 mg/kgbw	Ungváry et al.(1979)
p-Xylene	rat (**)	3900 mg/kgbw	Ungváry et al.(1979)
Isomer Mixture	rat (**)	5800 mg/kgbw	Ungváry et al.(1979)
Intraperitoneal (LD_{50})			
o-Xylene	mice (M)	1730 mg/kgbw	Mohtashamipur et al. (1985)
m-Xylene	mice (M)	1330 mg/kgbw	
p-Xylene	mice (M)	2110 mg/kgbw	Mohtashamipur et al. (1985)
Inhalation (LC_{50})			
Isomer Mixture	rats (M)	6700 ppm (4h)	Carpenter et al.(1975)
o-Xylene	mice (F)	4600 ppm (6h)	Bonnet et al.(1979)
m-Xylene	mice (F)	5300 ppm (6h)	Bonnet et al.(1979)
p-Xylene	mice (F)	3900 ppm (6h)	Bonnet et al.(1979)

* M : male
F : female

** sex not mentioned in English abstract.

i) Oral. Administration of a single oral dose of 3,500-10,000 mg of "commercial xylene"/kgbw to female rats resulted in mild congestion of the cells of the liver, the kidneys and the spleen (Muralidhara and Krishnakumari, 1980). Female rats treated with a mixture of xylene

isomers by gavage, at fatal doses (5950 mg/kgbw or higher), showed immediate sluggishness followed by "dullness", anaesthesia, narcosis, coma and death (Muralidhara and Krishnakumari, 1980).

ii) Intraperitoneal. A moderate lipid accumulation in the liver and an increase in serum ornithine carbamyl transferase activity was observed in guinea pigs treated with 1000 mg "xylene"/kgbw (DiVincenzo and Krasavage, 1974).

iii) Percutaneous. A 4h occluded, percutaneous administration of 4400 mg/kgbw of mixed xylenes to M rabbits resulted in the death of one rabbit out of three on the fifth day after exposure. No deaths were observed at a dose level of 1754 mg/kgbw (Hine and Zuidema, 1970).

iv) Inhalation. Exposure of M rats to 20,000 ppm of p-xylene resulted in dyspnoea, ataxia, hyper-reactivity to auditory stimuli, violent twitching, rigid tail, carpopedal spasm, profuse salivation and death in two hours (Furnas and Hine, 1958).

When rats were exposed to p-xylene vapour at concentrations of 1000, 1500 or 2000 ppm for 4h their serum enzyme activities increased in a dose-dependent fashion indicating hepatocellular damage (Patel et al.,1979).

Groups of 10 young M rats were exposed for a 4 h period to 580, 1300, 2800, 6000 and 9900 ppm of mixed xylenes (Carpenter et al.,1975). No effects were observed at 580 ppm. At 1300 ppm, the impaired coordination noted after two hours disappeared following the cessation of exposure. At 2800 ppm all rats became prostrate in 3.5 h. They recovered within one hour, but the impairment of coordination lasted one day. At 6000 ppm rats were prostrate in 30 min. and four died within 3.5 h. All survivors recovered promptly. At the 9900 ppm level all animals died within 2.25 h and at necropsy atelectasis, haemorrhage and interlobular oedema of the lungs were observed in 2 out of 16 rats. Exposure of 4 M cats to 9500 ppm of mixed xylene vapour for 2 h, resulted in a time-related pattern of salivation, ataxia, tonic and clonic spasms, and anaesthesia followed by death (Carpenter et al.,1975).

2. Irritation and Sensitisation.

2.1. Human

2.1.1. Skin irritation. A study in which 13 human volunteers immersed both hands in m-xylene for 20 minutes resulted in a burning sensation of the exposed skin after 10 minutes, which subsided within 10 minutes after the end of exposure. The exposed skin became very erythematous, but returned to normal within a few hours (Lauwerijs et al., 1978). In common with other hydrocarbon solvents, repeated or prolonged contact with xylenes will result in defatting of the skin which may lead to dryness, cracking, blistering or dermatitis. Xylenes are also irritant to mucous membranes (Gerarde, 1960).

2.1.2. Eye irritation. Six furniture polishers exposed to xylene suffered eye irritation and photophobia, the symptoms disappearing after a few hours. Minute corneal vacuoles were found, which healed completely in a few days leaving no scars. When 6 humans were exposed to vapours of xylene, toluene, and methyl-, ethyl- or butyl-acetate (the atmospheric concentrations were not specified), xylene was reported to be the least irritating (Schmid, 1956). Conjunctivitis and corneal burns have been reported following direct eye contact with liquid xylene (Clayton and Clayton, 1981). Xylene vapour is irritating to the mucous membranes of the eye (ILO, 1982). Four out of 7 volunteers experienced either intermittent or continuous eye discomfort (mild irritation) while inhaling 460 ppm of mixed xylenes vapour (Carpenter et al., 1975).

2.1.3. Skin sensitisation. In the maximisation test for contact sensitisers xylene did not produce skin sensitisation in any of 24 volunteers (Kligman, 1966).

2.2. Experimental

2.2.1. Skin irritation. Wolf et al.(1956) made 10 to 20 applications of undiluted xylenes of purity 95% (19% o-, 52% m-, 24% p-), either to the ears or to the shaved abdomen (occluded) of rabbits, for two or four weeks. These treatments resulted in moderate to marked erythema, and oedema, with superficial necrosis at both sites.

2.2.2. Eye irritation. Wolf et al.(1956) found that introducing two drops of mixed xylenes into the rabbit eye induced slight conjunctival irritation and very slight and transient corneal injury. Instillation of mixed xylenes in the rabbit eye (once/d for 2 d and subsequently 3 times/d for 3 d) resulted in swelling of the eyelids but no corneal vacuolisation (Carpenter and Geary, 1974). Cats exposed to commercial xylene vapour (concentration and duration not specified) developed corneal vacuoles (Browning, 1965).

2.2.3. Irritation on inhalation. Muller and Greff (1984) reported that exposure to 1450 ppm (6300 mg/m^3) of o- and p-xylene halved the respiratory rate of mice in a manner characteristic of sensory irritants.

3. Subchronic

3.1. Human

Six men were exposed to 100 ppm of m-xylene with peak concentrations of 200-400 ppm, for 6 h/d for 5 days, with a further 3 days exposure following a two day interruption at the weekend. Disturbances in reaction times were reported but balance was apparently affected only at 400 ppm. Tolerance against these effects seemed to develop over 5 subsequent exposure days. The effects appeared to correlate with blood xylene levels (Savolainen et al.,1979-a). In two other studies, 8 men were exposed for five days to m-xylene and after the weekend the exposure was repeated for a further day. In the first study the concentration was 90 ppm with peaks of 200 ppm, and in the second study it was 64 ppm with peaks of 400 ppm. The volunteers exercised four times a day on a bicycle ergonometer. It was reported that at 90 ppm there were acute deleterious effects on reaction time and manual coordination, while impairment of balance was seen only on the first days of exposure and re-exposure, possibly due to the development of tolerance. In the second study, no impairment of balance was noted, otherwise the findings resembled those previously described. Electroencephalographic measurements in 4 subjects showed "an increased number of slow transients of the occipital region". The authors concluded that these changes indicated a slight lowering of the vigilance level. Slight physical exercise seemed to antagonise the effects of xylene. No dose-response relationship between blood m-xylene concentration and psychophysiological effects was found. It was concluded that this lack of a relationship was probably due to the development of tolerance (Savolainen et al.,1980).

Savolainen et al.(1985) studied the effects of m-xylene on balance in 9 volunteers exposed to fixed (200 ppm) or fluctuating (135-400 ppm) concentrations during rest or periods of light work. The linear regression of eyes-closed/eyes-open body sway against blood m-xylene concentrations was statistically significant in some of the experiments, particularly those where exercise was combined with fluctuating xylene concentrations.

3.2. Experimental

3.2.1. Inhalation. Nine rats were exposed to 690 ppm of xylenes (27% o-, 52% m-, 21% p-xylene) 8 h/d, 6 d/wk for 110-130 d, and six rabbits to 1200 ppm 8 h/d, 6 d/wk for 40-55 d. In some animals the exposure resulted in paralysis of the hind legs, weight loss, transient anaemia, increases in blood urea and albumin, and hyperplasia of the bone marrow. Slight congestion in the kidneys, the liver, the heart, the adrenals, the lungs and the spleen were observed. Cellular desquamation of glomeruli, as well as necrosis of the convoluted tubules were also reported (Fabre et al.,1960). Because of the lack of experimental detail it is not possible to assess the significance of these findings.

Jenkins et al.(1970) exposed rats, guinea pigs, monkeys and dogs to o-xylene. The exposure was either to 780 ppm 8 h/d, 5 d/wk for 30 exposures or to 78 ppm continuously for 90 days. There were no significant changes in body weight or haematology data (WBC count, haemoglobin concentration and haematocrit only) compared to the controls. The results of histopathological examination of the heart, lung, liver, spleen and kidney, and additionally (in monkeys and dogs) the brain and spinal cord, were reported as "essentially negative". Since in the same study no haematological effects were observed in the above species exposed to 266 ppm of benzene, 8 h/d, 5 d/wk for 30 exposures or to 17.6 ppm continuously, for 90 and 127 d respectively, the negative findings with xylene should be viewed with caution.

Groups of 4 M rats and 4 M dogs were exposed 6 h/d, 5 d/wk for 13 weeks to 180, 460 and 810 ppm of mixed xylenes. No significant effects were reported in body weight, haematology, blood chemistry, urinalysis, organ weights, or macroscopic and microscopic pathology of either species at any concentration tested (Carpenter et al.,1975).

Thirty M rats were exposed to 3500 ppm of o-xylene for 8 h/d for 6 weeks. Fifteen animals were sacrificed after one week. Despite increased food and water intake, a slight decrease in body weight gain was observed. Liver weight also increased but histology showed no evidence of liver pathology. Enzyme, histochemical and ultrastructural studies revealed slight hepato-cellular damage (Tatrai and Ungvary, 1980).

3.2.2. Parenteral. When rats were injected intraperitoneally with 430-860 mg mixed xylenes/kgbw twice a day for 3 months there were no changes in the electrocardiograms (Morvai et al.,1976).

4. Mutagenicity

4.1. In humans

There was no increase in the frequency of sister chromatid exchanges or chromosomal aberrations in the lymphocytes of humans treated with xylenes (Gerner-Smidt and Friedrich, 1978), or in the lymphocytes of paint workers exposed to a mixture of aromatic solvents of which xylene was a major component (Haglund et al.,1980).

4.2. Experimental

4.2.1. Gene mutation. Neither the individual xylene isomers, an isomer mixture nor technical xylene showed any mutagenic activity in Salmonella typhymurium strains with and without metabolic activation (API, 1978-a-b; Lebowitz et al.,1979; Florin et al., 1980; Bos et al.,1981; Haworth et al.,1983). Negative results were also obtained in Salmonella the "preincubation protocol" (EPA, 1982). No mutagenic activity was observed in the mouse lymphoma assay (L5178Y, TK +/-) with technical xylene (API, 1978-a; Lebowitz et al.,1979). When Drosophila melanogaster was treated with technical xylene containing 18% ethylbenzene, there was a significant increase of sex-linked recessive lethal mutations (Donner et al.,1980). However, the authors were unable to confirm these findings when the individual components of the mixture (m-, o-xylene and ethylbenzene) were tested. It was concluded that further studies were needed to explain this discrepancy. This study has only been reported as an abstract.

4.2.2. Chromosomal effects. No clastogenic activity was observed in the bone marrow cells of rats treated intraperitoneally once (sacrificed at 6, 24 and 48 h after the treatment) or once each day for 5 days (sacrificed at 6 h after the last treatment) with technical xylene (API, 1978-a; Lebowitz et al.,1979). Groups of 6 M mice were injected intraperitoneally with o-, m-, and p-xylenes at increasing dose levels, the maximum being 70% of the LD_{50}. The doses were administered in two injections, 24h apart, and the animals were sacrificed 6 h after the second treatment. No increase of micronuclei in the bone marrow polychromatic erythrocytes was found (Mohtashamipur et al.,1985). In a subchronic study, rats were exposed by inhalation to 300 ppm of "mixed isomers" of xylenes, 6 h/d, 5 d/wk for 9, 14 and 18 weeks. No evidence of chromosomal aberrations in the bone marrow was found (Donner et al., 1980). No evidence of mutagenicity was found in a dominant lethal test conducted in mice treated subcutaneously, and in rats treated intraperitoneally, with 860 mg/kgbw of mixed xylenes (API, 1973).

4.2.3. Various. o-Xylene was investigated in a sperm abnormality assay. Rats (number per group not reported) were injected intraperitoneally with 430 and 1290 mg/kgbw of o-xylene in corn oil over two days. After 5 weeks, animals housed at temperatures of 20-24°C showed no significant increase in abnormal sperm over the controls. Rats housed at temperatures between 24 and 30°C after i.p. injection with 430 mg/kgbw of o-xylene were reported to have a statistically significant increase in the number of abnormal sperm. Few data were presented in this report (Washington et al.,1983). In view of the well-known relationship between high temperatures and sperm abnormalities, the authors put forward the hypothesis that o-xylene has a synergistic effect at higher temperatures.

In a mutation assay with Photobacterium phosphoreum, a positive response was obtained with xylene (Wecher and Scher, 1982). This test system is still undergoing validation.

Technical xylene was inactive in the Escherichia coli and Bacillus subtilis DNA-repair microsuspension assay (McCarroll et al., 1981a-b)

5. Chronic Toxicity and Carcinogenicity

5.1. Human. Haematological disorders including macrocytic anaemia, leukopenia, granulocytopenia, pancytopenia and bone marrow aplasia have been attributed to chronic occupational exposure to xylene (Glibert, 1935; Lob, 1952; Giammarinaro, 1956; Appuhn and Goldeck, 1957; Lachnit and Reimer, 1959). In all cases, however, exposure was to solvent mixtures known or suspected to contain benzene.

Browning (1965) examined the blood of 44 workers exposed to xylene and 70 photogravure workers exposed to benzene. No details of duration or levels of exposure were given. Over 80 percent of the xylene workers had blood pictures considered to be within "normal limits" while in the benzene-exposed workers injury to the haemopoietic system was reported as "characteristic".

Forde (1973) described a case of aplastic anaemia in a 61-year-old man who had worked in a laboratory with xylene for 13.5 years. Subsequent investigation revealed that his previous employment had involved heavy exposure to benzene. Blood tests carried out on 27 members of staff working with xylene showed that 12 had decreased platelet counts. Blood films and counts were reported as normal. The use of xylene was discontinued and the platelet counts returned to normal (the xylene used in the laboratory contained up to 0.2% benzene).

Hipolito (1980) reported 5 cases of chronic xylene poisoning in women working in unventilated histology laboratories, the exposure period ranging from 1.5 to 18 years. Three subjects did not experience any symptoms "for years" while 2 became ill within a year of the initial exposure. The signs and symptoms included chronic headache, chest pain, ECG abnormalities, dyspnoea, cyanosis of the hands, fever, leukopenia, malaise, impaired lung function, decreased ability to work, complete disability and mental confusion. No information was given on workplace exposure levels to xylene or other solvents that would have been used in this type of laboratory.

Dolora et al.(1982) reported that 12 workers exposed to a mixture of solvents (including toluene and xylenes) while engaged in the production of printing inks, had elevated urinary glucaric acid and serum antipyrine half-life times when compared with a group of 14 controls selected from

office personnel. The duration of employment varied between 1 and 22 years and periodical checks of the air concentration of toluene gave values of 10-70 mg/m^3 which were said to be correlated to some degree with hippuric acid excretion. Although no measurements of atmospheric xylene were made, it was concluded by the authors that both toluene and xylene induced hepatic monooxygenase activity in these workers.

A case control study on 15 cases of lymphocytic leukaemia and 30 matched industry controls selected from a previous epidemiological study on rubber industry workers was reported by Arp et al.(1983). The subjects were active or retired workers between 40 and 84 years of age. A review of previous solvent use, solvent specifications and job descriptions were used to identify exposure to specific solvents. Six subjects having lymphocytic leukaemia were 5.5 times more likely than the controls to have been exposed to xylene ($p=0.02$). The authors, however, observed that the relative risk estimates derived from the study are likely to be unreliable because of the small sample size. For the latter reason, and also the likely exposure to other aromatic hydrocarbons, including benzene, the possibility of an association between xylene exposure and lymphocytic leukaemia remains open to question.

In a study involving 35 spray painters, employed for between 2 and 24 years at 6 workplaces in two plants, evidence of haematological effects was reported (Angerer and Wulf, 1985). Exposures to o-, m- and p-xylene were found to be 2.1, 7.9 and 2.8 ppm respectively. However, the painters at all 6 locations had been additionally exposed to 4 ppm of ethylbenzene, and at two workplaces to n-butanol, 1,1,1-trichloroethane and C_9 aromatic hydrocarbons.

5.2. Experimental

As part of a study of the effect of irritant materials on benzo(a)pyrene-induced tumour production, Berenblum (1941) applied mixed xylenes, and 0.05% benzo(a)pyrene or 1% benzo(a)pyrene in xylene to mouse skin weekly for up to 28 weeks. The xylenes did not influence the tumour yield either when applied together, or alternately, with benz(a)pyrene, and did not produce tumours when applied alone.

Pound and Withers (1963) described experiments in which groups of 20 mice were given single subcutaneous injections of 0.25 ml of xylene on the right side of the back, from 6 to one days before the subcutaneous injection of 25 mg urethane. Thereafter, croton oil was applied weekly to the entire back for 20 weeks. These animals subsequently had a statistically significantly higher incidence of tumours on the treated side of the back compared with the contra-lateral side. This augmentation of tumour production was ascribed solely to the inflammation and hyperplasia induced by xylene. Similar effects were also found in groups of mice pretreated with other irritant substances(Pound, 1968). Further studies were conducted in which short exposure to ultraviolet light followed by treatment with croton oil was used to induce skin tumours in mice. Pretreatment of these mice with xylene also increased tumour formation (Pound, 1970).

Kashin et al.(1968) exposed 9 chinchilla rabbits to 12 ppm of m-xylene for 4 h/d for 12 months. The authors reported increases in plasma proteins acetyl cholinesterase, excretion of 17-ketosteroids in the urine, weight-loss, and a decreased immunological response. Few experimental details and no data on controls were presented in this study.

In a series of studies reported by Maltoni et al.(1983), a mixture of o-, m- and p-xylenes was given by gavage to groups of 40 M and 40 F Sprague Dawley rats at a dose of 500 mg/kgbw in olive oil, 4-5 d/wk for 104 wks. The animals were then observed for their remaining lifespan. A group of 50 M and 50 F rats given only olive oil, by gavage, served as controls. After 134 weeks, when survival was 6/40 M and 4/40 F among xylene-treated animals and 2/50 M and 5/50 F in the controls, four carcinomas of the oral cavity were reported in the xylene-treated rats compared with zero in the controls. Historical control data showed no carcinomas of the oral cavity among a total of 3,326 animals subjected to various control treatments. A single carcinoma of the stomach and 4 ""acanthomas and dysplasias" were also reported in xylene-treated rats but there were none in the controls. There were small increases in the incidence of malignant mammary tumours (xylene group = 7, controls = 4) and in leukaemias (xylene group = 6, controls = 3). The total number of malignant tumours in the xylene-treated rats was reported as 27 compared with 16 in the controls, the majority of these, with the exception of the carcinomas of the mouth and stomach, being relatively common in untreated rats (Maltoni, 1983). At the end of the

study (141 wks) the total number of malignant tumours in the xylene-treated rats was 44 in 36 of the 78 animals alive at 33 wk when the first malignant tumour was observed. This should be compared with 23 tumours in 21 of the 94 controls alive at the same time point. The majority of these increases were observed in F animals. "Haemolymphoreticular tumours" were also reported, there being 8 in the xylene-treated animals and 4 in the controls (Maltoni et al.,1985).
No detailed survival data, non-tumour pathology, body weights, food and water consumptions or statistical evaluation were presented in either report.

In a recently audited NTP study (Hejtmancik et al.,1986) groups of 50 F344 rats of each sex were administered mixed xylenes (9.1% o-, 60.2% m-, 13.6% p-xylene and 17% ethylbenzene) in corn oil, by gavage, at dose levels of 0, 250 or 500 mg/kgbw/d, 5 d/wk for 103 wk. Groups of 50 B6C3F1 mice of each sex were administered 0, 500 or 1000 mg/kgbw/d of xylenes on the same schedule. In an abstract of the study it was reported that there was no evidence of systemic toxicity and at no site was the incidence of non-neoplastic or neoplastic effects in dosed rats and mice considered to be related to xylene treatment. The results of this study, which was conducted at the same (rats) and higher (mice) dose levels than was the Maltoni study, did not confirm the increased tumour incidence reported by Maltoni and support the view that xylenes do not possess carcinogenic potential in rats and mice.

6. Chronic Neurobehavioural Effects

Sukhanova et al.(1969) studied 45 workers employed for between 6 months and 5 years in the production of xylene from petroleum. Exposure to xylene was reported to have varied between 15 and 40 ppm, and exposure to other hydrocarbons also occurred. One third of workers complained of headaches, irritability, insomnia, dyspepsia and tachycardia. 20% suffered from a "neurasthenic- or asthesio-autonomic syndrome" and 15% from "autonomic vascular dysfunction". In addition, a decreased glycogen and peroxidase content of neutrophils was also reported.

In recent years a number of epidemiological studies carried out on painters and other groups exposed to a wide range of solvents, including xylenes, have led certain investigators to conclude that prolonged exposure to such

materials may cause permanent effects on the central nervous system. The signs and symptoms reported are rather vague and ill-defined e.g. headaches, memory loss, fatigue and alteration in emotional reactivity. The syndrome has been given a variety of names including Danish painters' syndrome, neurasthenic syndrome, psycho-organic syndrome and pre-senile dementia. The studies suffered from a number of deficiencies including: exposure to many different solvents and other chemicals, a lack of quantitative exposure data, numerous confounding factors (such as alcohol consumption and drug intake) and non-matching of controls for intelligence. A recent cross-sectional epidemiology study (Triebig, 1985) showed no evidence of adverse neurobehavioural effects in 105 house painters when compared with 53 bricklayers, plumbers and mechanics. Measurements indicated exposures to xylenes of up to 7 ppm (6-8 h averages).

Ørbaek et al.(1985) investigated the long-term effects of solvents in 50 workers from a paint factory where xylenes was one of the eight solvents most frequently used. The authors concluded that there was evidence of exposure-related "brain dysfunction and neurasthenic/emotional problems" based on a 4% decrease in cerebral blood flow, "increased power in delta and beta bands of EEG's", poor performance in neuropsychological tests (14% of exposed workers) and psychiatric interviews.

In an extensive literature review carried out on this subject Grasso et al.(1984) concluded that, with the exception of CS_2 there is insufficient evidence to establish a causal relationship between exposure to solvents and permanent effects on the central nervous system. However, the need to carry out further research was recognised. An international workshop (CIIT, 1985) on the neurobehavioural effects of solvents came to similar conclusions. The authors note that several studies of the problem are in hand, e.g. in the UK, Germany and Holland.

7. Reproductive Effects

7.1. Human. An increase in menstrual disorders in women exposed to organic solvents has been reported (Michon, 1965; Syrovadko et al.,1973). In both studies, exposure was to solvent mixtures containing benzene, toluene and xylenes.

A case control study of children with CNS defects, based on data from the Finnish Registry of Congenital Malformations, was reported by Holmberg (1979). Of the 14 cases described, the mother of one child with hydrocephaly had been exposed during pregnancy to xylenes and a number of other hydrocarbon solvents used in the manufacture of rubber products. The woman had a previous history of bearing malformed offspring and the author suggested that this predisposition and parental age were more likely to be related to this defect (hydrocephaly) than was exposure to solvents. Three other cases of CNS defects were reported in which exposure was to white spirit containing some xylenes.

A relationship between agenesis of the sacrum and exposure to fat solvents during pregnancy was suggested by Kucera (1968). This hypothesis was based on 5 of 9 cases of spinal malformations in Czechoslovakia between 1959 and 1966, where exposure to a number of organic solvents occurred during pregnancy (in only one case was xylene exposure specifically identified), and on subsequent experimental studies in which xylene was reported to induce malformations in chick embryos. Following a review of additional cases of spinal malformations, bringing the total number up to 155, Kucera found the proposed association "less strong" (personal communication from Kucera cited by Barlow and Sullivan, 1982).

Mirkova et al.(1983) have cited epidemiological evidence for "antenatal pathology" in the offspring of women workers in contact with xylene. No further details are given.

7.2. Experimental

Twenty-nine pregnant rats were exposed to atmospheres containing 115 ppm (500 mg/m^3) of p-xylene 24 h/d, from days 1-20 of gestation. The authors reported increases in pre-implantation losses (32 versus 11% in controls) and in post-implantation losses (39 versus 5% in controls) which were attributed to maternal toxicity. No teratogenic effects were observed (Krotov and Chebotar, 1972).

Teslina (1974) administered "xylene" to groups of 32 pregnant rats at doses of 0.15 (1/50 of the LD_{50}) or 0.4 g/kgbw (1/20 of the LD_{50}) by subcutaneous injection on days 1-10, or 1-18, of pregnancy. Five rats out of 20 given 0.4 g/kgbw/d on days 1 to 18 died. Reduced weight gain, and kidney and

haematological changes were seen in the dams of all treated groups. Following dosing on days 1-10 there were pre-implantation losses of 58 and 38% in the groups given 0.4 and 0.15 g/kgbw respectively. Pre- and post-implantation losses of 69% occurred following dosing on days 1-18 and in addition foetal body weight was reduced in survivors at both dose levels. The observed effects should be considered as unspecific foetotoxic effects.

Groups of 20-26 pregnant CD1 mice were given mixed isomers of xylene, containing 17% ethylbenzene, in cotton seed oil, by gavage, 3 times a day from days 6-15 of gestation, at total daily doses of 520, 1030, 2060, 2580, 3100 or 4136 mg/kgbw. A group of 62 pregnant mice given the vehicle alone served as controls (Marks et al., 1982). Maternal mortality occurred at doses of 4130 and 3100 mg/kgbw/d. Increased liver weight was found in dams given 2060 and 2580 mg/kgbw/d. Reduced foetal body weight occurred in the groups given 2060 mg/kgbw and above. There were statistically significant increases in the incidence of cleft palate only at maternally toxic doses. The number of stunted foetuses and implantations were unaffected by xylene treatment, although the percentage of resorptions was statistically significantly increased at 3100 mg/kgbw. The occurrence of effects at maternally-toxic doses does not indicate a specific embryo-lethal or teratogenic effect.

A group of 20 pregnant rats was continuously exposed to 230 ppm of xylene vapour (10% o-xylene, 50% m-xylene, 20% p-xylene, 20% ethylbenzene) from days 9 to 14 of gestation, a group of 26 animals exposed to air only serving as controls. (Hudak and Ungváry, 1978). There were no maternal deaths or effects on maternal weight gain. The number of implantations, live foetuses and resorptions per dam, foetal weights, and the incidence of malformations were similar to the control values. There were statistically significant increases in the incidence of fused sternebrae and extra ribs in the xylene-exposed foetuses. Two foetuses with agnathia were also observed. Although the latter was not statistically significant, this abnormality was not observed in any of the other groups in this study including the controls.

The results of exposing groups of 20-30 pregnant rats to the individual xylene isomers, o-, m- or p-xylene, by inhalation, at 35, 350 or 700 ppm,

24 h/d from days 7 to 14 of pregnancy were reported by Ungväry et al.(1980). A group of 60 pregnant rats exposed to air only served as controls. Reduced food consumption was observed at the two higher dose levels for o-xylene and at the highest dose level for m- and p-xylene. Maternal mortality occurred among the animals exposed to 700 ppm of m-xylene, and the weight gain of the surviving animals was statistically significantly lower than control values. Increases in liver/body weight ratios occurred after exposure to all xylene isomers, but were only statistically-significant for the o-isomer. There was a more pronounced increase in the rough endoplasmic reticulum of the liver tissue in the groups exposed to o-xylene. There was evidence of retarded foetal development at 350 and 700 ppm of o-xylene, and at 700 ppm of m- and p-xylene. This correlated well with the reduced maternal food intake. In addition, inhalation of the m- or p-isomers at the highest concentration produced an increase in the incidence of extra ribs. The passage of o-xylene across the placenta was also demonstrated. Exposure to 700 ppm of p-xylene also caused post-implantation losses. The agnathia found in the previous study (Hudak and Ungväry, 1978) on mixed xylenes was not seen.

The foetotoxicity of p-xylene in relation to maternal sex-steroid production was investigated by Ungväry et al.(1981). Groups of 20 pregnant rats were exposed 24 h/d on day 10, or on days 9 and 10, of gestation, to an atmosphere containing 700 ppm of p-xylene. Two hours after exposure, uterine and ovarian blood flow was measured, and blood samples taken from these vessels and the femoral vein were assayed for 17 β-oestradiol and progesterone. Uterine and ovarian blood flow and hormone secretion were unaffected by the exposure. Foetal weight and the hormone levels in peripheral blood were, however, reduced. It was postulated that p-xylene in the liver induced mixed-function oxidase which increased hormone metabolism, and that the resulting hormone imbalance was responsible for the foetotoxicity (Ungväry et al.,1980).

The foetotoxic and teratogenic effects of o-, m- and p-xylene in the mouse have been investigated by Nawrot and Staples (1980). Doses of 0.30, 0.75 and 1.00 ml/kgbw of each isomer were administered to CD1 mice by gavage from days 6-15 of gestation, and at a dose of 1.00 ml/kgbw from days 12-15. Following dosing on days 6-15, maternal toxicity (unspecified) and an increase in resorptions occurred only at the highest dose of m-xylene.

These effects, together with an increased incidence of cleft palate, were also found at the high and middle dose levels of the o- and p-isomers. Dosing on days 12-15 was reported significantly to increase maternal mortality for all isomers, and the incidence of cleft palate in the groups administered p-xylene. Further studies in which m-xylene was administered by gavage at doses of 0.75 or 1.00 ml/kgbw showed no maternal or foetal effects at the low dose when treatment was over days 12-15. Dosing on days 6-15 was reported to result in a small but statistically significant increase in cleft palates at the high dose in the absence of overt maternal toxicity. No data were reported in the abstract.

Shigeta et al.(1983) reported a dose-related increase in the incidence of extra ribs, and delayed ossification, in the offspring of mice exposed to 0, 500, 1000, 2000 or 4000 ppm of "xylene", 6 h/d from days 6-12 of gestation. The incidences of these findings in the various groups were not given. A reduction in foetal weight gain was also reported in the 2000 and 4000 ppm groups. There was no indication of whether maternal toxicity occurred at these exposure levels. These results suggest that there was possibly a retardation of growth in the foetuses, but provide no evidence of teratogenicity.

The teratogenic potential of a sample of xylene containing approximately 52, 11 and 0.31% of the m-, o- and p- isomers respectively, and 36% of ethylbenzene, was investigated in rats by inhalation exposure (API, 1978-c). Groups of 15 pregnant rats were exposed to 0, 100 or 400 ppm of xylene from day 6 to day 15 of gestation. There was no evidence of maternal toxicity or major foetal abnormalities in any of the treated groups. A statistically significantly greater number of foetuses with "unusual" retarded ossification was found, however, in the 400 ppm group. Since the majority of these foetuses (72%) came from only three litters, all members of which were small at delivery, it was considered uncertain whether they indicated foetotoxicity.

Mirkova et al.(1983) reported the results of a study in which pregnant Wistar rats (total, 160) were exposed 6 h/d, 5 d/wk to atmospheres containing approximately 10, 50 or 500 mg/m^3 (2.3, 11.5, 115 ppm) of technical xylenes from days 1-21 of pregnancy. No data on the dams were given in the study. At 50 and 500 mg/m^3 "statistically" significant