JACC Report

No 7

Ethylbenzene
CAS: 100-41-4

August 1986

ISSN-0773-6339-7

ECETOC

BRUSSELS, 1 AUGUST 1986

Joint Assessment of Commodity Chemicals

No. 7

ETHYLBENZENE

CAS: 100-41-4

European Chemical Industry
Ecology & Toxicology Centre

ISSN 0773 - 6339 - 7

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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 this task is not repeated.

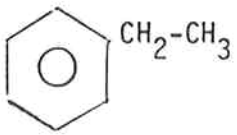
It should be noted that in a JACC review only the uses of the chemical as such are considered, i.e. its occurrence as an impurity in other products is not normally taken into account. It should also be emphasised that in a JACC review only that scientific information which can be fully assessed is considered.

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

CONTENTS

A. CHEMICAL IDENTITY

Chem. Abstr. Services Reg. No.: 100-41-4
RTECS No. : DA 07000000
EEC No. : 601-023-00-4
Synonyms : phenyl ethane, EB
Formula : C_8H_{10}, $C_6H_5(C_2H_5)$



B. PRODUCTION, TRANSPORT, USES AND DISPOSAL

About 90% of the ethylbenzene (EB) produced commercially is made by reaction of benzene and ethylene, and the remainder by fractionation of petroleum. As it is not economically justifiable to purify EB from the latter source it remains a component (up to 25%) of mixed xylenes (Landau et al.,1975; DGMK, 1984), which being mostly used in gasoline (the remainder is used as an industrial solvent) does not leave the refinery as a discreet product.

EB is used mainly in the manufacture of styrene. The total production of EB in 1983 was around 3 million tonnes in Western Europe and around 4 million tonnes in North America. Approximately 5 million tonnes of EB per year occur in catalytic reformate which is blended into gasoline (Santodonato et al.,1980).

EB is stored and/or transported in drums, bulk-carriers and tankers although it is mostly produced and used on the same site. As almost all EB is directly converted into styrene, disposal is not normally necessary, but can be achieved by burning.

C. PHYSICAL AND CHEMICAL PROPERTIES*

Physical form (0°C, 760 mm Hg)	: liquid
Molecular weight	: 106.16
Boiling point, °C	: 136.2
Melting point, °C	: -94.95
Density (25°/4°C)	: 0.86258
Vapour density (air=1)	: 3.7
Vapour pressure, mm Hg (kPa) at 20°C	: 9.31 (1.24)
Refractive index, $n^{25°}$	: 1.49319
Solubility in water, mg/litre (20°C)	: 152
Soluble in	: ethyl alcohol, ethyl ether and most other organic solvents
Flammability limits (% vol in air)	: 0.99-6.70
Flash point (closed cup) °C	: 15
Saturation % in air (760 mm Hg - 26°C)	: 1.03
Conversion factors	
(25°C, 760 mm Hg) 1 ppm (v/v)	: 4.35 mg/m³
1 mg/m³	: 0.233 ppm (v/v)

*Gerarde, 1963; Verschueren, 1977; Sax, 1979.

The odour threshold concentration in river water is 0.14 mg/l (Rosen et al.,1963).

D. ANALYTICAL TECHNIQUES

1. Physico-chemical Methods

1.1. In air

Gas chromatography is the preferred method of analysis (NIOSH, 1977). Bardodej and Bardodejova (1966) and Yamamoto and Cook (1968) have used UV-spectrometry. For air sampling, EB can be concentrated in detection tubes or other diffusion samplers with an adsorbent. In this approach a detection range of 40-1300 mg/m³ (9 - 300 ppm) is expected although it may be lower if the desorption efficiency is adequate (NIOSH, 1977). An automated gas chromatographic technique described by Hester and Meyer (1979) has, potentially, a much higher sensitivity in the low ppb range, although the actual limit of detection of EB was not determined.

1.2. In water

Different authors have determined EB in water using the "head space" technique coupled to GLC (Grob, 1973), in combination with mass spectrometry (Kleopfer and Fairlen, 1972; Burnham et al., 1972) or an IR detector (Rosen et al., 1963). A "purge and trap" technique for the GC determination of EB in water, with an 81% recovery and good precision down to 20 ppb, was recently described by Warner and Beasley (1984).

1.3. In polystyrene and food

The British Standards Institute has described the measurement of styrene and other volatile hydrocarbons, including EB, in polystyrene by a gas chromatographic technique of sensitivity claimed to be 10 ppm (BSI, 1978). The usual method for determining EB in food (also based on a method for styrene) is by extraction with methyl alcohol and water, distillation of the monomer and methyl alcohol, and re-extraction into n-hexane followed by gas chromatography. The extraction is based on a method published by Petrova et al.(1970) whose actual method of measurement was by UV absorbance.

2. Measurement of Urinary Metabolites

One of the best indices of human exposure to EB is the concentration of mandelic acid excreted in urine. Bardodej and Bardodejova (1970) used a paper chromatographic procedure to detect the urinary metabolites. Mandelic acid was determined by spectrometry after reaction with ferric chloride, and by polarography or UV spectrometry after oxidation to benzaldehyde and acetophenone, respectively, which were isolated by steam distillation. Gromiec and Piotrowski (1984) used gas chromatography to determine mandelic acid after extraction from urine by diethyl ether. Gas chromatographic urinalysis for minor metabolites of EB has been proposed by Engström (1984). The method enables the simultaneous determination of several metabolites. Because mandelic acid is also a metabolite of styrene, this method cannot be used for mixed exposures.

E. ENVIRONMENTAL DISTRIBUTION AND FATE

1. Environmental Distribution

Because of its significant vapour pressure (9.3 mm Hg) and low water solubility (152 ppm), EB will disperse in the atmosphere if released. Daniels

et al.(1982) calculated the percentage distribution of xylenes, which have similar vapour pressures and water solubilities, as follows : air, 99.1%; water, 0.7%; soil, 0.1%; sediment, 0.1%. A solubility of 186 $mg.l^{-1}$ in sea water has been quoted (Heitmüller et al.,1981). Four-hour aeration of an aqueous solution containing 100 ppm of EB resulted in its complete removal (McKinney et al., 1956). Ninety-nine % of the EB was lost in 48 h from sea water initially containing between 1 and 5 ppm (Benville and Korn, 1977). Because of its low specific gravity EB floats on water.

2. Degradation

2.1. Breakdown in the atmosphere

Different authors (ECETOC, 1983) have shown that EB is phototransformed by reaction with OH radicals, the half-life being about 1 day (Pitts et al.,1977; Mill et al., 1981). The phototransformation with ozone is very slow, having a half-life of 1.4×10^4 days (Mill et al.,1981).

2.2. Breakdown in the hydrosphere

The BOD* of EB was determined after 6, 9 and 20d and biodegradation corresponding to, respectively, 32, 36 and 45% of the ThOD* were found (EPA, 1979). Biodegradation of EB by phenol-acclimatised microorganisms in activated sludge resulted in the removal of 27% of the 500 mg/l originally present after 12 hours (McKinney et al.,1956).

Marion and Malaney (1963) found that activated and aerated sludge from 3 municipal waste-treatment plants oxidised EB, the oxidation being essentially complete after 168 hours at 20°C.

Kappeler and Wuhrman (1978) isolated 4 different cultures of Pseudonomas active in degrading EB, 3 giving rise to 1-phenylethanol as an intermediate breakdown product. Bestetti and Galli (1984) isolated a strain of Pseudomonas fluorescens with the ability to degrade EB and 1-phenylethanol. They showed that the degradation proceeded through acetophenone and catechol, followed by degradation by catechol-2,3 dioxygenase resulting in ring cleavage.

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

2.3. Breakdown in soil

It has been shown that several species of soil organisms (including Pseudomonas and Achromobacter) are capable of utilizing EB as a sole carbon source (Claus and Walker, 1964; Gibson et al., 1968, 1973) and that the fungus Nocardia tartaricans ATCC 31190 can convert EB into 1-phenylethanol and acetophenone under certain conditions (Cox and Goldsmith, 1979).

3. Bioaccumulation

Yoshida et al.(1983) and Mackay et al.(1980) measured the octanol/water partition coefficients and found log P_{ow}'s of 3.15 and 3.11 respectively, which suggests that EB has a moderate potential to bioaccumulate, corresponding to a bioconcentration factor of about 100 (Veith et al.,1979). However, in the tests so far performed on living organisms such a degree of bioconcentration did not occur. When Manila clams (Tapes semidecussata) were exposed, for eight days, to an aqueous solution containing 0.08 ppm of EB, the maximum tissue levels reached were 0.50 ppm after 9 days. After removal from the contaminated water, rapid depuration from the clam tissue occurred, with a reduction of the EB concentration to below the detection limit (0.13 ppm) in seven days (Nunes and Benville, 1979). A similar finding was reported for Coho salmon (Oncorhynchus kisutch) and starry flounder (Platichthys stellatus) where EB in the water-soluble fraction of Prudhoe Bay crude oil (0.9 ppm) showed only slight bioaccumulation (biocencentration factor less than 20 in muscle tissue, liver and gills after a maximum of 6 weeks exposure) and rapid depuration (Roubal et al.,1978).

F. EXPOSURE LEVELS AND STANDARDS

1. Hygiene Standard - Air

A Threshold Limit Value (TLV)(8 h time weighted average) of 100 ppm (435 mg/m³) with a Short-Term Exposure Limit of 125 ppm (545 mg/m³) has been adopted by the ACGIH (1985-86). These values are based on the irritant properties of the vapour. The German MAK value (DFG,1985) is also 100 ppm. These values are typical for many other countries where exposure levels are recommended.

ACGIH (1985-86) has proposed two Biological Exposure Indices for mandelic acid in urine: 2,000 mg/l of urine or 1,500 mg/g creatinine, as a mean value

for a group of workers at the end of the shift or at the end of the working week.

2. Levels in Air

Since gasoline may contain between 1 and 6% of EB (DGMK, 1984), it is one of the largest sources of EB emissions. A study, by the West German Bundesgesundheitsamt, of aromatic hydrocarbons inside and immediately outside buildings showed that the average concentration of EB was about 13 µg/m³ (3 ppb), with little difference between interior and exterior measurements (Seifert and Abraham, 1982). A comparison between rural and urban locations in the UK showed that there was a range of concentrations from 11.3 (rural) to 33.9 ppb (motorway) (Thorburn and Colenutt, 1979). In South African cities, levels of 1.5-3.2 ppb have been reported (Louw and Richards, 1977). These authors tabulated values for other European and American cities which are compatible with their own and the German study, and thus the higher UK values are somewhat anomalous.

3. Presence in Water

Kawamura and Kaplan (1983) found 9 ng/l (ppt) of EB in the rainwater of Los Angeles. The Commission of the European Communities (CEC-1976) reported EB levels which in most cases were less than 1 µg/l (ppb). This was also true in a more recent study of 30 Canadian water-treatment facilities where the average level of EB was less than 1 µg/l, with a maximum in treated, potable water of 7 µg/l (Otson et al., 1982). Analysis of surface sea-water in the Gulf of Mexico showed levels of EB from 0.6 to 4.4 ng/l (Sauer et al., 1978).

4. Presence in Food

Very little data are available on naturally-occurring levels of EB in non-packaged food although it has been identified in the volatiles of roasted filberts (Kinlin et al.,1972). An important use of polystyrene is in the manufacture of food packaging products and thus EB may migrate from these materials into the food (Heydanek et al., 1979). Crompton and Myers (1968) reported a residual EB level of 0.06% by weight in finished polystyrene products. These residual amounts vary, according to the grade of polystyrene, from 0.02 to 0.1% (Kirk Othmer, 1983).

Tan and Okada (1978) published data on the migration of EB from polystyrene cups into various foods. The EB content of the cups ranged from 108 to 424

ppm. The following EB levels were found : in sour milk beverage, <0.0025 - 0.006 ppm; in noodle soup, 0.015 - 0.021 ppm; in noodle curry, 0.089 - 0.153 ppm; and in wantan, 0.009 - 0.028 ppm. Similar values for the EB content of food packaging materials were recently obtained by CIVO (1985).

G. TOXICOLOGICAL DATA

1. Acute Toxicity

1.1. Human

No adverse health effects were observed in human volunteers exposed to EB in air at levels of up to 85 ppm for 8 h. At exposure levels of greater than 100 ppm mild subjective complaints, including vertigo, sleepiness and headache, were reported (Bardodej and Bardodejova, 1970).

From the results of animal studies, Gerarde (1960) concluded that EB, like many hydrocarbons, may cause severe chemical pneumonitis following aspiration of the liquid, but there are apparently no case reports of aspiration pneumonitis in humans. Most of the other effects of acute exposure to EB relate to the irritant effects of its vapour (cf. 2.1.2).

1.2. Experimental

The acute oral toxicity of EB is low. Wolf et al.(1956) reported an LD_{50} of 3.5 g/kgbw for rats (sex not specified), there being some slight, unspecified liver and kidney changes evident at autopsy. In another study, the acute oral LD_{50} in male rats was reported to be approximately 5.5 ml/kgbw (4.7 g/kgbw) (Smyth et al.,1962).

The acute dermal toxicity of EB is also low. The dermal LD_{50} for rabbits was reported to be greater than 5 g/kgbw (Smyth et al.,1962; Moreno, 1974).

The acute inhalation 4h LC_{50} in female rats was 4,000 ppm (Smyth et al.,1962).

In Table 1 are summarised the effects observed in acute inhalation experiments carried out with guinea pigs.

Table 1

Acute Toxicity of EB Vapours to Guinea Pigs (Yant et al.,1930)

Concentration (ppm)	Response
1,000	No severe disturbance after exposure for several hours.
3,000	No serious symptoms after 1 hour exposure.
5,000	Fatal in 30 to 60 minutes.
10,000	Fatal in a few minutes.

The symptoms observed were unsteadiness, ataxia and narcosis. Similar findings have been reported in the mouse (Gerarde, 1960), concentrations of 3,500 ppm of EB vapour causing prostration, and of 10,000 ppm causing death.

2. Irritation and Sensitisation

2.1. Human

Skin irritation. No specific skin irritation study on humans has been carried out on EB. Experience with hydrocarbons in general has shown that repeated and/or prolonged skin contact with hydrocarbons will result in dermatitis, probably caused primarily by the solvent action on the lipid components of the skin (the so-called defatting dermatitis).

Eye and respiratory irritation. Yant et al.(1930) reported the following findings in men exposed to EB vapour. Exposure to 5,000 ppm caused an intolerable irritation of the eyes and mucous membranes of the nose, and at 2,000 ppm EB was immediately irritant to the eye and the nose. Exposure for 6 minutes to 2000 ppm resulted in dizziness, although the nasal irritation was less noticeable. At a concentration of 1,000 ppm, EB irritated the eyes at the moment of exposure, but tolerance developed on continued exposure. At 200 ppm, the irritant effect of EB vapour on the eye has been reported to be transient (Gerarde, 1963).

No information was found on the effects of liquid EB on the eye.

Skin sensitisation. EB does not appear to be a skin sensitising agent. A maximisation test (Kligman, 1974) conducted on 25 volunteers at a concentration of 10% in petrolatum produced no sensitisation reaction.

2.2. Experimental

Skin irritation. Undiluted EB has been shown to produce moderate irritation when applied to the unoccluded skin of rabbits (Smyth et al.,1962) and to intact and abraded rabbit skin under 24h occlusion (Opdyke, 1975).

The application of undiluted EB to the ear and to the shaved abdomen of rabbits, 10 to 20 times over 2 to 4 weeks, resulted in moderate irritation (Wolf et al.,1956). There was erythema and oedema with superficial necrosis, resulting in an inflamed appearance with exfoliation of large patches of skin. The results of this study are in agreement with the reported human experience of dermatitis following repeated, prolonged contact of the skin with hydrocarbons.

Eye irritation. The placing of two drops of undiluted EB directly into the eyes of rabbits resulted in slight conjunctival irritation but no effects on the cornea (observations were made at 3 min., 1 h, and 1, 2 and 7 d) (Wolf et al.,1956). Smyth et al.(1962) reported slight conjunctival irritation with some reversible corneal injury in rabbits.

Skin Sensitisation. No animal sensitisation studies have been reported.

Respiratory irritation. Studies carried out with EB in mice gave an RD50 (concentration necessary to depress respiratory rate by 50%) of 4,060 ppm (Nielsen and Alarie, 1982). The potency of the (C_1-C_6)-alkyl benzenes was found to increase with chain length, n-hexyl benzene having an RD50 of 350 ppm. Alarie's proposed conversion factor of 0.03 for estimating appropriate TLV's from the RD50s gives a value in agreement with the established TLV for EB (Alarie, 1981).

3. Subchronic and Chronic Toxicity

3.1. Human

In recent years a number of epidemiological studies carried out on painters and other groups exposed to a wide range of solvents including EB, 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: Danish painter's syndrome, neurasthenic

syndrome, psycho-organic syndrome and presenile dementia. There are no specific studies which implicate EB as a causal agent, but, as a component of mixed xylenes, EB is present in paints and other solvent-containing products. These studies suffered from a number of deficiencies including: simultaneous 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 the 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. The measured exposures to EB were of up to 3 ppm (6-8 h averages).

In an extensive literature review (Grasso et al., 1984) on this subject it was 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.

In a study involving 35 spray painters, employed for between 2 and 24 years at 6 workplaces in two plants, alterations of blood cell counts have been observed (Angerer and Wulf, 1985). On average, the number of lymphocytes was higher than that of segmented granulocytes. Erythrocyte and haemoglobin levels of the spray painters were lower than those of the controls. The levels of exposure to o-, m- and p-xylene and EB were 2.1, 7.9, 2.8 and 4 ppm respectively. At three workplaces there was, in addition, an exposure to toluene of up to 1.5 ppm. At one workplace a butanol concentration of 1.2 ppm, and at another an average concentration of 1,1,1-trichloroethane of 36 ppm, were recorded. Thus it is difficult to attribute the effects to EB or any other of the chemicals present.

The authors note that several studies of this problem are in hand, e.g. in the UK, Germany and Holland.

3.2. Experimental

3.2.1. Oral. Wolf et al.(1956) administered 13.6, 136, 408 and 680 mg/kgbw/d of EB to groups of 10 female rats, 5d/wk for 6 months. It was administered by stomach tube as an olive oil solution emulsified with a 5 to 10% aqueous solution of gum acacia. The total daily volume was never greater than 2 to 3 ml/rat. A group of 20 rats served as controls and were given doses of 2.5 ml of the vehicle. Haematological examinations (total erythrocytes and leucocytes, haemoglobin content, and differential white blood cell count) were made on selected animals of the control and test groups at varying intervals, usually after 20, 40, 80 and 130 doses. It should be noted that only females were used in this study and no indication was given of the range of organs which were examined histopathologically. No haematological changes were induced by EB, but slight histopathological changes were reported, i.e. cloudy swelling of hepatocytes and the renal tubular epithelium at 408 and 680 mg/kgbw. Liver and kidney weights increased slightly at these dose levels. The no-observed-effect level was 136 mg/kgbw.

3.2.2. Inhalation. Inhalation studies have been carried out in rats, guinea pigs, rabbits and rhesus monkeys (Wolf et al.,1956). In rats, groups of 10 to 25 male and female animals were exposed to EB at 400, 600 and 1250 ppm, and males only to 2200 ppm, for 7-8 h/d, 5d/wk for between 5 and 7 months. Guinea pigs (groups of 5-10) and rabbits (groups of 1-2) were similarly exposed, but up to a maximum concentration of 1250 ppm. Rhesus monkeys (groups of 1-2) were similarly exposed up to a maximum of 600 ppm.

In rats, a moderate depression of growth was observed at 2200 ppm. Small increases in liver and kidney weight were seen at all dose levels, with slight cloudy swelling of hepatocytes and renal tubular cells at 1250 and 2200 ppm. In guinea pigs, rabbits and rhesus monkeys, no effects were seen at 400 ppm. In guinea pigs, slight increases in liver weight and depression of growth occurred at levels greater than 400 ppm. In rabbits and rhesus monkeys, slight histopathological changes in the testes were reported at 600 ppm, the effects being described as degeneration of the germinal epithelium. It should be noted that male and female monkeys were used at 600 ppm, but only females at 400 ppm, and only one male rabbit was exposed at each of the lower doses. A

no-effect level for testicular atrophy in monkeys was not therefore identified. No haematological effects were observed. In view of the lack of detail in the report, and the small number of monkeys and rabbits used, it is impossible to comment on the significance of the findings and the validity of the no-effect levels.

In a 7 m inhalation study (Ivanov, 1964) groups of four rabbits (sex not mentioned) were exposed to 2.3, 23 and 230 ppm of EB, 4h/d, 7d/wk. A variety of effects was described including : neuromuscular, neurochemical and haematological effects, and hepatic and renal pathology. The no-effect level was 2.3 ppm. The limited scope of the study does not allow comment on the validity of these findings. No haematological effects were reported after the exposure of several species to much higher EB concentrations (Wolf et al.,1956).

Short-term studies on the effects of EB on dopamine and noradrenaline levels and turnover in various parts of the rat brain have been carried out by Andersson et al.(1981). Six male rats were exposed to 2,000 ppm of EB for 6 h/d for 3 consecutive days. The authors concluded that EB produces discrete increases of dopamine and noradrenaline levels and turnover in various parts of the hypothalamus and the median eminence. They suggested that the changes could lead to disturbed brain function, for example in neuroendocrine, mental and motor control. EB was also found to produce a selective reduction of prolactin and corticosterone secretion. It seems possible that the increase of dopamine and noradrenaline turnover could in part be responsible for the inhibition of prolactin. In view of the lack of our understanding of the toxicological significance of these changes, the authors' final conclusion, while interesting, would seem rather speculative. Furthermore, only one, high, exposure level was used which makes extrapolation to occupational exposure conditions.

Male Wistar rats (5 per dose level per time point) were exposed 6 h/d, 5 d/wk to 0, 50, 300 or 600 ppm of EB, and sacrificed after 2, 5, 9 or 16 weeks of exposure (Elovaara et al.,1985). A variety of biochemical endpoints was measured and it was concluded that at levels of 300 ppm and above EB can induce proliferation of hepatocyte SER with increases in associated enzymes, but does not cause liver cell necrosis.

4. Mutagenicity, Clastogenicity and Cytotoxicity

4.1. Human

No data are available.

4.2. Experimental

4.2.1. Point mutations. EB was not mutagenic towards Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, with or without metabolic activation (Florin et al.,1980; Nestmann et al.,1980; Dean et al.,1985). In addition, the potential metabolites of EB, i.e. mandelic acid, phenylglyoxylic acid and hippuric acid, gave negative results in the same strains (Milvy and Garro, 1976). A preliminary communication from the NTP (1985) also indicates that EB does not induce point mutations in Salmonella typhimurium. EB was not mutagenic towards Saccharomyces cerevisiae strains D7 and XV 185-14C when tested without metabolic activation (Nestmann and Lee, 1983). It gave negative results in strain JD1 with and without activation (Dean et al.,1985).

In an API study (1978-a) a xylene mixture containing 36.1% of EB was evaluated in Salmonella typhimurium (TA-1537, TA-1538 and TA-98) and the mouse lymphoma assay (TK1/-L51784). Negative results were obtained in both tests, with and without metabolic activation.

4.2.2. Chromosomal effects. EB was not mutagenic in a chromosomal in vitro test on cultures of rat liver cells (Dean et al.,1985). It had a marginal effect on sister chromatid exchanges in human lymphocytes cultured in vitro when a high concentration, 10 mmole, was used (Norpa and Vainio, 1983). Studies by the NTP (1985) in Chinese hamster ovary cells are reported, in a preliminary communication, to show that EB does not induce chromosome aberrations or sister chromatid exchange.

Rats were exposed by inhalation to 300 ppm of a xylene mixture containing 18.3% of EB, 6 h/d, 5 d/wk, for 9, 14 and 18 weeks. There was no excess of chromosomal aberrations in the bone marrow of these rats when compared to controls (Donner et al.,1980). In the API (1978-a) study cited above, a xylene mixture containing 36.1% EB (cf. 4.2.1.) produced no significant increases in chromosome aberrations in the bone marrow cells of rats.

4.2.3. Recessive lethal EB did not cause any increase in the spontaneous recessive-lethal frequency in the Drosophila recessive lethal test (Donner et al.,1980).

4.2.4. Cytotoxicity and biochemical effects. EB was one of a major group of solvents found to have low intrinsic cytotoxicity in vitro (Holmberg and Malmfors, 1974). It had a destabilising action on the membranes of rat liver lysosomes and mitochondria in vitro (Sgaragli et al.,1975-b). EB inhibited oxygen consumption in cultured hamster brown fat cells (Pettersson et al.,1980), and it also inhibited the cell growth of ascites sarcoma BP8 cells (Pilotti et al.,1980) and caused a high degree of cell membrane damage in cultured human lung fibroblasts (Thelestam et al., 1980). At a concentration of 106 mg/l, EB caused almost complete haemolysis of human red blood cells (Sgaragli et al.,1975-a).

A variety of biochemical changes has been described following the administration of EB. Subcutaneous injections stimulated liver regeneration in partially hepatectomised rats (Gershbein, 1975). There were no changes in liver arylhydrocarbon hydroxylase after male rats were given an intraperitoneal injection of 500 mg/kgbw of EB in 0.5 ml of paraffin, in contrast to the effect of styrene (Roberfroid et al.,1978). None of these findings are unexpected and are probably non-specific effects common to many solvents.

5. Carcinogenicity

5.1. Human.

A mortality study (Nicholson et al.,1978) carried out on 560 styrene polymerisation workers exposed to (amongst other materials) styrene, benzene and EB for at least 5 years, suggested a possible risk of leukaemia/lymphoma. Since exposure was to several substances, including benzene, it is questionable whether the effects could be associated with EB. No studies demonstrating an association between the exposure of humans to EB and an increased risk of cancer have been reported.

5.2. Experimental

An oral study on several aromatic hydrocarbons, including EB, in rats was recently published by Maltoni et al.(1985). Sprague-Dawley rats (40 M, 40 F) were administered 500 mg/kgbw/d of EB in olive oil, by gavage, 4 or 5 d/wk, for 104 wks ("end of the experiment"), and then kept under observation until spontaneous death. A control group (50 M, 50 F) was administered olive oil alone. After 141 weeks, at the end of the experiment the total number of malignant tumours was 31 in the 77 animals of the exposed group alive at 33 wks (when the first malignant tumour was observed) compared with an incidence of 23 in 94 animals of the control group alive at 33 wks. In a preliminary report of this study, 4 animals were found to have hepatomas (2 in the control group) and a variety of malignant tumours were also found in other tissues (Maltoni et al.,1983). These included kidney adenocarcinoma, carcinoma of the uterus, osteosarcoma, bladder carcinoma, and Harderian gland adenocarcinomas. The total number of each of these specific tumours was either 1 or 2. The authors concluded that EB caused an increase in the incidence of total malignant tumours, although there was no increase in the incidence of any specific type of tumour. Considering the limited amount of data presented, the use of a single, high dose-level and the lack of statistical evaluation and historical control data, it is difficult to draw a firm conclusion from this study.

The National Toxicology Programme in the USA had scheduled a carcinogenicity study with EB in the rat and mouse, but at present this has been deferred (NTP, 1985).

6. Reproductive Effects

6.1. Human

No data on humans have been reported.

6.2. Experimental

Hardin et al.(1981) reported a study performed by Andrew et al.(1981). New Zealand white rabbits and Sprague-Dawley rats were exposed to 100 and 1000 ppm of EB in air, 6 to 7 h/d, on days 1-24 and 1-19 of gestation, respectively. The rats had already been exposed (7 h/d, 5 d/wk) 3 weeks prior to mating. The target number of litters per group was 20 for rabbits and 30 for rats, but breeding difficulties reduced the size of the rabbit

groups to approximately 15. All the pregnant animals were sacrificed on the day before term (day 21 for rats, day 30 for rabbits) and the litters were collected. The rabbits produced significantly less live pups per litter at both exposure levels, although the number of implantations and the number dead or resorbed did not differ from those of the control group in a statistically significant way. Maternal toxicity, reflected in increased liver, kidney and spleen weights, was observed in rats exposed at 1000 ppm. A "possible reduction" in fertility was observed in rats at both exposure levels. There was a significant increase in the incidence of extra ribs in both of the rat groups exposed at 1000 ppm during gestation, and in the group exposed to filtered air pregestationally, and to 100 ppm of EB during gestation. Extra ribs are not in themselves regarded as a teratogenic response although Kimmel and Wilson (1973) have suggested that such an increased incidence may indicate teratogenic potential at higher levels of exposure. The results of this study suggest that there is a potential effect on fertility, and a potential embryotoxic effect in rats, at exposure levels above 1000 ppm.

Tatrai et al.(1982) exposed CFY rats to EB at levels of 600, 1200 and 2400 mg/m^3 (about 150, 300, 600 ppm) for 24 h/d from day 7 to 15 of pregnancy. They reported that EB, i) caused mild maternal toxicity at all exposure levels, ii) increased the incidence of skeletal retardation, and iii) caused a decrease of foetal weight at the highest concentration. The incidence of extra ribs, and of litters with internal malformations, increased at the highest concentration. Sacral dysplasia with abnormal tail developed in two cases at the highest concentration. Since the structural changes seen in the foetuses did not reflect specific teratogenic effects and were associated with maternal toxicity they are not regarded as indicating teratogenic potential.

The teratogenic potential of a xylene mixture containing 36% of EB was investigated in rats exposed by inhalation (API, 1978-b). Groups of 15 pregnant rats were exposed, from day 6 to day 15 of gestation, to 0, 100 or 400 ppm of the mixture. There was no evidence of maternal toxicity or major foetal abnormalities in any of the treated groups. There was a statistically-significant increase in the number of foetuses with "unusual" retarded ossification in the 400 ppm group. Since the majority of these

foetuses (72%) came from only three litters in which all members were small at delivery, it is uncertain whether the changes were compound-related.

In a reproduction study performed by API (1983) rats were exposed to mixed xylenes containing 12.8 % of EB for approximately 6 months at concentrations of up to 500 ppm. There was no evidence of treatment-related teratogenic or reproductive effects.

The structural changes seen in the above studies reflect non-specific embryotoxicity rather than specific teratogenicity, as they occur at maternally toxic doses. Khera (1984, 1985) reported that after the exposure of experimental animals to a variety of chemicals, and physical agents, maternal toxicity resulted in similar foetal deviations.

7. Kinetics and Metabolism

7.1. Human

7.1.1. Absorption. The vapour of EB is not absorbed by the skin (Gromiec and Piotrowski, 1984) but the liquid is very easily absorbed. Dutkiewicz and Tyras (1967) have shown that the absorption rate was 22 to 33 mg/cm²/h when the whole hand was immersed for 1h in an aqueous solution of EB. This can be compared with the absorption rate of benzene of 0.4 mg/cm²/h.

EB is well absorbed when inhaled. Bardodej and Bardodejova (1966) exposed volunteers (number not indicated) to 23, 43, 46 or 85 ppm during 8h, and found that 64% of the inhaled EB was absorbed by the respiratory tract. Åstrand et al.(1978) exposed 12 volunteers to a mixture of 40% EB and 60% xylenes, at 100 and 200 ppm for 2h, and found a respiratory uptake of 60% of the xylene. Gromiec and Piotrowski (1984) exposed 6 volunteers to 4, 8, 19, 47 ppm of EB for 8h and found a lung retention of 49±5%.

7.1.2. Distribution. Wolf (1976) and Wolf et al.(1977) reported finding EB in trace amounts in the subcutaneous fat of 21 out of 25 workers exposed to a variety of chemicals, including EB, in a styrene polymerisation plant. The level of exposure to EB was said to have been between 1 and 3 ppm, with occasional excursions above this.

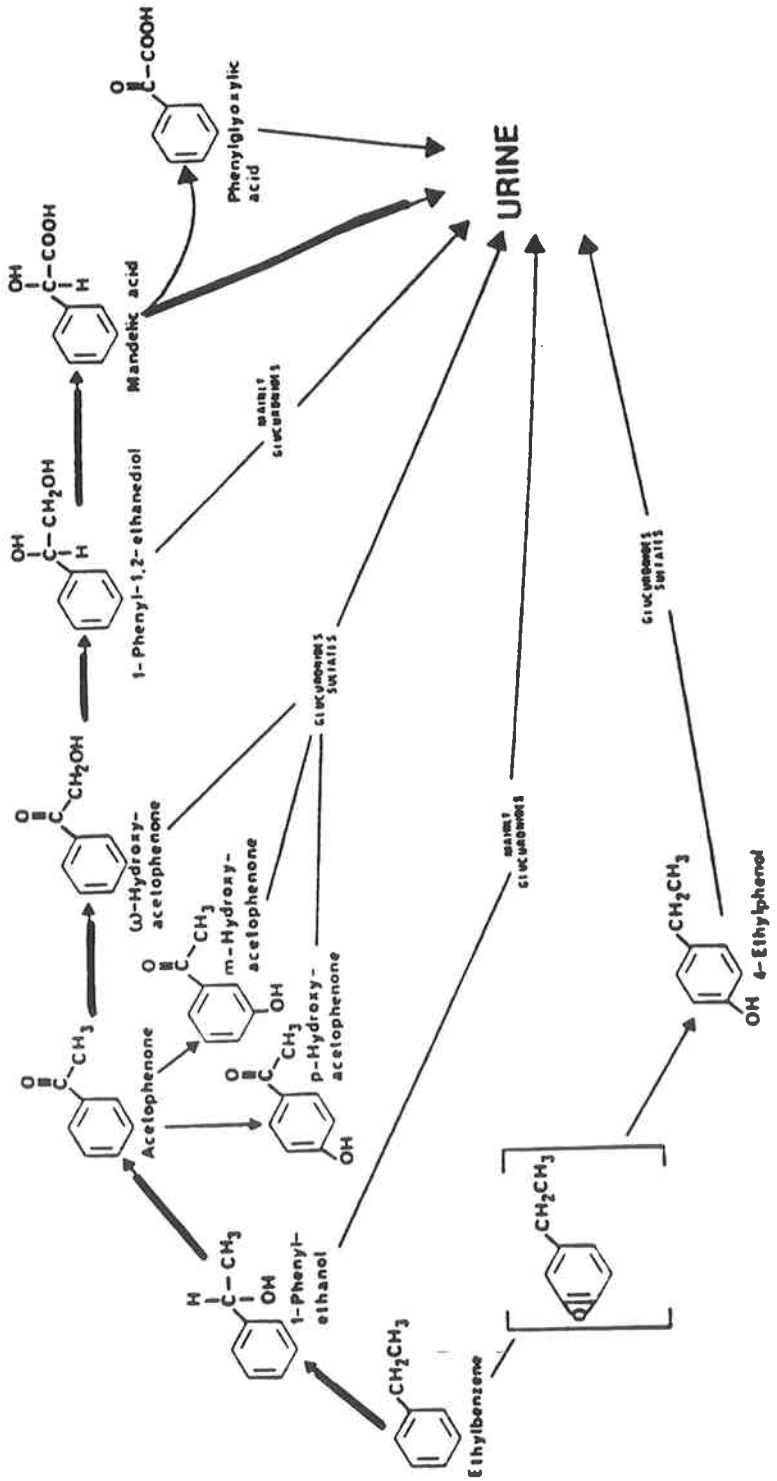
Engström and Bjurström (1978) exposed 12 people for 30 min. to an atmosphere containing 100-200 ppm of the vapour of a mixture of 40% EB and 60% xylenes. The amount of EB taken up by the body correlated highly with the amount of body fat. There was, however, a negative correlation between the concentrations in adipose tissue and the degree of obesity. EB appeared at levels ranging from 4 to 9 ng/kg of adipose tissue, as early as 30 min. after exposure.

7.1.3. Biotransformation The metabolism of EB by humans has been studied mainly through the identification of urinary metabolites as almost all absorbed EB is transformed and excreted via the urinary tract. Engström et al.(1984) recently proposed a metabolic scheme for the disposition of EB in man (see Fig.1). The main metabolites in man exposed by inhalation were demonstrated to be mandelic acid and phenylglyoxylic acid. Metabolic conversion proceeded mainly through side-chain oxidation, whereas ring oxidation was of minor quantitative importance.

Bardodej and Bardodejova (1970) found that the urinary excretion products in exposed volunteers, expressed as the % of the retained EB, were :

- mandelic acid, 64%
- phenylglyoxylic acid, 25%
- 1-phenylethanol (methylphenylcarbinol), 5%

Gromiec and Piotrowski (1984) found a similar figure for mandelic acid excretion in urine, accounting for 55% of the absorbed EB. Similarly, Engström et al.(1984) confirmed that mandelic and phenylglyoxylic acids accounted for 90% of the urinary metabolites of EB.



major route (added by the present authors)

Fig.1. Metabolic scheme for EB in man (Engström et al.,1984)

Using a more sensitive method than did Bardodej and Bardodejova (1970), Angerer and Lehnert (1979) demonstrated that a small amount of phenolic derivatives can be found in the urine of people exposed to EB. About 1.1 to 1.4% of the retained EB was metabolized to 2-ethylphenol. Recently, Engström et al.(1984) found that 4-ethylphenol, p-hydroxyacetophenone and m-hydroxyacetophenone are also formed, and together account for about 4% of the total amount of transformed EB. The formation of an epoxide intermediate is not thought to constitute a key pathway. Indeed, if during the p-hydroxylation of the ring the 3,4-epoxide is formed, it must be very unstable because none of the other metabolites which are usually formed from arene-oxides, such as dihydrodiols, catechols or mercapturic acid, are found.

Apparently, the rate of conversion into mandelic acid is much lower when EB enters the body in liquid form across the skin. Dutkiewicz and Tyras (1967) found that the 24h urinary excretion of mandelic acid in volunteers exposed to an aqueous solution of EB corresponded to only around 4 to 5% of the total EB absorbed through the skin of the hand.

7.1.4. Excretion. Absorbed EB is mainly excreted in the urine as mandelic and phenylglyoxylic acids (Bardodej and Bardodejova, 1970; Grigor'eva and Klyuzko, 1971; Åstrand et al.,1978; Engström et al.,1984; Gromiec and Piotrowski, 1984). These acids account for 90% of the EB absorbed from the lungs. Only 4 to 5% of the retained EB is estimated to be exhaled without transformation (Åstrand et al.,1978). According to Gromiec and Piotrowski (1984), the urinary elimination of mandelic acid is biphasic, with half-lives of 3.1 and 24.5 hours. According to Wolf (1976) the respiratory half-life of EB is between 0.5 and 3 hours.

7.1.5. Application to biological monitoring. No reference could be found to the biological-monitoring of exposed workers via the analysis of EB itself in the expired air or in blood, although it would be a more specific method in the case of mixed exposure to other closely-related chemicals. The best practical index of human exposure to have been proposed is the determination of biotransformation products excreted in the urine. Several experiments on human volunteers have shown that the best correlation between the excretion of urinary metabolites and exposure is found when urine is collected during the two last hours of the exposure

period (Bardodej and Bardodejova, 1970; Engström et al.,1984; Gromiec and Piotrowski, 1984). In addition, it was shown that there is a very good correlation between the level of exposure to EB and the excretion of mandelic acid in urine, after exposure by inhalation to a concentration of 150 ppm for 4h (Engström et al.,1984), 23 to 85 ppm for 8h (Bardodej and Bardodejova, 1970) and 4 to 47 ppm for 8h (Gromieck and Piotrowsky, 1984).

Gromiec and Piotrowski (1984) have proposed the determination of urinary mandelic acid as an indicator of exposure to low concentrations of EB vapour. They suggested determining either the rate of urinary excretion of mandelic acid (mg/h) or, alternatively, the concentration of mandelic acid/g creatinine in the urinary fraction taken during the last 2 hours of the working shift. They stated that the detection limit of the test is equivalent to an air concentration of about 2.3 ppm (10 mg/m^3), corresponding to an absorbed dose of 20 mg. This range satisfies the requirement of all current occupational exposure limits. Bardodej and Bardodejova (1970), using a rather insensitive analytical method (i.e. UV spectrophotometry or polarimetry), found a mandelic acid urinary excretion of 2,000 mg/l of urine or 1,500 mg of mandelic acid/g creatinine, corresponding to a calculated exposure level of 100 ppm. At the same time they found high amounts of other metabolites. The studies of Bardodej and Bardodejova (1970) were limited to relatively high EB concentrations in the air, but Gromiec and Piotrowsky (1984) showed that the measurement is also valid for much lower levels of exposure. They used a gas chromatographic procedure with a greater sensitivity and found a level of mandelic acid of 10 mg/l urine, or 20 mg/g creatinine in urine, which corresponds to a calculated exposure level of 23 ppm of EB.

An alternative method is to determine the urinary excretion of 2-ethylphenol which could be more specific for EB exposure in the case of simultaneous exposure to other closely-related chemicals (Angerer and Lehnert, 1979). These authors estimated that on exposure to 100 ppm (the occupational exposure limit), 12-15 mg of 2-ethylphenol would be excreted in the urine during 24 h.

As mandelic acid and phenylglyoxylic acid are also the principal urinary metabolites of styrene (IPCS, 1983), the quantitative determination of these metabolites cannot be used as a biological indicator of human exposure to EB in the case of mixed exposure.

7.2. Experimental

7.2.1. Absorption and distribution. Liquid EB is easily absorbed by the gastro-intestinal tract or through the skin. The vapour is readily absorbed via the respiratory tract. This was qualitatively demonstrated in a number of toxicity studies showing that intoxication occurs after EB absorption by these routes in various animal species. The available quantitative data for absorption in rats indicate that about 44% of the inhaled EB is retained (Chin et al.,1980-b) which is in agreement with the data on humans. Tsuruta (1982) found that the penetration of liquid EB across the excised rat skin *in vitro* occurred at a rate of 0.006 mg/cm²/h, compared to 0.2 mg/cm²/h for benzene. These data are in contrast with the absorption data on humans from Dutkiewicz and Tyras (1967)(cf. 7.1.1).

7.2.2. Biotransformation and excretion. EB is oxidised in animals through pathways similar to those in humans, the major pathway being side-chain oxidation (Gerarde and Ahlstrom, 1966). However, an essential difference is that in most animal species the transformation continues up to benzoic acid (via the acetophenone route), leading to the excretion of hippuric acid after conjugation with glycine. This conjugate is generally one of the main urinary metabolites, together with mandelic acid, in the rat and dog (Chin et al.,1980-a) and the rabbit (Smith et al.,1954, El Masry et al.,1956). The metabolic pathway proposed by Engström (1984) for rats is shown in Fig.2. During the first stage, hydroxylation of the ethyl-chain, EB undergoes a specific stereochemical hydroxylation by microsomes (McMahon and Sullivan, 1966). Only 8% of the absorbed EB is eliminated unchanged by the lungs (Chin et al.,1980-b).

Hydroxylation of the aromatic nucleus is a minor pathway. In the rabbit this phenolic pathway accounted for less than 1% of the EB absorbed (Kiese and Lenck, 1974). 4-Ethylphenol eliminated in the rat accounts for 0.3% of the total urinary metabolites (Bakke and Scheline, 1970).

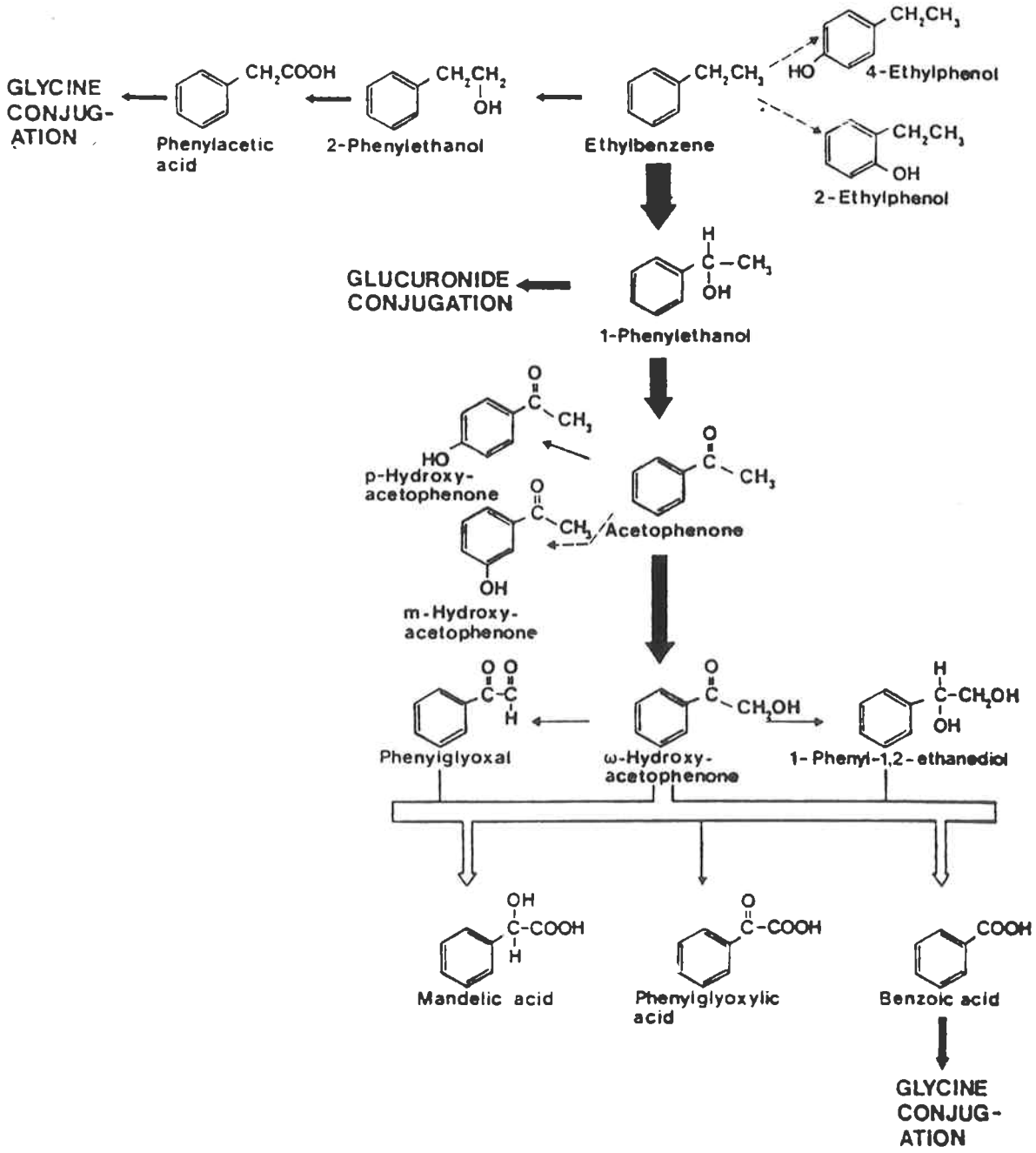


Fig.2. Metabolism of ethylbenzene as reconstructed from urinary metabolites in rats. The thickness of the arrows directly represents the relative importance of the respective routes; the broken arrows mean that only trace amounts were found. Unclear pathways are depicted by open arrows (Engström, 1984)

These phenolic metabolites are present in urine in the form of sulfur conjugates (Gerarde and Ahlstrom, 1966; Elovaara et al.,1984).

As EB is usually present in xylene mixtures, exposure often occurs simultaneously to both materials. It has been demonstrated in the rat that the metabolism of each is not qualitatively changed by the presence of the other. However, the amount of EB metabolites excreted is changed, the elimination of EB being delayed by the presence of xylenes (Elovaara et al.,1984). Angerer and Lehnert (1979) suggested that after inhalation of xylene-EB mixtures by man, the oxidation of the EB aromatic nucleus is favoured over that of xylenes.

H. ECOTOXICOLOGICAL DATA

1. Toxicity to Aquatic Organisms

The volatility of EB presents technical difficulties in testing for aquatic toxicity. Flow-through systems which allow the continual renewal of the EB solution in the test vessel are necessary to maintain its concentration. As the majority of the studies on fish, invertebrates and algae summarised in Tables 2, 3 and 4 were performed under static conditions, which allow losses by volatilisation, the results must be viewed carefully. The concentrations quoted in the tables are nominal concentrations.

In addition to the results in Table 2, Morrow et al.(1975) reported that following the exposure of young Coho salmon (Oncorhynchus kisutch) to EB the mortality increased after 96h exposure to 10 mg/l (ppm), and was 100% after 24 h exposure to 50 mg/l. In an embryo-larval test on the fathead minnow (Pimephales promelas) no adverse effects were observed at the highest concentration tested, i.e. 0.44 mg/l (EPA, 1980). No other data are available concerning the chronic toxicity of EB to fish.

TABLE 2
Acute Toxicity of Ethylbenzene to Fish

Species	LC_{50} in mg/l	Reference
FRESHWATER		
Rainbow trout (*Salmo gairdneri*)	14 (96h)	Johnson and Finley (1980)
Bluegill (*Lepomis macrochirus*)	32 (96h)	Pickering and Henderson (1966)
	150 (96h)	Buccafusco et al. (1981)
	160 (96h)	EPA (1980)
	88 (96h)	Johnson and Finley (1980)
Channel catfish (*Ictalurus punctatus*)	210 (96h)	Johnson and Finley (1980)
Fathead minnow (*Pimephales promelas*)	42-49 (96h)*	Pickering and Henderson (1966)
Golden orfe (*Leuciscus idus*)	44 (48h)	Juhnke and Luedemann (1978)
Goldfish (*Carassius auratus*)	94 (96h)	Pickering and Henderson (1966)
Guppy (*Lebistes reticulata*)	97 (96h)	Pickering and Henderson (1966)
MARINE		
Striped bass (*Morone saxatilis*)	4 (96)	Benville and Korn (1977)
Sheepshead minnow (*Cyprinodon variegatus*)	280 (96)**	Heitmuller et al. (1981)

* values for, respectively, hard and soft water

** this value is greater than the solubility of EB in seawater

TABLE 3
Acute Toxicity of Ethylbenzene to Invertebrates

Species	LC_{50} in mg/l	Reference
FRESHWATER		
Water flea (*Daphnia magna*)	184 (24h)(EC_{50})*	Bringmann and Kuehn (1982)
	75 (48h)	Leblanc (1980)
MARINE		
Bay shrimp (*Crago franciscorum*)	0.49 (96h)	Benville and Korn (1977)
	2.2 (24h)	
Grass shrimp (*Palaemonetes pugio*)	15 - 17 (24h)	Potera (1975)
" " " " , larvae	10 (24h)	Potera (1975)
Copepod (*Nitocra spinipes*)	16 (24h)	Potera (1975)
Mysid shrimp (*Mysidopsis bahia*)	88 (96h)	EPA (1978)
Dungeness crab (*Cancer magister*)	13 (96h)	Caldwell et al. (1977)
" " " " , larvae	40 (48h)	Caldwell et al. (1977)

* EC_{50}, immobilisation. This value is above the water solubility.

The low LC_{50} values found for the Bay shrimp (Table 3) (Benville and Korn, 1977) probably result from the fact that the concentrations were measured only at the end of the exposure period. The authors reported a rather high loss of EB during the whole period.

The rotifer Dicranophorus forcipatis was grown in the presence of ethyl benzene at concentrations of 0.02, 0.20 and 2.0% (v/v) at 22-23°C and the number of individuals was counted after 24 and 48 h and 6 days. Growth at the three concentrations was initially inhibited but recovery occurred later. The inhibition, and time necessary for recovery, were dose-related (Erben, 1978).

TABLE 4
Toxicity of Ethylbenzene to Algae

Species	No-Observed-Effect Concentration for Cell Growth Inhibition, or 50% Photosynthetic Inhibition (PhI), mg/l	Reference
FRESHWATER		
Green algae		
Scenesdesmus quadricauda	NOEC > 160 (8d)*	Bringmann and Kuehn (1978)
Chlamydomonas angulosa	PhI, 51	Hutchinson et al. (1980)
Chlorella vulgaris	PhI, 63	Hutchinson et al. (1980)
Selenastrum capricornutum	NOEC > 440 (4d)*	EPA (1978)
Blue-green algae		
Microcystis aerugenosa	NOEC, 33 (8d)	Bringmann and Kuehn (1978)
MARINE		
Skeletonema costatum	NOEC > 440 (4d)*	EPA (1978)

* Above water solubility.

2. Toxicity to Terrestrial Plants

On exposing leaves of the runner bean (Phaseolus multiflorus) and parsnip (Pasticana sativa) to hydrocarbons at a range of vapour concentrations for 1h it was found that the concentrations causing no damage and those completely killing the leaves were close. It was therefore not possible to make precise EC_{50} estimates. Values of 27 and 48 mg/l, respectively, were found for EB (Ivens, 1952).

3. Toxicity to Microorganisms

No-observed-effect levels are summarised in Table 5.

TABLE 5

Toxicity of Ethylbenzene to Microorganisms

Species	No-Observed-Effect Level for Cell Growth Inhibition, in mg/l	Reference
PROTOZOA		
Flagellate (Chilomonas paramaecium)	> 56 (72h)	Bringmann and Kuehn (1981)
Ciliate (Uronema parduczi)	> 110 (72h)*	Bringmann and Kuehn (1981)
Flagellate (Entosiphon sulcatum)	140 (72h)*	Bringmann and Kuehn (1979)
BACTERIA		
Pseudomonas putida	12 (72h)	Bringmann and Kuehn (1979)

* Above water solubility.

An EB concentration of 500 mg/l was toxic to sludge from one conventional activated sludge plant but non-toxic to sludge from another (Marion and Malaney, 1963). EB added to an undiluted anaerobic sludge at 35°C for 5 h caused growth inhibition at concentrations of 150 and 500 mg/l (Hovious et al.,1973). A concentration of 320 mg/l of EB reduced the degradative activity of an unacclimatised, acetate-enriched, methane culture by 50% (Chou et al.,1978).

4. Fish Tainting

When yellow perch (Perca flavescens) were exposed to EB for 7d according to a protocol described by Teal (1959), tainting of the fish occurred. The threshold level below which tainting could not be detected was 0.5 mg/l.

I. SUMMARY AND CONCLUSIONS

Ethylbenzene (EB) is produced in large volume and is mostly converted into styrene at the site of its manufacture. The largest source of emission to the environment is from gasoline. It is expected that EB, after emission, will be

present mainly in the air where it will be rapidly photodegraded. It is inherently biodegradable in the hydrosphere.

EB does not bioaccumulate in marine and freshwater aquatic species. It is slightly toxic to most of the freshwater and marine aquatic organisms in which it has been tested. The hazard of EB to aquatic species is low because of its low solubility, high volatility and inherent biodegradability.

The limited human data, and the experimental data, suggest that EB is of low acute systemic toxicity following exposure by the oral, dermal and inhalation routes. It is expected that repeated and prolonged contact with the human skin will lead to dermatitis, as with other hydrocarbons. EB at high vapour concentrations is severely irritating to the human eye and to the mucous membranes of the upper respiratory tract of mice.

Studies performed in the 1950s on animals repeatedly exposed to EB have generally shown a low toxicity. In contrast with benzene, EB appears to cause no haematological effects. Oral and inhalation studies performed with several species showed effects at high doses, on the liver, kidney and testes, but the design of the experiments do not permit no-effect levels to be defined. The current evidence is thus inadequate as basis for setting occupational and oral exposure standards.

As EB has often been included in discussions of the toxicity of solvents as a group, it might be worth considering epidemiological and health assessment studies if a suitable cohort can be identified. It is appreciated that it will be difficult to identify a group exposed exclusively to EB, i.e. without simultaneous exposure to other aromatic hydrocarbons.

Studies in two species have shown no specific teratogenic effects. Skeletal retardations occurred only at high dose levels which were maternally toxic. At lower doses, which were not maternally toxic, no effects were found in the offspring.

The metabolic profile of EB has been quite well described. The major metabolic pathways do not involve an epoxide intermediate or other known, highly-toxic metabolites. In humans, EB is almost completely converted into mandelic and phenylglyoxylic acids which are rapidly excreted in urine. The excretion of

mandelic acid in urine can be a useful index for the biological monitoring of exposure to EB vapour, but in some cases, e.g. combined exposure with styrene, it may not be sufficiently specific. Data on absorption via human skin indicate that EB is rapidly absorbed, in contrast to more recent in vitro data on animals. Further data on skin absorption would be helpful to elucidate this discrepancy.

EB and its main metabolites were not mutagenic in a variety of tests with different end-points.

There is little data on carcinogenicity. The only available study has not been well reported and is not adequate to permit any firm conclusion to be drawn. In the light of the negative mutagenicity results, and the absence of any other incriminating evidence from the information on metabolism and human experience, the carcinogenic potential, if any, would appear to be low.

J. FIRST AID AND SAFE HANDLING ADVICE

1. First Aid and Medical Treatment

1.1. Inhalation

The patient should be removed to fresh air and kept warm and at rest. If breathing ceases, or becomes weak and irregular, artificial respiration and oxygen should be administered.

1.2. Eye contact

The eye should be irrigated thoroughly with eyewash solution or clean water for at least 10 minutes. Medical attention should always be obtained.

1.3. Skin contact

Contaminated clothing should be removed and the affected area of the skin thoroughly be flushed with water. Soap should be used if available. If skin irritation persists, medical attention should be obtained.

1.4. Ingestion

Vomiting should not be induced but medical attention should be obtained, since ingestion of ethylbenzene can cause aspiration into the lungs, leading to chemical pneumonitis.

2. Safe Handling

2.1. Personal protection

Atmospheric levels should be minimised and kept as far as reasonably practicable below the recommended occupational exposure limit. Skin and eye protection should be worn and suitable respiratory protection should be readily available.

2.2. Flammability/explosion hazards

The vapour of EB is heavier than air and may travel along the ground, so that ignition is possible distant from the source. Adequate ventilation should be provided and smoking prohibited. The substance can generate electrostatic charges as a result of flow, agitation, etc. Any electrical equipment in the vicinity should be "explosion-protected" and of a type in accordance with local legal requirements.

2.3. Storage

Drums should be stored in a well-ventilated area, away from direct sunlight and other sources of heat, and separated from oxidants. Compressed air must not be used for filling, discharging or handling operations.

3. Management of Spillages and Waste

3.1. Spillage

In all cases of leakage, naked flames should be extinguished. Smoking and sparks must be avoided. Contact with the skin, eyes and clothing are to be avoided. Plastic gloves, goggles (or a face shield) and boots should be worn, and breathing of the vapour avoided.

For small spillages the liquid should be absorbed on sand, earth or sawdust, shovelled up, and removed to a safe place for subsequent disposal by burning. The contaminated area should be flushed with plenty of water.

For large spillages, sand or earth should be used to prevent the spilt liquid from spreading. The liquid should be transferred to a salvage tank if possible; otherwise it should be treated as for small spillages. The local authorities (particularly the fire service) should be informed at once if the spilt liquid enters the surface water drains since there will be a potential explosive hazard.

3.2. Disposal

Residues containing ethylbenzene, whether from road/rail tanks, bulk storage or shipment, should be collected for controlled disposal. The methods which are, in principle, available include re-use and burning. The residues should not be buried or dumped in a landfill. When selecting the disposal procedure, due consideration should be given to safety aspects and to any local or national regulations.

3.3. Fire

Fire extinguishers containing carbon dioxide, dry chemical or foam are recommended. Toxic gases (such as CO) may be released in a fire involving ethylbenzene. Flashback along a vapour trail may occur.

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decreases in mean foetal weights and "significant" increases in post-implantation loss occurred. In addition, the authors reported an increased incidence of haemorrhages/haematomas, internal hydrocephalus, and microphthalmia in the 500 mg/m³ dose group, and reduced ossification of the sternum and skull in the two highest dose groups. Impaired post-natal development of the offspring from a proportion of the animals from the 50 and 500 mg/m³ groups which were allowed to litter, was also reported. The effects included "delayed physical and functional maturation" and a variety of biochemical changes in the liver, brain, lung and heart. Because of the lack of details and, in particular, of information on possible maternal toxicity, the significance of the observed effects cannot be assessed.

The effects of mixed xylenes on reproductive performance have been investigated in M and F rats (API 1983). Groups of animals were exposed by inhalation to 0 (30 M, 60 F), 60, 250 (10 M, 20 F) or 500 ppm (20 M, 40 F), 6 h/d for 131 days prior to mating, during mating, during pregnancy and (for females allowed to deliver) from day 5-20 of lactation. In addition, two further groups of 10 M and 20 F were exposed to 500 ppm of xylenes, and then mated with untreated animals. No adverse effects of xylene exposure were observed in any of the F_0 adults, either while still alive or on post-mortem and histological examination. Reproductive performance, litter size and pup survival rate were also unaffected by treatment with xylenes. Mean pup weights from the groups exposed to 60, 250 or 500 ppm were slightly lower than those of the controls, this being statistically significant on day 4 of lactation following a cross-fostering procedure. The mean pup body weights were still lower at day 21 of lactation but the differences were only statistically significant in the 500 ppm group. A teratological investigation was carried out using foetuses from 12 animals exposed to 500 ppm of xylenes and 20 controls. There were no signs of toxicity in the dams. Small increases in the mean number of resorptions and in the incidence of foetuses with at least one variation in ossification were found, and there was a slightly lower mean foetal weight in the xylene-exposed groups when compared with the controls. These differences, with the exception of the weights of the female foetuses, were not statistically significant. There were no increases in the incidence of external soft tissue or skeletal malformations in the xylene-treated animals.

Although some of the studies reported above (Hudak and Ungváry, 1978; Nawrot and Staples, 1980; Mirkova et al.,1980) have been interpreted by the authors as providing evidence of teratogenic potential, the data are not reported in sufficient detail to permit an independent validation of these conclusions. More recent teratology and multigeneration studies (API, 1983), carried out and reported in accordance with internationally accepted standards, do not indicate that xylene has any teratogenic potential. Also, in a recent review of data on developmental effects, Hood and Ottley (1985) concluded that whilst foetotoxic effects have been observed at high exposure levels there is no clear case to suggest that exposure to xylenes can lead to teratogenic effects.

8. Kinetics and Metabolism

8.1. Human

8.1.1. Absorption and distribution. As with many other volatile lipophilic solvents, xylenes are absorbed into the blood on inhalation of the vapour, ingestion of the liquid, or contact with the intact skin. In blood they are bound to erythrocytes, dissolved in chylomicrons and adsorbed on lipoproteins (Browning, 1965).

The pulmonary uptake of technical xylenes (containing 40.4% ethylbenzene, 1.4% p-xylene, 49.4% m-xylene and 8.8% o-xylene) was measured in twelve male subjects exposed to either 200 or 100 ppm, at rest for 30 mins and during light work for 90 mins (Åstrand et al.,1978). In both experiments the uptake by the lung was estimated to be about 60% of that inhaled and the amount of unchanged xylene expired was between 4 and 5% of the retained dose. Similar values for the pulmonary uptake and excretion of m-xylene have been reported by Riihimäki et al.(1979 a-b).

The rate of absorption of m-xylene through human skin following immersion of both hands in xylene has been reported as 2 $\mu g/cm^2/min$. (Engström et al.,1977), 2.45 $\mu g/cm^2/min$. (Lauwerijs et al.,1978), and 2.1 $\mu g/cm^2/min$. (Riihimäki, 1979-b). The total amount absorbed after 15 minutes was roughly the same as the total pulmonary absorption resulting from inhalation exposure to 100 ppm for the same period (Engström et al.,1977). The amount of percutaneously absorbed xylene following the immersion of both hands in a 1:1 (v/v) mixture of m-xylene and isobutanol saturated with water was found to be similar to that reported above.

However, a 50% reduction in xylene absorption occurred with a 1:1 xylene-isobutanol mixture, the reduction being attributed to a "conspicuous dehydration of the skin" by the isobutanol (Riihimäki, 1979-b).

The percutaneous absorption of m-xylene resulting from exposure to vapour concentrations of 600 ppm of the xylene for 3.5 h was estimated at 0.006 µmole/cm²/h (Riihimäki and Pfaffli, 1978). One subject with "atopic dermatitis" absorbed more than 3 times the quantity of xylene vapour absorbed by the subjects with normal skin. Engström and Riihimaki (1979) estimated that 3.7-8.0% of the m-xylene uptake was distributed to adipose tissue, the proportion increasing during physical exercise. The median elimination half-time of xylenes from subcutaneous fat was found to be 58 h (range 25-128 h) and it was suggested that some accumulation would occur on repeated exposure until a steady state was achieved. The amount of xylene taken up was found to be "highly correlated" with the amount of body fat (Engström and Bjurström, 1978).

Dowty et al. (1976) identified xylenes, along with nine other volatile organic materials of low molecular weight, in both the maternal and cord blood from 11 patients, proving that xylenes can cross the placenta. The actual levels of xylenes in maternal and cord blood were not given.

8.1.2. Metabolism. In man, over 95% of xylene retained on inhalation is excreted as methylhippuric acid, and 1-2% as xylenols (Sedivec and Flek, 1976-a; Riihimäki et al., 1979-a-b; Engström et al.,1984). The measurement of urinary methyhippuric acids as a means of monitoring xylene exposure is discussed in chapter D-2. Ogata et al.(1970) reported that the total quantity of methylhippuric acid excreted up to 18 h after the end of a period of exposure to xylene was proportional to the cumulative exposure (ppm x hours) and was equivalent to 72% of the m-xylene absorbed. Sedivek and Flek (1976-b) found that the estimation of the metabolites of the different xylene isomers and their mixture, at a ratio 1:1:1 in urine samples collected over the last 3 h of an 8 h shift, did not give a reliable indication of xylene exposure. All-shift (8 h) or 24 h urine samples, however, did give a reliable measure of previous

xylene exposure when the metabolite excretion was expressed in terms of mg methylhippuric acid/kgbw.

Glycine conjugation of benzoic and methylbenzoic acid may be the rate-limiting step in toluene and m-xylene metabolism since the maximum excretory capacity of the kidneys for hippurate is known to be considerably larger than the maximum rate of benzoic acid conjugation (Riihimaki, 1979-a). The maximum rate of excretion of combined glycine and glucuronic acid conjugates in a 70 kg man was estimated at 190 µmol/min. Using these data and assuming that 60% of inhaled m-xylene is retained, the authors estimated that the conjugating capacity could be saturated by the inhalation of 780 ppm of xylene at rest or 270 ppm of xylene during heavy work.

Since technical grades of xylenes contain ethylbenzene, a number of studies have been carried out to investigate the influence of each material on the metabolism of the other. Angerer and Lehnert (1979) suggested that, in man, ethylbenzene is preferentially oxidised at the aromatic nucleus thereby competitively inhibiting the oxidation of the aromatic ring in xylene. Engström et al.(1984), however, reported that in man simultaneous exposure to ethylbenzene and m-xylene resulted in a reduction in the 24 h urinary excretion of the metabolites of both materials compared with the excretion of metabolites following separate exposures. The profile of urinary metabolites of both materials was the same following both separate and combined exposures.

8.2. Experimental

8.2.1. Absorption and distribution. Several studies of the distribution of xylenes in mammalian tissues have been carried out. Fabre et al.(1960) reported high xylene levels in the fat, brain and bone marrow of rabbits exposed to 3 mg of xylene/l., 8 h/d, 6 d/wk for 130 days. The distribution of ^{14}C-m-xylene in mouse tissues was investigated by low-temperature whole-body autoradiography (Bergman, 1979). Immediately following inhalation exposure to 10 µl (10 microcuries) for 10 min, high levels of "volatile" radioactivity were found in the body fat, bone marrow, brain (white matter), spinal cord and nerves, liver and kidney. It persisted in nerve tissue for up to 1 h and in body fat for up to 8 h after inhalation. "Non-volatile" radioactivity (xylene metabolites)

appeared rapidly in blood, lung, liver, and kidney. Biliary excretion was inferred from the increasing amount of non-volatile radioactivity in the intestinal contents, 2-8 h after inhalation.

Carlsson (1981), using liquid scintillation counting, demonstrated the rapid accumulation of ^{14}C-p-xylene by fatty tissues. Elovaara (1982) reported that the inhalation of m-xylene at 50, 400 or 750 ppm for 2 wk resulted in a dose-dependant uptake of m-xylene into the perirenal fat of rats.

8.2.2. Metabolism (Fig.1). The metabolism of xylenes in animals, as in man, proceeds principally by oxidation of one of the methyl groups, leading to the formation of toluic acids. In rabbits, 60% of xylene was excreted as o-toluic acid, mainly unconjugated, and as glucuronide ester with small amounts of glycine conjugate. A greater percentage of the m- and p-xylenes (81 and 88% respectively) were oxidised to toluic acids, these being excreted mainly as glycine conjugates with small amounts as the free acids or their conjugates with glucuronic acid. "Non-acidic" phenols (xylenols) accounted for 2-4% of the dose (Bray et al.,1949; Bray et al.,1950). The formation of xylenols from all three isomers was confirmed by Bakke and Scheline (1970) who found dimethylphenols in amounts equivalent to 0.1, 0.9 and 1% of the dose, respectively, in the urine of rats administered o-, m- or p-xylenes. Small amounts of 2-methylbenzyl alcohol were also found in the urine of the rats administered o-xylene, and 3-methylbenzyl alcohol was tentatively identified in the urine of those administered m-xylene. No 4-methylbenzyl-alcohool was found in the urine of the rats administered p-xylene.

The formation of arene oxides as intermediates in the metabolism of xylenes to xylenols has been suggested (Jerina et al.,1971; Kaubisch et al.,1972). Van Doorn et al.(1980) reported a decreased hepatic glutathione concentration in rats administered xylenes by i.p. injection, o-xylene being the most effective and causing a reduction of approximately 75%. Urinary thioether excretion was also enhanced in these animals and was most pronounced after the administration of o-xylene. In this case the compound was identified specifically as o-methylbenzyl mercapturic acid (10-20% of the administered dose) suggesting that

Proposed Mammalian Metabolism of Xylenes

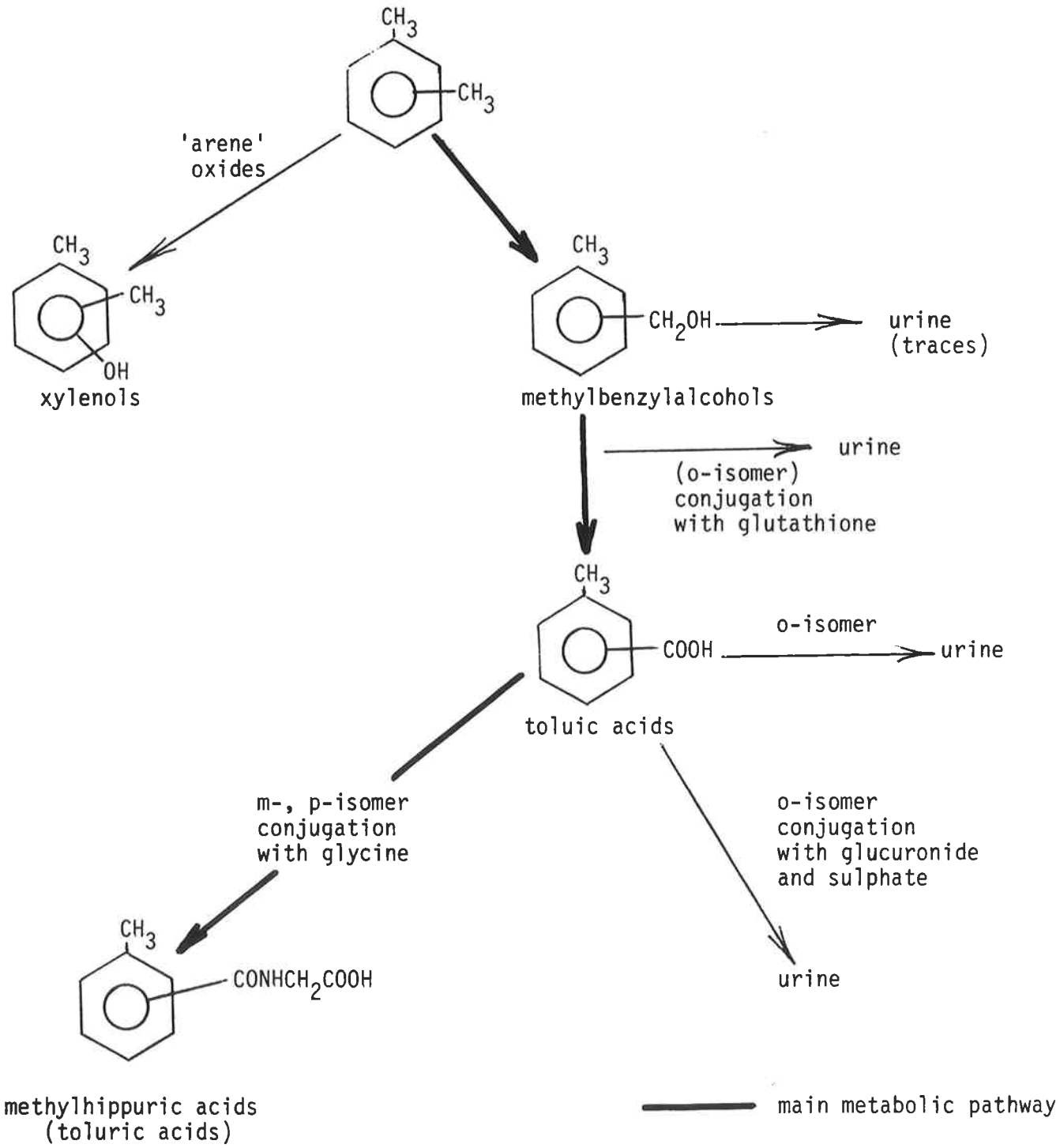

Fig. 1

a reactive intermediate resulting from side-chain metabolism rather than oxidation of the aromatic nucleus was responsible for the depletion of the hepatic glutathione.

Further studies (Van Doorn et al.,1981) have shown that not only xylenes but the corresponding alcohols are converted into thio-compounds and that methyl benzyl sulphates can alkylate the nucleophile 4-(p-nitrobenzyl) pyridine in vitro. These findings suggest that side-chain hydroxylation followed by sulphate ester formation is responsible for the reaction with glutathione. It was suggested that the high yield of mercapturic acids following o-xylene administration was due to, (a) the relatively low affinity of o-methylbenzyl alcohol for alcohol dehydrogenase, (b) the high affinity for sulphotransferase, and (c) the high electrophilic reactivity of the o-methylbenzyl sulphate compared with the other methylbenzyl alcohols and sulphate esters.

Patel et al.(1978-a-b) found that exposure of rabbits to 1000 ppm of p-xylene, 4 h/d for 1 or 2d, caused a loss of pulmonary microsomal p-xylene hydroxylase activity and cytochrome P450. They also found that in order to inactivate pulmonary cytochrome P450 in vitro, metabolic conversion of p-xylene to p-tolualdehyde was necessary. Since rabbit lung is deficient in aldehyde dehydrogenase (Carlone and Fouts, 1974) it was suggested that the inactivation of the lung enzymes in vivo was due to the formation of p-tolualdehyde in the liver which was then transported to the lung. Smith et al.(1982) were, however, unable to detect the release of p-tolualdehyde by livers perfused with ^{3}H-p-xylene, although they showed that derivatives covalently bound to protein were formed in perfused rabbit lungs, lending further support to the hypothesis that a reactive intermediate is formed. The inhibition of aldehyde dehydrogenases in the rat by disulphuram treatment has been found to have only a marginal effect on the hepatic oxidation of m-xylene in vitro, and on xylene-induced hepatic microsomal enzyme induction and glutathione depletion. Renal microsomal enzyme induction was found to be unaffected (Elovaara et al.,1982).

The induction of hepatic, and to a lesser extent renal, microsomal cytochrome P450 and related enzyme activities by xylenes has been reported by Savolainen et al.(1978); Toftgård et al.(1981); Elovaara et

al.(1980); Pyykko (1980) and Tatrai et al.(1981). The enzyme induction appeared to be of the "phenobarbitone type" (Toftgård et al.,1981) and of the three isomers p-xylene was the least potent inducer (Toftgård and Nilsen, 1982). The induction of microsomal enzymes by xylenes has been found to be potentiated by simultaneous exposure to ethanol (Savolainen et al.,1978; Elovaara et al.,1980).

The metabolic interaction of m-xylene and ethylbenzene simultaneously administered in rats was reported by Elovaara et al.(1984). In rats exposed 6 h/d for 5 days to different atmospheric concentrations of a 3:1 xylene/ethylbenzene mixture, the daily urinary output of xylene metabolites compared with ethylbenzene metabolites was lower than would be expected from the molar ratio in the inhaled mixture. The molar ratio of xylene and ethylbenzene in perirenal fat was the same as the ratio of the two solvents in expired air (which was considered to reflect the relative concentration in the blood). Xylene metabolites were excreted faster than were those of ethylbenzene with increasing dose and duration of exposure. On day 2 there was an abrupt increase in the metabolite excretion rate in the animals exposed to the 600/200 ppm mixture. This dose was subsequently found to increase hepatic microsomal metabolising activity.

H. ECOTOXICOLOGICAL DATA

1. Toxicity to Aquatic Organisms

The volatility of the xylenes presents technical difficulties in aquatic toxicity testing. Flow-through systems which allow the continual renewal of the xylene solution in the test vessel are necessary to maintain the concentration of such volatile materials. As the majority of the studies on fish, invertebrates and algae summarised in Table 3, 4 and 5 were performed under static conditions, which allowed losses by volatilisation, the results must be viewed carefully. The concentrations quoted in the Tables are expressed as norminal concentrations.

TABLE 3
Acute Toxicity of Xylenes to Fish

Species	LC_{50} (mg/l) ortho	meta	para	mixture	Reference
FRESHWATER					
- Rainbow trout (Salmo gairdneri)		3.8 (96h) embryo-larval stage		13.5 (96h) 6.7-10.0 (96h)	Walsh et al.(1977) Johnson and Finley (1980) Black and Birge (1982)
- Goldfish (Carassius auratus)	13 (24h)	16 (24h)	15 (24h)	37 (96h) soft H_2O	Bridié et al.(1979-a) Pickering and Henderson (1966)
- Zebra fish (Brachydanio rerio)				20 (48h)	Slooff (1979)
- Bluegill sunfish (Lepomis macrochirus)				12.1-15.0 (96h) 21 (96h) soft H_2O	Johnson and Finley (1980) Pickering and Henderson (1966)
- Fathead minnow (Pimephales promelas)				27 (96h) soft H_2O 29 (96h) hard H_2O	Pickering and Henderson (1966)
- Guppy (Poecilia reticulata)	40 (14d)	43 (14d)	40 (14d)	35 (96h) soft H_2O	Koenemann (1981) Pickering and Henderson (1966)
- Golden Orfe (Leucisus idus melanotus)				86 - 308 (48h)	Juhnke and Luedemann (1978
MARINE SPECIES					
- Striped bass (Morone saxatilis)	11 (96h)	9.2 (96h)	2 (96h)		Benville and Korn (1977)

TABLE 4
Acute Toxicity of Xylenes to Invertebrates

Species	LC_{50} or EC_{50} or LD_{50} : mg/l				Reference
	ortho	meta	para	mixture	
RUSTACEA					
reshwater					
Water flea (Daphnia magna)				32 (3h) >100<1000 (24h) 165 (24h) (immobilisation)	Nischiuchi (1981) Dowden and Bennett (1965) Bringmann and Kühn (1982)
larine					
· Bay shrimp (Crago franciscorum)	1.3 (96h)	3.7 (96h)	2.0 (96h)		Benville and Korn (1977)
Grass shrimp (Palaemonetes pugio)				7.4 (96h)	Rice et al. (1977)
Crab (Cancer magister)	6 (96h)	12 (96h)			Caldwell et al. (1977)
NSECTS					
Mosquito larvae (Aedes aegypti)				14 (24h)	Berry and Brammer (1977)

TABLE 5
Acute Toxicity of Mixed Xylenes to Algae

Species	EC_{50}(mg/l)	NEL(mg/l)	Reference
REEN ALGAE			
· Chlamydomonas angulosa	46 (3h) (photosynthesis)		Hutchinson et al. (1980).
· Chlorella vulgaris	105 (3h) (photosynthesis)		Hutchinson et al. (1980)
· Scenedesmus quadricauda		>200 (8d) (cell growth inhibition)	Bringmann and Kühn (1978)
LUE-GREEN ALGAE			
· Mycrocystis aeruginosa		>200 (8d) (cell growth inhibition)	Bringmann and Kühn (1978)

Cod eggs (Gadus morrhua) were exposed to sea water solutions of xylenes. Treatment during fertilisation with m- and p-xylene induced significant decreases in fertilisation rate at concentrations greater than 10 mg/l. The o-isomer, however, had little effect. All three isomers significantly affected the early cleavage pattern of fertilised cod eggs at concentrations of 2-7 mg/l (Kjorsvik et al.,1982).

Xylene has been found significantly to depress the maximal net photosynthesis in the marine diatom Phaeodactylum tricornutum after exposure to a concentration of 5 mg/l for 2 h (Kusk, 1981).

No ecotoxicity studies of longer duration were found in the literature and in view of the high volatility of xylenes are probably not appropriate.

Though the mechanisms of toxicity of the xylenes are not well understood, there is evidence suggesting that they increase the permeability of the cell membranes. This conclusion is drawn from a number of studies with xylenes and structurally-similar materials (Bernheim, 1974). Other studies by Morrow (1974) and Morrow et al.(1975) suggest that changes in gill permeability in Coho salmon result in ionic imbalance and CO_2 poisoning. These mechanisms are similar to those attributed to benzene, which has been extensively investigated.

2. Toxicity to Terrestrial Organisms

2.1. Invertebrates, insects

When 5 µl of "xylene" was topically applied to pupae of Sarcophaga crassipalpis (flesh fly), emergence of the adults was completely inhibited (Denlinger et al., 1980).

2.2. Higher plants

On exposing the leaves of the runner bean (Phaseolus multiflorus) and parsnip (Pastinaca sativa) to a range of vapour concentrations of hydrocarbons for 1 h it was found that there was a relatively small difference between concentrations causing no damage and those completely killing the leaves. It was therefore not possible to make precise EC_{50} estimates. The respective values of these concentrations were 4500 and 6700 ppm for o-xylene, and 5600 and 9200 ppm for p-xylene (Ivens, 1952).

2.3. Amphibia

Black and Birge (1982) treated the embryo larvae of the leopard frog (Rana pipiens) with m-xylene and found a 96 h LC_{50} of 3.5 mg/l.

3. Toxicity to Microorganisms

No-observed-effect levels are summarised in Table 6.

TABLE 6

Toxicity of Mixed Xylenes to Microorganisms

Species	No-Observed-Effect Level, (growth inhibition) mg/l	Reference
PROTOZOA		
- Saprozoic flagellate (Chilomonas paramaecium)	> 80 (48h)	Bringmann and Kühn (1981)
- Bacteriovorous flagellate (Entosiphon sulcatum)	> 160 (72h)	Bringmann and Kühn (1981)
- Bacteriovorous ciliate (Uronema parduczi)	> 160 (20h)	Bringmann and Kühn (1981)
BACTERIA		
- Pseudomonas putida	> 200 (16h)	Bringmann and Kühn (1977)

I. SUMMARY AND CONCLUSIONS

The largest sources of xylene emissions result from its use in gasoline and as a solvent. From the physico-chemical characteristics of the xylenes it can be concluded that xylenes will largely partition to the atmosphere where they will be rapidly phototransformed. Residual amounts present in the hydrosphere will rapidly biodegrade.

The calculated and experimentally-determined bioconcentration factors in aquatic species indicate that xylenes have a low bioaccumulation potential. A limited number of studies have shown that rapid depuration occurs following termination of exposure.

Experimental studies in animals show that xylenes have a low acute toxicity by the oral, dermal and inhalation routes. Like other hydrocarbons, xylenes are

skin irritants on repeated and prolonged contact, and both vapour and liquid xylenes cause reversible eye irritation.

In man, one death attributable to accidental, excessive xylene exposure has been reported. The effects most frequently found in man are respiratory irritation, gastrointestinal disturbances and narcosis. The CNS-depressant effects are reversible and appear to be similar to those produced by a large number of other organic solvents . In controlled studies on humans minimal CNS effects have been reported following exposure to xylene vapour. Although it has been suggested that long-term exposure leads to permanent damage to the CNS, the evidence for it is , as yet, unconvincing. Reversible impairment of liver and kidney function in man have also been reported after massive exposure to the vapour.

In many early reports in which a variety of haematological changes, including aplastic anaemia, were attributed to xylene exposure, concomitant exposure to benzene was either known or suspected. It is therefore probable that the observed blood dyscrasias were due to benzene rather than xylenes, a conclusion which is supported by the results of more recent animal studies showing that xylenes are devoid of the myelotoxic effects characteristic of benzene.

Xylenes cross the placenta in both animals and man. Case control studies have led to claims of an association between exposure to organic solvents (including xylene) during pregnancy and the occurrence of congenital malformations in the offspring. In the majority of cases exposure was to a variety of solvents and was ill-defined. These data on humans therefore provide only a tenuous link between exposure to xylenes and foetal malformations. However, recent teratology and multigeneration studies, in accordance with internationally-accepted procedures did not indicate that xylene have any teratogenic potential. Less extensive investigations have shown that they produce foetal loss, delays in foetal development, reduced foetal body weight and increases in the incidence of skeletal and soft-tissue anomalies. It has been suggested that the observed effects may be caused by hormonal imbalance resulting from the induction of hepatic mixed-function oxidase by xylenes. Overall, there is no clear evidence which suggests that xylenes have teratogenic potential.

An increased incidence of tumours of the oral cavity and of total tumours has been described in rats administered high oral doses of xylenes, but this study has not been reported in detail. Results from a recently-completed 2-year NTP

study in which rats and mice were administered xylenes by gavage, at doses which were the same as, or higher than, those in the previous study, provided evidence that xylenes are not carcinogenic. These data, together with the lack of demonstrable mutagenic/genotoxic potential in a number of different systems, suggest that it is unlikely that xylenes are carcinogenic.

Xylenes are readily absorbed via the respiratory tract, through the skin and from the gastrointestinal tract. They are distributed to a variety of tissues in amounts proportional to the fat content. In both animals and man most of the absorbed xylenes are metabolised by oxidation of one of the methyl groups to methyl benzoic acids which are readily excreted via the kidneys as a glycine or glucuronic acid conjugate. Small amounts of xylenols are also formed, and are thought to arise from a rearrangement of intermediate arene oxides. Xylenes have been shown to induce hepatic, and to a lesser extent, renal microsomal enzymes in a manner similar to that of phenobarbital.

Under static experimental conditions, mixed xylenes or the three xylene isomers appear slightly toxic to freshwater fish, invertebrates, algae and protozoa and are moderately toxic to marine fish and invertebrates. Taking into account their high volatility, rapid atmospheric phototransformation, biodegradability and aquatic toxicity, it is considered that the hazard of xylenes to aquatic organisms in the environment is low.

J. FIRST AID AND SAFE HANDLING ADVICE

1. First Aid and Medical Treatment

1.1. Inhalation

The patient should be removed to fresh air and kept warm and at rest. If breathing ceases, or becomes weak and irregular, artificial respiration should be applied and oxygen administered. Medical attention should be obtained.

1.2. Eye contact

The eyes should be thoroughly irrigated with eyewash solution or a large amount of water for at least 10 minutes. Medical attention should always be obtained.

1.3. Skin contact

Contaminated clothing should be removed and the affected area of the skin thoroughly flushed with water. Soap should be used if available. If skin irritation persists, medical attention should be obtained.

1.4. Ingestion

Vomiting should not be induced. The patient should be kept under medical surveillance as aspiration of xylene into the lungs may cause a chemical pneumonitis.

2. Safe Handling

2.1. Personal protection

Atmospheric levels should be kept as far as is reasonably practicable below the recommended occupational exposure limit. Skin and eye protection should be worn and suitable respiratory protection should be readily available.

2.2. Flammability/explosion hazards

Adequate ventilation should be provided and smoking prohibited. Any electrical equipment used should be protected against explosion and of a type in accordance with local legal requirements. Contact with sulphuric acid, nitric acid and strong oxidizers may cause fire and explosions.

2.3. Storage

Drums should be stored in a well-ventilated area away from sources of ignition, heat and sun. There is no limitation to the storage period but the maximum storage temperature should not exceed 40°C.

2.4. Transport precautions

The flow of xylenes, e.g. by pumping, may generate electrostatic charges, and therefore it should be insured that all equipment is adequately earthed.

3. Management of Spillages and Waste

3.1. Spillage

In all cases involving leaks, naked flames should be extinguished. Smoking and the formation of sparks must be avoided. Contact with the skin, eyes and clothing are to be avoided. Gloves, goggles (or a face shield) and boots should be worn, and breathing of the vapour avoided. The vapours are

heavier than the air and may spread along the floors, creating a risk of explosion and poisoning in closed, restricted areas.

For small-scale spillages the material should be absorbed on paper towels and the paper burnt in a suitable location, away from combustible materials.

For medium-scale spillages the liquid should be absorbed with sand or earth, shovelled up and removed to a safe place for subsequent disposal by burning. The contaminated area should be flushed with plenty of water.

For large-scale spillages, the spilt liquid should be prevented from spreading by the use of sand or earth. The liquid should be transfered to a salvage tank if possible, otherwise it should be treated as for small spillages. The local authorities (particularly the fire service) should be informed at once if the spilt liquid enters the surface-water drains since there will be an explosive hazard.

3.2. Disposal

Residues containing xylenes, whether from road/rail tanks, bulk storage or shipment should be collected for controlled disposal. The methods which are, in principle, available include re-use and burning. The residues should not be buried or dumped in a landfill. When selecting the disposal procedure, due consideration should be given to safety aspects and to any local or national regulations.

3.3. Fire

Fire extinguishers containing carbon dioxide, dry chemical or foam are recommended. Toxic gases (such as CO) may be released in a fire involving xylenes. Flashback along a vapour trail may occur.

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The TF acknowledges the help of Drs. R. Markerian and A. Maki from Exxon Corp., Research and Environmental Health Division, East Millstone, N.J.

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