ETHYLBENZENE

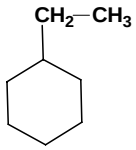
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 100-41-4
Chem. Abstr. Name: Ethylbenzene
IUPAC Systematic Name: Ethylbenzene
Synonyms: EB; ethylbenzol; α-methyltoluene; phenylethane

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_8H_{10} Relative molecular mass: 106.17

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid with an aromatic odour (Coty *et al*., 1987)
(*b*) *Boiling-point*: 136.1 °C (Lide & Milne, 1996)
(*c*) *Melting-point*: –94.9 °C (Lide & Milne, 1996)
(*d*) *Density*: 0.8670 g/cm^3 at 20 °C (Lide & Milne, 1996)
(*e*) *Spectroscopy data*: Infrared, ultraviolet [97], nuclear magnetic resonance and mass spectral data have been reported (Lide & Milne, 1996)
(*f*) *Solubility*: Slightly soluble in water (152 mg/L at 20 °C) (ECETOC, 1986) and chloroform; miscible with diethyl ether and ethanol (Lide & Milne, 1996)
(*g*) *Volatility*: Vapour pressure, 1.28 kPa at 25 °C (Lide & Milne, 1996); relative vapour density (air = 1), 3.7 (Verschueren, 1996); flash-point (closed-cup), 15 °C (Coty *et al*., 1987)

(*h*) *Octanol/water partition coefficient (P)*[1]: log P, 3.15 (Verschueren, 1996)
(*i*) *Conversion factor*[2]: $mg/m^3 = 4.34 \times ppm$

1.1.4 *Technical products and impurities*

Because ethylbenzene is used almost exclusively to produce styrene, the product specification on ethylbenzene is set to provide a satisfactory feedstock for styrene production. Levels of cumene, *n*-propylbenzene, ethyltoluenes and xylenes in ethylbenzene are controlled to meet the required styrene purity specification. A typical sales specification is as follows: purity, 99.5 wt% min.; benzene, 0.1–0.3 wt%; toluene, 0.1–0.3 wt%; *ortho*-xylene + cumene, 0.02 wt% max.; *meta*-xylene + *para*-xylene, 0.2 wt% max.; allylbenzene + *n*-propylbenzene + ethyltoluene, 0.2 wt% max.; diethylbenzene, 20 mg/kg max.; total chlorides (as chlorine), 1–3 mg/kg max.; and total organic sulfur, 4 mg/kg max. (Coty *et al*., 1987).

1.1.5 *Analysis*

Selected methods for the analysis of ethylbenzene in various matrices are given in Table 1. Ethylbenzene can be determined in biological material (blood, subcutaneous fat, plant foliage, fish samples) using head-space gas chromatography (GC), GC with mass spectrometry, and GC with flame ionization detection (WHO, 1996a).

Determination of mandelic acid in urine has been recommended as a biomarker of exposure to ethylbenzene. Several methods can be used to determine mandelic acid in urine samples. These include derivatization of the acid and GC analysis (detection limit, 1.0 mg/L); isotachophoresis (detection limit, 0.04 mmol/L); and high-performance liquid chromatography (detection limit, 0.01 mmol/L) (WHO, 1996a).

1.2 Production

Ethylbenzene was first produced on a commercial scale in the 1930s in Germany and the United States. The ethylbenzene–styrene industry remained relatively insignificant until the Second World War, when the demand for synthetic styrene–butadiene rubber prompted accelerated technology improvements and tremendous capacity expansion (Coty *et al*., 1987).

Almost all ethylbenzene is produced commercially by alkylating benzene with ethylene, either in the liquid phase with aluminium chloride catalyst or in the vapour phase with a synthetic zeolite or Lewis acid catalyst (Coty *et al*., 1987; Cannella, 1998).

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[1] Partition coefficients of ethylbenzene for other media (water/air, blood/air, oil/air, oil/water and oil/blood) have also been measured (Sato & Nakajima, 1979)

[2] Calculated from: $mg/m^3 = (\text{relative molecular mass}/24.45) \times ppm$, assuming a temperature of 25 °C and a pressure of 101 kPa

Table 1. Selected methods for the analysis of ethylbenzene

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Air	Adsorb (charcoal); desorb (carbon disulfide)	GC/FID	1–10 µg/sample	Department of Health and Human Services (1994) [NIOSH Method 1501]
Drinking, ground, and surface water	Purge (inert gas); trap (Chromosorb W); desorb into capillary GC column	GC/MS	0.03–0.06 µg/L	Environmental Protection Agency (1995a) [Method 524.2]
Drinking water and raw source water	Purge (inert gas); trap (Chromosorb W); desorb into capillary GC column	GC/PID	0.01–0.05 µg/L	Environmental Protection Agency (1995b) [Method 502.2]
Wastewater, municipal and industrial	Purge (inert gas); trap (Tenax or OV-1 on Chromosorb W); thermally desorb into GC column	GC/PID	0.2 µg/L	Environmental Protection Agency (1999a) [Method 602]
	Purge (inert gas); trap (Tenax or OV-1 on Chromosorb W or silica gel); thermally desorb into GC column	GC/MS	7.2 µg/L	Environmental Protection Agency (1999b) [Method 624]
	Add isotope-labelled analogue; purge (inert gas); trap (Tenax or OV-1 on Chromosorb W or silica gel); thermally desorb into GC column	GC/MS	10 µg/L	Environmental Protection Agency (1999c) [Method 1624B]
Solid waste matrices[b]	Purge (inert gas); trap (Tenax or Chromosorb W) *or* thermally desorb *or* headspace sampling *or* direct injection into capillary GC column	GC/PID	0.005 µg/L	Environmental Protection Agency (1996a) [Method 8021B]

Table 1 (contd)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
	Purge (inert gas); trap (Tenax or Chromosorb W) *or* thermally desorb *or* headspace sampling *or* direct injection into capillary GC column	GC/MS	0.03–0.06 µg/L	Environmental Protection Agency (1996b) [Method 8260B]

[a] Abbreviations: GC/FID, gas chromatography/flame ionization detection; GC/MS, gas chromatography/mass spectrometry; GC/PID, gas chromatography/photoionization detection
[b] Includes: groundwater, sludges, caustic and acid liquors, waste solvents, oily wastes, mousses, tars, fibrous wastes, polymeric emulsions, filter cakes, spent carbons, spent catalysts, soils, and sediments

Worldwide capacities for the production of ethylbenzene in 1985 and 1995 are presented in Table 2.

Information available in 1999 indicated that ethylbenzene was manufactured by nine companies in the United States, eight in Japan, seven in China, four in the Republic of Korea, two each in Brazil, Canada, France, Germany, Poland, Romania, the Russian Federation and the United Kingdom and one each in Australia, Belgium, Bulgaria, the Czech Republic, Iran, Italy, Mexico, the Netherlands, Singapore, Slovakia, Spain, Taiwan and the Ukraine (Chemical Information Services, 1999).

Table 2. Worldwide capacity for production of ethylbenzene in 1985 and 1995 (thousand tonnes)

Location	Capacity	
	1985	1995
North America	5900	7048
South America	380	NR
Western Europe	3820	5157
Eastern Europe	1630	1841
Japan	1470	3587
Asia, Oceania and Far East (except Japan)	640	2644
Other (including the Middle East and Africa)	390	1158
Total	14 230	21 435

From Coty *et al*. (1987); Cannella (1998)
NR, not reported

1.3 Use

Ethylbenzene is almost exclusively (> 99%) used as an intermediate for the manufacture of styrene monomer. Styrene production, which uses ethylbenzene as a starting material, consumes approximately 50% of the world's benzene production. Less than 1% of the ethylbenzene produced is used as a paint solvent or as an intermediate for the production of diethylbenzene and acetophenone. The ethylbenzene present in recovered mixed xylenes is largely converted to xylenes or benzene (Coty *et al*., 1987; Cannella, 1998).

Ethylbenzene has been added to motor and aviation fuels because of its anti-knock properties. Estimates of ethylbenzene in gasoline have ranged from < 1–2.7% (Fishbein, 1985; IARC, 1989; Backer *et al*., 1997).

Ethylbenzene is also used as a negative photoresist solvent in the semiconductor industry (Ladou & Rohm, 1998) and as a general solvent and diluent (Angerer *et al*., 1994).

Ethylbenzene is also present in commercial mixed xylenes at levels up to 25%, and, as such, is present in many paints and lacquers, printing inks, insecticides and solvents in the rubber and chemical manufacturing industries (Fishbein, 1985; ECETOC, 1986).

1.4 Occurrence

1.4.1 *Natural occurrence*

Ethylbenzene may occur naturally, as it has been found in orange peel, parsley leaves (Górna-Binjul *et al*., 1996), dried legumes (WHO, 1996a) and other foodstuffs.

1.4.2 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1999), as many as 200 000 workers in the United States were potentially exposed to ethylbenzene (see General Remarks). National estimates of workers potentially exposed in other countries were not available.

Measured airborne and blood concentrations of ethylbenzene in several occupational settings are presented in Tables 3 and 4, respectively. Most occupational exposures to ethylbenzene result from use of products containing technical grades of mixed xylenes. No ethylbenzene was found from off-gassing of cured paint in a hyperbaric pressure chamber under normal atmospheric pressure, but under higher pressures, levels of 0.4–4.5 ppm [1.7–19.5 mg/m^3] were measured (Lillo *et al*., 1990). Silk screen operations were found to entail exposure levels of less than 4 mg/m^3 (Verhoeff *et al*., 1988). Ethylbenzene may also be present in low-grade toluene preparations (Inoue *et al*., 1995).

Ethylbenzene exposure occurs in the chemical processing industries, including the rubber and plastics industries. Ethylbenzene emissions during the production of mixed

Table 3. Levels of occupational exposure to ethylbenzene

Source	Type of sample	Concentration[a] (mg/m^3)	Range[b] (mg/m^3)	No.[c]	Reference
Dip painting	Personal	AM, 10 ± 4.7 GM, 9.0 ± 6.6	Max., 22	30	Kawai *et al*. (1992)
Dip painting	Personal	GM, 3.9 ± 14	Max., 49	121	Kawai *et al.* (1991)
Varnishing and priming vehicles and metal pieces	Personal	AM, 4.0 ± 39	–	35	Angerer & Wulf (1985)
Varnishing and priming vehicles and metal pieces	Area	AM, 7.1 ± 16.4	–	192	Angerer & Wulf (1985)
Spray-painting aircraft	Personal	AM, 48.5	7.8–89.6	23	Vincent *et al*. (1994)
Paint or plastic-coated wire production or printing or painting workshops	Personal	GM, 7.8 ± 14.8	Max., 191	360	Inoue *et al.* (1995)
Oil refinery, outside (the control room) operators	Personal	AM, 0.08 ± 0.17	L&UCL, < 0.03–0.12	30	Rappaport *et al.* (1987)
Gasoline transport drivers	Personal	AM, 0.08 ± 0.10	L&UCL, 0.05–0.11	44	Rappaport *et al.* (1987)
Gasoline service station attendants	Personal	AM, 0.06 ± 0.06	L&UCL, 0.04–0.08	38	Rappaport *et al.* (1987)
Jet mechanics	Personal	GM, 0.02 ± 3.8	Max., 1.3	92[d]	Holm *et al.* (1987)
	Personal	GM, 0.07 ± 9.7	Max., 8.0	46[e]	
Coal-tar-free paving	Personal	AM, 0.09	< 0.03–1.27	77	Norseth *et al.* (1991)
Solvent used in histology laboratory	Area	AM, 178 ± 78 Med., 182	–	16[f]	Angerer & Lehnert (1979)
	Area	AM, 148 ± 61 Med., 161	–	16[f]	

[a] All 8-h time-weighted averages reported except as noted. AM, arithmetic mean ± arithmetic standard deviation; GM, geometric ± geometric standard deviation; Med., median
[b] Max., maximum level found; L&UCL, lower and upper confidence limits
[c] No., number of measurements
[d] 4-h TWA measurements
[e] 5-min TWA measurements
[f] 30-min TWA measurements taken consecutively during one day

Table 4. Ethylbenzene concentrations in the blood of occupationally exposed workers

Source	Concentration (μg/L)[a]	Range (μg/L)	No.[b]	Reference
Varnishing and priming vehicles and metal pieces	AM, 61.4 (SD, 62.3)	–	35	Angerer & Wulf (1985)
Before pumping regular gasoline	Med., 0.10	0.02–0.73	26	Backer *et al*. (1997)
After pumping regular gasoline	Med., 0.16	0.06–1.40	26	Backer *et al*. (1997)
Before pumping ethanol-blended gasoline	Med., 0.11	0.04–0.55	22	Backer *et al*. (1997)
After pumping ethanol-blended gasoline	Med., 0.16	0.06–0.64	22	Backer *et al*. (1997)
Solvent use in histology laboratory	AM, 69	50–80	4	Angerer & Lehnert (1979)
Nonsmoking firefighters in Kuwaiti oil fields	Med., 0.53	0.082–2.8	25	Etzel & Ashley (1994)

[a] AM, arithmetic mean; SD, standard deviation; Med., median
[b] No., number of measurements

xylenes occur from the reactor, distillation and crystallization vents, from storage units, from loading and handling of ethylbenzene and from leaks, so that xylene production workers are likely to have exposure. The total emissions of ethylbenzene from the catalytic reformate production of xylene in the United States in 1978 were estimated to have been 970 000 kg. Occupational exposure during the production of styrene was considered to be minimal or unlikely due to the enclosed nature of the styrene production process. Unfractionated crude oil contains 1–2.5% by weight of C_6–C_8 aromatics, mainly toluene, the xylenes and ethylbenzene, and oil refining therefore is also likely to result in exposures (Fishbein, 1985). Ethylbenzene has been detected in bitumen fumes during road paving (Norseth *et al.*, 1991).

Another source of occupational exposure to ethylbenzene is the production and handling of gasoline and other fuels in which it is a component (Rappaport *et al.*, 1987; Backer *et al.*, 1997).

A source of ethylbenzene exposure to physicians and nurses in the operating room may be electrocautery smoke generated from dissection of tissues and cauterization of blood vessels (36 μg/m^3 maximum detected in an area sample) (Sagar *et al*., 1996). Exposures to ethylbenzene from solvent use also occurred in a histology laboratory (Angerer & Lehnert, 1979).

1.4.3 *Environmental occurrence*

Ethylbenzene is widely distributed in the environment (principally due to its use as a solvent alone and as a component of mixed xylenes, and as a fuel additive), generally at very low levels in both ambient and indoor air, water, sediment soil and biota. Large quantities have been emitted during its production, use and disposal. The highest levels of ethylbenzene found in the environment are often associated with industrial operations, and it is one of the most commonly found substances at hazardous waste sites. Ethylbenzene is also found in motor vehicle emissions, some food samples, cigarette smoke and consumer products and has been detected in human and animal tissues (Fishbein, 1985; ECETOC, 1986; Lawryk *et al.*, 1995; WHO, 1996a; Agency for Toxic Substances and Disease Registry, 1997a,b; Environmental Protection Agency, 1999d).

Human exposure to ethylbenzene occurs mainly via inhalation of vapour and/or mist and, to a smaller extent, by dermal contact or ingestion. Ethylbenzene is produced by the incomplete combustion of natural materials, making it a component of smoke from forest fires and cigarettes. It is also a constituent of asphalt and naphtha (Agency for Toxic Substances and Disease Registry, 1997a; WHO, 1996a).

(*a*) *Air*

Ethylbenzene is ubiquitous in urban and rural atmospheres, resulting primarily from vehicle, petroleum and industrial emissions (ECETOC, 1986; Shah & Heyerdahl, 1988). Because of its high vapour pressure and low solubility, released ethylbenzene will disperse into the atmosphere. More than 99% of ethylbenzene can be expected in the air compartment (ECETOC, 1986; WHO, 1996a). Ethylbenzene undergoes atmospheric transformations with photolytically generated hydroxyl radicals, and an atmospheric half-life of about 65 hours has been estimated in the United States (Agency for Toxic Substances and Disease Registry, 1997a).

Air levels of ethylbenzene have been measured in Austria, Finland, Germany, Italy, the Netherlands, Sweden and the United States and were reported to range from < 2 µg/m^3 to > 100 µg/m^3 in urban areas (Table 5). Measurements in rural areas were lower (< 2 µg/m^3) (WHO, 1996a). The range of measured indoor air levels overlaps with those measured outdoors, but when outdoor and indoor levels are compared for a specific house, higher levels of ethylbenzene are usually found indoors (De Bortoli *et al.*, 1986; Minoia *et al.*, 1996; Wallace *et al.*, 1989). Other sources of emissions are consumer products such as solvents, adhesives, fabric and leather treatments, liquid process photocopiers and pesticides (Hodgson *et al.*, 1991; Sack *et al.*, 1992; Wallace *et al.*, 1987a,b; 1989; Kostiainen, 1995; WHO, 1996a; Agency for Toxic Substances and Disease Registry, 1997a).

Tobacco smoke is a major contributor to indoor air concentrations of ethylbenzene (Wallace & Pellizzari, 1986; Wallace *et al.*, 1987a,c). In an Environmental Protection Agency Total Exposure Assessment Methodology (TEAM) study carried out between

Table 5. Occurrence of ethylbenzene in air

Source	Arithmetic mean concentration (μg/m^3)	No.[a]	Location	Reference
Urban air	1.3–6.5 (median)	724	USA	Edgerton *et al.* (1989)
	1.1 (median)	8723	USA	Kelly *et al.* (1994)
	0.9–2.8	~1050	Netherlands	Guicherit & Schulting (1985)
	6.0–22.0 (annual means)	12	Germany	Bruckmann *et al.* (1988)
	7.4	15	Italy	De Bortoli *et al.* (1986)
	< 2	54	Austria	Lanzerstorfer & Puxbaum (1990)
	13	5	Germany	Seifert & Abraham (1982)
	6.2–100	260	Sweden	Jonsson *et al.* (1985)
Rural sites	< 2	NR	NR	WHO (1996a)
Indoor air (homes)	13	30	Germany	Seifert & Abraham (1982)
	3.2 2.41 (median)	50	Finland	
	10 (range, 1.5–161)	230	Germany	Gold *et al.* (1993)
	27	15	Italy	De Bortoli *et al.* (1986)
	6.46 (winter) 8.15 (spring) 4.35 (summer) 13.98 (autumn)	754	Canada	Fellin & Otson (1994)
	4.34	95	USA	Shah & Heyerdahl (1988)
	3.5–8.3	783	USA	Wallace & Pellizzari (1986)
	4–6	346	Italy	Minoia *et al.* (1996)
	0.8 nonsmokers (breath samples)	322	USA	Wallace & Pellizzari (1986)
	2.6 smokers (breath samples)	198	USA	Wallace & Pellizzari (1986)
	6.3 (median) (personal air monitoring)	347	USA	Wallace *et al.* (1986)
Indoor air (office buildings)	0.5 (geometric mean)	384	USA	Daisey *et al.* (1994)
	7.0–19	4	USA	Hodgson *et al.* (1991)

NR, not reported
[a] No., number of measurements

1980 and 1984 in the United States measuring the personal air exposures and exhaled breath concentrations for 198 smokers and 322 non-smokers, smokers showed significantly higher breath concentrations of ethylbenzene, compared to nonsmokers. The indoor air concentrations (geometric means) of ethylbenzene in homes with smokers ($n = 345$) were 8.3 μg/m^3 in the fall and winter, significantly higher ($p < 0.05$) than those

in homes without smokers (n = 164), 5.1 μg/m^3. The levels of ethylbenzene during the spring and summer in homes with smokers (n = 169) and homes without smokers (n = 105) were the same, 3.5 μg/m^3 (Wallace & Pellizzari, 1986). Nonsmokers exposed at work had significantly higher levels of ethylbenzene than unexposed nonsmokers (Wallace *et al.*, 1987c).

Ethylbenzene concentrations averaged over eight parallel commuter trips in an automobile and train in Gothenborg, Sweden were 17.9 and 2.1 μg/m^3, respectively (Löfgren *et al.*, 1991)

Ethylbenzene has been shown to be released from volatile organic chemical-laden wastewater in municipal sewer systems in the United States (Quigley & Corsi, 1995).

According to the Environmental Protection Agency (1999d) Toxics Release Inventory (TRI) in 1997, air emissions of ethylbenzene from 1005 industrial facilities were approximately 4 000 000 kg in the United States, which accounted for about 92% of the total environmental releases of ethylbenzene.

(*b*) *Water*

Ethylbenzene, usually at < 1 μg/L, is found only infrequently in drinking water from ground or surface sources (Table 6).

The levels of ethylbenzene in surface water are generally less than 0.1 μg/L in non-industrial areas. In industrial and urban areas, concentrations of up to 15 μg/L ethylbenzene have been reported (WHO, 1996a,b). The Commission of the European Communities also reported in 1976 that ethylbenzene levels in water were, in most cases, less than 1 μg/L (ECETOC, 1986).

Releases of ethylbenzene to water come from a variety of sources including: industrial discharges (Snider & Manning, 1982), fuel spillages (Tester & Harker, 1981), leaking petroleum pipelines or leaking underground storage tanks (Cotruvo, 1985), landfill leachate (Barker, 1987; Hallbourg *et al*., 1992; Chen & Zoltek, 1995; Beavers *et al*., 1996) and inappropriate disposal of wastes containing ethylbenzene (Eiceman *et al*., 1986).

Ethylbenzene was listed as one of the 58 most frequently detected chemicals associated with groundwater contamination in the United States. It was detected in over 4% of the surface water samples and 11% of the groundwater samples analysed at the 1177 National Priority List (NPL) sites (Agency for Toxic Substances and Disease Registry, 1997a).

Surface water discharges of ethylbenzene from 1005 industrial facilities in 1997 in the United States amounted to 2600 kg, which accounted for about 0.06% of the total environmental releases (4 280 000 kg), according to the Environmental Protection Agency (1999d) Toxics Release Inventory.

(*c*) *Soil and sediments*

Ethylbenzene can be released to soils from a variety of sources (Fishbein, 1985; ECETOC, 1986; WHO, 1996a; Agency for Toxic Substances and Disease Registry,

Table 6. Occurrence of ethylbenzene in water

Source	Arithmetic mean concentration of positive samples	Frequency of positive samples	Location	Reference
Drinking-water	0.8 µg/L	3/466	USA	Cotruvo (1985)
	0.94 µg/L (median)	2/280	USA	Westrick *et al.* (1984)
	0.87 µg/L (median)	3/321	USA	Westrick *et al.* (1984)
	0.74 µg/L (median)	1/186	USA	Westrick *et al.* (1984)
	< 1 µg/L	NR	Canada	Otson *et al.* (1982)
Seawater	1.8–22 ng/L	NR	USA	Gschwend *et al.* (1982)
	0.4–4.5 ng/L	8/8	USA	Sauer *et al.* (1978)
	46.3 ng/L	1/48	United Kingdom	Dawes & Waldock (1994)
Ambient surface water	< 5.0 µg/L (median)	110/1101	USA	Staples *et al.* (1985)
Polluted surface water	0.005–15 µg/L	2/2	Spain	Gomez-Belinchon *et al.* (1991)
	10–26 µg/L	NR	USA	Storage and Retrieval of Water Quality Information (1986)
Polluted groundwater	12–74 µg/L	NR	Canada	Barker (1987)
	7.5–1110 µg/L	4/4	United Kingdom	Tester & Harker (1981)
	30–300 µg/L	NR	Netherlands	Van Duijvenboden & Kooper (1981)
	92–450 µg/L	NR	USA	Stuermer *et al.* (1982)
Industrial effluents	10–100 µg/L	4/25	USA	Perry *et al.* (1979)
	> 100 µg/L	2/25	USA	Perry *et al.* (1979)
	< 3.0 µg /L (median)	101/1368	USA	Staples *et al.* (1985)
	1–2 µg /L	59/1475	USA	Cole *et al.* (1984)
	~35 µg/kg	1/1	USA	Snider & Manning (1982)

NR, not reported

1997a), including spillage of gasoline and other fuels (Tester & Harker, 1981; Sauer & Tyler, 1995), leaking underground storage tanks (Cotruvo, 1985), leaching from landfill sites (Barker, 1987) and disposal of solvents and household products such as paint, cleaning and degreasing solvents, varnishes and pesticides (Agency for Toxic Substances and Disease Registry, 1997a).

The median concentration of ethylbenzene found in sediment samples was 5.0 µg/kg dry weight, with ethylbenzene being detected in 11% of the 350 samples collected between 1980 and 1982 in the United States Environmental Protection Agency's STORET water quality database (Staples *et al.*, 1985).

Releases of ethylbenzene in 1997 to land from 1005 industrial facilities in the United States amounted to 24 590 kg, which accounted for about 0.4% of the total

environmental releases according to the Environmental Protection Agency (1999d) Toxics Release Inventory. An additional estimated 253 500 kg of ethylbenzene or 5.9% of total environmental releases were released via underground injection.

(*d*) *Food*

There are few data on concentrations of ethylbenzene in foodstuffs. It has been identified as a trace component in the volatiles from honey, jasmine, papaya, olive oil and cheese flavour and in the neutral component of roast beef flavour isolate (Min *et al*., 1979; Fishbein, 1985). Trace quantities of ethylbenzene have been detected in split peas (13 μg/kg), lentils (5 μg/kg) and beans (mean, 5 μg /kg; maximum 11 μg /kg (Lovegren *et al*., 1979). Concentrations of ethylbenzene in orange peel (23.6 ng/g dry weight) and in parsley leaves (0.257 μg/g dry weight) have been reported (Górna-Binjul *et al*., 1996).

Mean concentrations of ethylbenzene in freshwater fish samples in the Canadian Arctic in 1985 and 1986 ranged from 2.45 to 49.6 μg/kg in muscle tissue and from 1.81 to 46.3 μg/kg in liver tissue from turbot; in white fish muscle tissue samples, levels ranged from 7.46 to 104 μg/kg (Lockart *et al*., 1992). Ethylbenzene was detected in 43 of 138 fish samples at 16 of 42 sites in Japan in 1986, with concentrations ranging from 1.0 to 9.8 μg/kg wet weight (detection limit, 1 μg/kg wet weight) (WHO, 1996a).

Migration of ethylbenzene from polystyrene into various foods has been reported. The following ethylbenzene levels were found: sour milk beverages, < 2.5–6 μg/L; noodle soup, 15–21 μg/L; noodle curry, 89–153 μg/kg and wantan soup 9–28 μg/L (ECETOC, 1986). Migration of ethylbenzene from polystyrene containers into dairy products resulted in concentrations of ethylbenzene ranging from 2 to 4 μg/kg in yoghurt and 4 μg/kg for chocolate dessert (Ehret-Henry *et al*., 1994).

Ethylbenzene has been shown to migrate at levels of < 6–34 μg/kg from samples of thermoset polyester (containing up to 25 mg/kg ethylbenzene) into pork during cooking (Gramshaw & Vandenburg, 1995).

Concentrations of ethylbenzene were determined in olives and olive oils exposed to gasoline vapours from gasoline-powered engines, either on the tree or during storage. The concentrations of ethylbenzene in the air of storage sites ranged from 7 to 88 μg/m^3. Three days after storage, levels in oil in olives ranged from 15 to 55 μg/kg and in pressed oil from 6 to 60 μg/kg (Biedermann *et al.*, 1996).

(*e*) *Consumer products*

In a survey of volatile organic chemicals in 1159 household items including household cleaners and polishes, paint-related products, fabric and leather treatments, cleaners for electronic equipment, oils, greases and lubricants, adhesive-related products, automotive products and miscellaneous products, ethylbenzene was identified in 157 of 658 (24%) of the products tested. The highest mean concentrations and percentage of products in each category in which ethylbenzene was found were as follows: 7.2% w/w in 7.5% of automotive products, 2.4% w/w in 47.8% of paint-related

products and 1.0% w/w in 11.8% of fabric and leather treatment products (Sack *et al*., 1992; Agency for Toxic Substances and Disease Registry, 1997a).

(*f*) *Tobacco smoke*

In a 1962 study, levels of ethylbenzene in mainstream cigarette smoke from cigarettes of Argentina, Russia and the United Kingdom were found to range from 7 to 20 μg/g cigarette weight (typical cigarette weight is 1 g) (Johnstone *et al*., 1962). In the United States, the amount of ethylbenzene in mainstream smoke from a single cigarette containing 16 mg of tar and nicotine was 8 μg (Wallace *et al*., 1987c).

Hodgson *et al*. (1996) determined the concentration of several volatile organic chemicals related to the environmental tobacco smoke in smoking environments. The average emission factor for ethylbenzene for six brands of cigarettes was 101 μg per cigarette (range, 83–142 μg per cigarette). The average concentration of ethylbenzene in five smoking areas ranged from 1.3 to 8.7 $\mu g/m^3$.

Conkle *et al*. (1975) measured trace quantities of ethylbenzene in the expired air of eight male subjects ranging in age from 23 to 47 years. Ethylbenzene was detected in five of the eight subjects, (range, 0.78–14 μg/h), with smokers having the highest levels.

(*g*) *Human tissues*

Ethylbenzene was measured in the blood of 631 non-occupationally exposed people in the United States (as a subset of the Third National Health and Nutrition Examination Survey, at mean and median levels of 0.11 and 0.06 μg/L, respectively (Ashley *et al*., 1994). In an earlier study, the authors reported a mean ethylbenzene concentration of 0.12 μg/L in 13 blood samples (Ashley *et al*., 1992).

In venous blood samples collected from 13 non-smokers and 14 cigarette smokers, the concentrations of ethylbenzene tended to be higher in smokers. The median and mean levels of ethylbenzene in non-smokers were 431 and 651 ng/L, respectively (range, 175–2284 ng/L), compared with smokers with median and mean levels of 535 and 837 ng/L, respectively (range, 378–2697 ng/L) (Hajimiragha *et al*., 1989).

Ethylbenzene was detected (no concentrations reported) in human milk samples from eight of 17 lactating women in three urban areas in the United States (Pellizzari *et al*., 1982).

Ethylbenzene was measured in 96% of the 46 composite samples analysed for volatile organic chemicals in the 1982 National Adipose Tissue Survey conducted by the Environmental Protection Agency in the United States. Although a wet tissue concentration range of not detected (detection limit, 2 ng/g) to 280 ng/g was cited, the average concentration was not reported (Agency for Toxic Substances and Disease Registry, 1997a).

1.5 Regulations and guidelines

Occupational exposure limits for ethylbenzene are given in Table 7.

The determination of mandelic acid in urine is recommended as a biological exposure test for ethylbenzene. The Biological Exposure Index (BEI) Committee of the American Conference of Governmental Industrial Hygienists recommends a mandelic acid concentration in urine of 1.5 g/g creatinine [about 10 mmol/L] as a BEI for ethylbenzene exposure. BEIs represent the levels of the determinants that are most likely to be observed in biological samples collected from healthy workers exposed by inhalation to air concentrations at the level of the TLV. Urine specimens must be collected during

Table 7. Occupational exposure limits and guidelines for ethylbenzene

Country	Year	Concentration (mg/m^3)	Interpretation[a]
Australia	1993	435	TWA
		545	STEL
Belgium	1993	434	TWA
		543	STEL
Czech Republic	1993	200	TWA
		1000	STEL
Denmark	1993	217	TWA
Finland	1998	220	TWA
France	1993	435	TWA
Germany	1999	440 (sk)	TWA
Hungary	1993	100 (sk)	TWA
		200	STEL
Ireland	1997	435	TWA
		545	STEL
Japan	1993	435	TWA
Netherlands	1997	215 (sk)	TWA
Philippines	1993	435	TWA
Poland	1998	100 (sk)	TWA
		350	STEL
Russian Federation	1993	435	TWA
		50	STEL
Slovakia	1993	200	TWA
		1000	STEL
Sweden	1993	200	TWA
		450	STEL
Switzerland	1993	435	TWA
		1275	STEL
Turkey	1993	435	TWA
United Kingdom	1993	435	TWA

Table 7 (contd)

Country	Year	Concentration (mg/m^3)	Interpretation[a]
United States			
ACGIH (TLV)[b]	1999	435	TWA
NIOSH (REL)	1999	545	STEL
OSHA (PEL)	1999	435	TWA
		545	STEL
		435	TWA

From Finnish Ministry of Social Affairs and Health (1998); American Conference of Governmental Industrial Hygienists (ACGIH) (1999); Deutsche Forschungsgemeinschaft (1999)

[a] Abbreviations: TWA, time-weighted average; STEL, short-term exposure limit; sk, skin designation; PEL, permissible exposure limit; REL, recommended exposure limit; TLV, threshold limit value

[b] The following countries follow the exposure limits suggested by the ACGIH: Bulgaria, Colombia, Jordan, Republic of Korea, New Zealand, Singapore and Viet Nam

the last four hours of the last shift of the working week. The BEI Committee recommends the determination of ethylbenzene in end-exhaled air collected before the shift as a confirmatory test for ethylbenzene exposure. The concentration in end-exhaled air collected 16 hours after the fourth exposure of the working week should be about 2 ppm [8.7 mg/m^3] if the exposure at the TLV of 100 ppm [434 mg/m^3] is maintained (American Conference of Governmental Industrial Hygienists, 1999).

2. Studies of Cancer in Humans

Some 200 ethylbenzene-production workers in Czechoslovakia [exact number not stated] between 1964 and 1985 were monitored twice a year for mandelic acid excretion (Bardodej & Círek, 1988). The mean age of workers exposed to ethylbenzene was 36.6 years and their mean length of employment was 12.2 years. The authors stated that cancer incidence among chemical workers in the industrial complex (of comparable age and length of employment) not engaged in ethylbenzene production was about three times the national average, whereas in the group of ethylbenzene production workers, no tumours had been reported over the 10 previous years. [The Working Group noted that no precise figures were given to substantiate these assertions; in addition, co-exposure to benzene was present, and the age of the workers and length of follow-up were not sufficient for a proper evaluation of cancer risk in relation to exposure to ethylbenzene.]

A mortality study was conducted among 560 styrene production and polymerization workers employed for at least five years on 1 May 1960 at a plant in the United States (Nicholson *et al*., 1978). Exposures other than ethylbenzene included benzene, toluene and styrene. Follow-up covered the period from 1 May 1960 (or the 10th anniversary of employment in the plant) through 31 December 1975. Eighty-three deaths were observed versus 106.4 expected, including 17 cancer deaths (versus 21.0 expected). Among these, one death from leukaemia (0.79 expected) and one death from lymphoma (1.25 expected) occurred. A further review of additional death certificates from recent years revealed additional cases of leukaemia and lymphoma. [The Working Group noted that these figures were not formally included in the follow-up period for which the analysis was performed and should be interpreted as a case report. Ethylbenzene was a raw material used in the production of styrene, and it is reasonable to assume its presence through the remainder of the process, albeit at low levels, because it has been detected in polystyrene food packaging (Section 1.4.3(*d*)). This study does not permit the evaluation of cancer risk among ethylbenzene-exposed workers, since mortality data are not presented separately for this group].

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

Rat: Groups of 50 male and 50 female Sprague-Dawley rats, seven weeks of age, were administered 0 or 800 mg/kg bw ethylbenzene (purity, 99.57%) by stomach tube in 1 mL extra-virgin olive oil solution daily on four days per week for 104 weeks. The experiment was terminated at 123 weeks. In a second experiment, groups of 40 male and 40 female Sprague-Dawley rats received 500 mg/kg bw ethylbenzene per day according to the same regimen, while 50 male and 50 female Sprague-Dawley rats comprised control groups receiving olive oil only. In this second experiment, the rats were permitted to live out their life span, up to 145 weeks. Survival was affected by treatment in both experiments, being recorded as an 'intermediate reduction' in animal numbers in both males and females. At 800 mg/kg, there was an increase in the incidence of tumours of the nasal cavity [type unspecified] (2% incidence in females versus 0% in controls) and neuroesthesioepitheliomas (6% in males versus 0% in controls) and a borderline increase in oral cavity cancer (6% in females versus 2% in controls) (Maltoni *et al.*, 1985, 1997). [The Working Group noted the lack of details on numbers of animals with specific tumours, adjustments for survival, historical control data, and statistical analysis.]

3.2 Inhalation exposure

3.2.1 *Mouse*

Groups of 50 male and 50 female B6C3F$_1$ mice, six weeks of age, were exposed to ethylbenzene (purity, > 99%; impurities included 62 ± 3 ppm cumene) by inhalation in whole-body exposure chambers at concentrations of 0, 75, 250 or 750 ppm [0, 325, 1083 or 3250 mg/m^3] for 6 h per day on five days per week for 103 weeks. The dose levels were selected on the basis of results from 13-week studies. Survival and body weights of the exposed and control groups were similar. There were statistically significant increases in the incidences of alveolar/bronchiolar adenomas in high-dose (750 ppm) males and of hepatocellular adenomas + carcinomas in high-dose (750 ppm) females (see Table 8). These neoplastic lesions were accompanied by statistically significant increases in the incidence of alveolar epithelial metaplasia in the lungs of high-dose males and of eosinophilic foci of cellular alteration in the livers of high-dose females (Chan *et al*., 1998; National Toxicology Program, 1999). [The Working Group noted that the statistically significant increases related only to adenomas in both liver and lung and that these increased incidences were within the historical control range.]

3.2.2 *Rat*

Groups of 50 male and 50 female Fischer 344/N rats, six weeks of age, were exposed to ethylbenzene (purity, > 99%) by inhalation in whole-body exposure chambers at concentrations of 0, 75, 250 or 750 ppm for 6 h per day on five days per week for 104 weeks. Survival was similar among the female groups (31/50, 31/50, 34/50 and 35/49 at 0, 75, 250 and 750 ppm, respectively) but was significantly decreased in the high-dose males compared with that of control males (15/50, 14/50, 13/50 and 2/50 at 0, 75, 250 and 750 ppm, respectively). The mean body weights of exposed males and females were 5–10% lower than those of the control animals. As shown in Table 9, there was a statistically significant increase in incidence at the high dose (750 ppm) in males of renal tubule adenomas and carcinomas combined after standard (single section) evaluation. After step-sectioning of the kidney, additional adenomas elevated the increase in the incidence of renal tumours in females also to statistical significance. Accompanying the neoplastic lesions in the kidneys was a significant increase in the incidence of focal renal tubule hyperplasia, judged to be a precursor stage of adenoma, in high-dose males after standard (single section) evaluation and at the high dose in both males and females after step-sectioning of the kidney (Chan *et al*., 1998; National Toxicology Program, 1999).

Table 8. Incidence of primary tumours in B6C3F$_1$ mice exposed to ethylbenzene by inhalation

Tumour site	Animals with tumours							
	Males				Females			
	0 ppm	75 ppm	250 ppm	750 ppm	0 ppm	75 ppm	250 ppm	750 ppm
Liver adenomas	0/50	0/50	0/50	0/50	6/50	9/50	12/50	16/50*
Liver carcinomas	0/50	0/50	0/50	0/50	7/50	4/50	3/50	12/50
Lung adenomas	5/50	9/50	10/50	16/50**	4/50	4/50	5/49	8/50
Lung adenocarcinomas	2/50	1/50	5/50	3/50	0/50	2/50	0/49	0/50

From National Toxicology Program (1999)
* $p < 0.05$, logistic regression test
** $p < 0.01$, logistic regression test

Table 9. Incidence of primary tumours in Fischer 344 rats exposed to ethylbenzene by inhalation

Tumour site	Animals with tumours							
	Males				Females			
	0 ppm	75 ppm	250 ppm	750 ppm	0 ppm	75 ppm	250 ppm	750 ppm
Single sections								
Kidney adenomas	0/50	3/50	2/50	4/50*	0/50	0/50	0/50	1/50
Kidney carcinomas	0/50	0/50	1/50	3/50				
Kidney adenomas and carcinomas combined	0/50	3/50	3/50	7/50**				
Step sections								
Kidney adenomas and carcinomas	3/50	2/50	8/50	18/50**	0/50	0/50	1/50	7/50*
Combined								
Kidney adenomas and carcinomas	3/50	5/50	8/50	21/50**	0/50	0/50	1/50	8/50**

From National Toxicology Program (1999)
* $p < 0.05$, logistic regression test
** $p < 0.01$, logistic regression test

3.3 Carcinogenicity of metabolites

1-Phenylethanol [α-methylbenzyl alcohol]

3.3.1 *Oral administration*

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, nine to 10 weeks of age, were administered 1-phenylethanol (food grade) by gavage at doses of 0, 375 and 750 mg/kg bw in corn oil five times per week for 103 weeks. Body weight was decreased in both males (6–18%) and females (8–16%) at the high dose. No significant difference in survival was observed in either sex. There was no increase in the incidence of tumours in either sex (National Toxicology Program, 1990).

Rat: Groups of 50 male and 50 female Fischer 344 rats, seven to eight weeks of age, were administered 1-phenylethanol (food grade) by gavage at doses of 0, 375 and 750 mg/kg bw in corn oil on five days per week for 103 weeks. Survival in males in both the low-dose (after week 86) and high-dose groups was significantly lower than that of the controls. The survival of the high-dose female rats was significantly lower than that of the vehicle controls after week 40. Renal tubule adenomas were observed in males: 0/50 control, 1/50 mid-dose and 5/50 high-dose groups ($p < 0.05$, Fisher's exact test; $p = 0.011$, Cochran-Armitage trend test). One carcinoma was observed in low-dose males. Additional step-sections on kidneys resulted in a further increase in the number of adenomas: 1/50 control, 7/50 low-dose and 10/50 high-dose animals. No significant tumour response was observed at any other site in either males or females (National Toxicology Program, 1990) [The Working Group noted the poor survival both in males and females due to accidental deaths related to gavage.]

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

Ethylbenzene is a significant component of technical xylenes (see Section 1.4.2). The toxicology of these products has been reviewed (WHO, 1997). Xylenes themselves have been evaluted by IARC as not classifiable as to their carcinogenicity to humans (Group 3) (IARC, 1999).

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Ethylbenzene is rapidly absorbed after inhalation exposure of humans, as shown by the excretion of ethylbenzene metabolites and tissue retention of ethylbenzene in exposed workers and volunteers (Engström & Bjurström, 1978; Engström, 1984a; Drummond *et al.*, 1989). There occurs rapid absorption upon dermal application of

ethylbenzene as the neat liquid (absorption rate, 22–33 mg/cm^2/h) or as an aqueous solution (rate, 118–215 μg/cm^2/h) (Dutkiewicz & Tyras, 1967).

The metabolism of ethylbenzene in humans occurs along one major pathway which is oxidation at the α-carbon, yielding 1-phenylethanol (also called α-methylbenzyl alcohol) as the primary product. A metabolic scheme is presented in Figure 1. The α-carbon of ethylbenzene is a prochiral centre and hydroxylation thus yields a chiral product. The issue of stereoselectivity has been addressed in animal studies (see Section 4.1.2).

While some 1-phenylethanol is excreted in the urine as its glucuronic acid conjugate, its major fate is oxidation to acetophenone, which involves loss of the chiral centre. The majority of the acetophenone undergoes oxidation at the ω-carbon, giving the α-keto alcohol, ω-hydroxyacetophenone. In addition, small amounts of the ring-hydroxylation products *para*- and *meta*-hydroxyacetophenone are excreted in the urine. The further metabolism of ω-hydroxyacetophenone is both complex and obscure. This compound undergoes carbonyl reduction giving the chiral diol, 1-phenyl-1,2-ethanediol (also referred to as phenylethyleneglycol), while the primary alcohol may be oxidized to an aldehyde, giving phenylglyoxal. Taken together, these three compounds, ω-hydroxyacetophenone, phenylglyoxal and 1-phenyl-1,2-ethanediol are the precursors of three metabolites, namely mandelic acid, phenylglyoxylic acid and benzoic acid (excreted as hippuric acid, its glycine conjugate), but the exact interrelationships are uncertain (Engström, 1984a; Korn *et al.*, 1992).

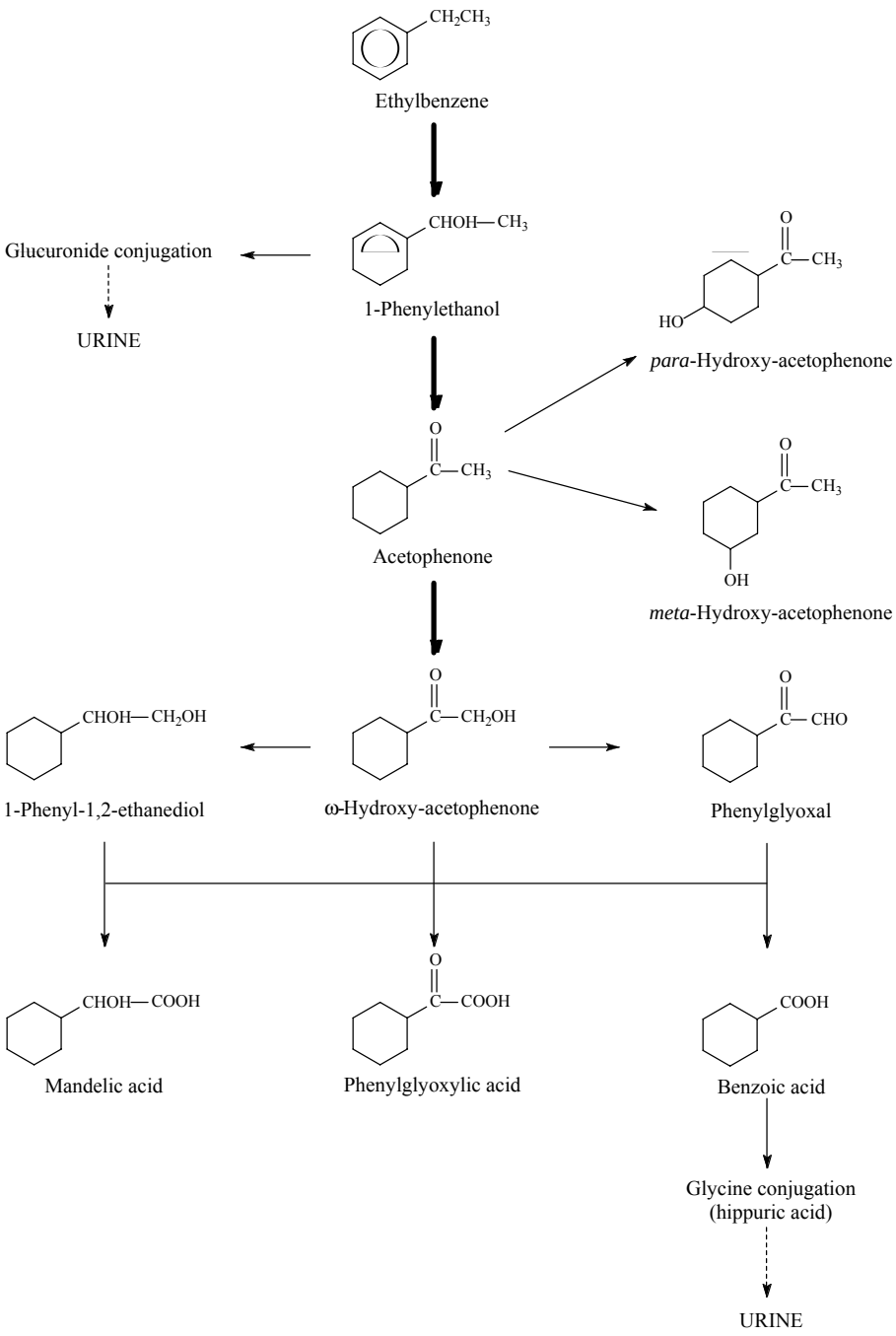
It is interesting to note that the mandelic acid excreted in human urine after exposure to ethylbenzene is predominantly the *R*-enantiomer, in contrast to the 1.2:1 mixture of *R*- and *S*-mandelic acid excreted after styrene exposure. Styrene and ethylbenzene share many common metabolic pathways, but there are evident differences in their stereoselectivity between the two compounds and this provides a means for selective monitoring of exposure to these solvents (Drummond *et al*., 1989; Korn *et al.,* 1992).

4.1.2 *Experimental systems*

When rats were kept for 6 h in an atmosphere containing [^{14}C]ethylbenzene, radioactivity was found in organs and tissues, including intestine, kidney, liver and adipose tissue for up to 42 h afterwards (Chin *et al*., 1980). Blood concentrations of ethylbenzene in rats after a 2-h inhalation were proportional to its concentration in the atmosphere (Freundt *et al*., 1989). After exposure to an atmosphere containing 600 ppm [2.60 g/m^3] ethylbenzene for 6 h, peak blood levels of ethylbenzene occurred at the end of the exposure, falling rapidly thereafter. Ethylbenzene was detected in brain, liver, kidney and adipose tissue; the time courses of brain, liver and kidney concentrations were broadly similar to those in the blood, but there was considerable retention in adipose tissue (Elovaara *et al.,* 1990).

Ethylbenzene was well absorbed through the skin of HRS/J hairless mice, the absorption rate being 37 ± 31 μg/cm^2/min (Susten *et al*., 1990).

Figure 1. Metabolism of ethylbenzene



From Engström (1984b)

The pattern of urinary metabolites in animals is qualitatively similar to that described for humans (see Section 4.1.1). In the rat, the principal pathway is α-hydroxylation to 1-phenylethanol, ultimately leading to excretion of *R*-mandelic acid and phenylglyoxylic acid as major metabolites. Another pathway is oxidation at the ω-carbon of the side-chain giving rise to 2-phenylethanol, which is further oxidized to phenylacetic acid. Minor metabolites found in rat urine include 1-phenylethanol, ω-hydroxyacetophenone and benzoic and phenylacetic acids, together with their glycine conjugates, hippuric and phenaceturic acids (Engström, 1984a,b; Drummond *et al.*, 1989).

After exposure to atmospheres containing 300 and 600 ppm [1.30 and 2.60 g/m^3] ethylbenzene for 6 h, Wistar rats excreted 83% and 59% of the estimated dose as ethylbenzene metabolites in the urine in 48 h, respectively. The principal metabolites were 1-phenylethanol, ω-hydroxyacetophenone and phenylacetic, mandelic, phenylglyoxylic and benzoic acids, accompanied by smaller amounts of 1-phenyl-1,2-ethanediol, phenylglyoxal, acetophenone and *para*-hydroxyacetophenone (Engström, 1984b).

When Wistar rats were exposed to 50, 300 or 600 ppm [0.22, 1.30 and 2.60 g/m^3] ethylbenzene intermittently for up to 16 weeks, the urinary recovery of metabolites increased with dose but not linearly. The metabolic pattern of ethylbenzene was affected by exposure level but not by the duration of administration. The amounts of 1-phenylethanol and ω-hydroxyacetophenone increased with increasing exposure, but those of phenylglyoxylic acid and hippuric acid decreased (Engström *et al.*, 1985).

The stereochemical aspects of the fates of 1-phenyl-1,2-ethanediol and mandelic acid in rats have been examined by Drummond *et al*. (1990). The proportions of a dose of 1-phenyl-1,2-ethanediol converted to phenylglyoxylic and mandelic acids depend upon its stereochemistry. The *R*-diol is preferentially converted to *R*-mandelic acid (30% of the dose in 48 h) with 15% of the dose as phenylglyoxylic acid. In contrast, after administration of the *S*-diol, the major product is phenylglyoxylic acid (46% of the dose) with 16% as mandelic acid (*R*/*S* 80:20).

S-Mandelic acid undergoes a chiral inversion, possibly by reversible oxidation to phenylglyoxylic acid. When *S*-mandelic acid was administered, some 80% of the dose was recovered as phenylglyoxylic acid in 48 h with 16% as mandelic acid (*R*/*S* 80:20). However, when racemic mandelic acid was given, 46% was excreted as phenylglyoxylic acid and 47% as *R*-mandelic acid.

4.2 Toxic effects

4.2.1 *Humans*

In a long-term study (~20 years) of about 200 ethylbenzene production workers exposed to an undefined concentration of this compound, none of the workers showed changes in haematological parameters or serum enzyme levels as a measure of liver function (Bardodej & Círek, 1988).

4.2.2 *Experimental systems*

The acute oral LD_{50} (lethal dose for 50% of the animals) of ethylbenzene has been estimated to be 3.5–5.5 g/kg body weight (bw) in rats (Wolf *et al*., 1956; Smyth *et al*., 1962). Smyth *et al*. (1962) reported the LC_{50} (lethal concentration in air for 50% of the animals) in female rats to be 4000 ppm [17.3 g/m^3] for a 4-h exposure.

(*a*) *In-vivo studies*

Male New Zealand White rabbits (2200 g) were exposed to 750 ppm [3.25 g/m^3] ethylbenzene for 12 h per day for seven days. Twelve or 24 h following the final day of exposure, the rabbits were killed and their brains dissected. Ethylbenzene depleted both striatal and tubero-infundibular dopamine levels (Mutti *et al*., 1988). In male Sprague-Dawley rats exposed to 2000 ppm [8.70 g/m^3] ethylbenzene for 6 h per day for three consecutive days and killed 16–18 h following the last exposure, ethylbenzene increased dopamine and noradrenaline levels and turnover in the hypothalamus and the median eminence. Ethylbenzene exposure also reduced the secretion of prolactin and increased dopamine turnover within the dopamine–cholecystokinin-8 immunoreactive nerve terminals of the nucleus accumbens (Andersson *et al*., 1981).

In a series of studies described by Wolf *et al.* (1956), female rats and male and female rats (strain not indicated) were administered ethylbenzene by gavage (13.6, 136, 408 or 680 mg/kg bw per day) or inhalation (400, 600 or 1250 ppm [1.74, 2.60 or 5.42 g/m^3] for 7–8 h per day respectively, for 6–7 months. Rabbits (1 or 2 per concentration) and guinea-pigs (5–10 per concentration) were exposed to 400, 600 or 1250 ppm ethylbenzene and rhesus monkeys (1 or 2 per concentration) to 400 and 600 ppm ethylbenzene for 6–7 months. Toxicity was evaluated by the following criteria: appearance and behaviour, haematological findings, blood urea nitrogen, organ and body weights, histopathological findings and bone marrow counts [no details were provided on these specific measurements of toxicity and the results were reported as indicators of an effect: slight (+) or moderate (++)]. No haematological changes were induced by ethylbenzene in any species. In rats, ethylbenzene caused an increase in kidney and liver weight with slight cloudy swelling in the liver and of the renal tubular epithelium, following both gavage and inhalation exposure. Liver weights were slightly increased in guinea pigs and monkeys exposed to 600 ppm ethylbenzene, with slight histopathological effects noted in the testes of rabbits and monkeys.

Male and female Fischer 344 rats (six weeks of age) and $B6C3F_1$ mice (seven to nine weeks of age) and New Zealand White rabbits were exposed by inhalation to 0, 99, 382 or 782 ppm [0, 0.43, 1.66 or 3.40 g/m^3] ethylbenzene and 0, 382, 782 or 1610 ppm [0, 1.66, 3.40 or 6.99 g/m^3] ethylbenzene, respectively, for 6 h per day on five days per week for four weeks. At 782 ppm, both rats and mice exhibited an increase in mean liver weight and liver-to-body weight ratio. There were no alterations in clinical chemistry, urinalysis or gross or microscopic changes in any of the species tested that were attributable to exposure to ethylbenzene. The authors noted that the

absence of abnormalities in liver histopathology and clinical chemistry indicates that these increases were due to adaptive induction of hepatic mixed-function oxidase rather than toxicity (Crag *et al*., 1989). This has been supported by the investigations described below, demonstrating that ethylbenzene induces rat cytochrome P450 (Toftgård & Nilsen, 1982; Elovaara *et al*., 1985).

Liver and kidney microsomes were prepared from male Sprague-Dawley rats (200–300 g) exposed by inhalation to 2000 ppm [8.70 g/m^3] ethylbenzene for 6 h per day for three days. Exposure to ethylbenzene caused an increase in hepatic cytochrome P450 concentration and in the hydroxylation of *n*-hexane and benzo[*a*]pyrene. NADPH-cytochrome c reductase and 7-ethoxyresorufin *O*-deethylation activity was increased in both liver and kidney microsomes (Toftgård & Nilsen, 1982). Elovaara *et al*. (1985) demonstrated that exposure of male Wistar rats (~ 342 g) by inhalation to 0, 50, 300 or 600 ppm [0, 0.22, 1.30 or 2.60 g/m^3] ethylbenzene for two, five, nine or 16 weeks caused a dose-related increase in hepatic microsomal protein content along with increased NADPH-cytochrome c reductase, 7-ethoxycoumarin-*O*-deethylase and UDP-glucuronosyl-transferase activities. The latter two activities increased in a concentration-dependent manner in kidney microsomes. Ethylbenzene did not deplete liver glutathione, but slightly increased kidney glutathione levels. At 600 ppm ethylbenzene, there was no increase in serum alanine aminotransferase activity and liver cells showed slight proliferation of smooth endoplasmic reticulum but no necrosis.

In one study, Yuan *et al*. (1997a) demonstrated that daily intraperitoneal injections for three days of 10 mmol/kg bw ethylbenzene to male Holtzman rats (seven weeks of age) modulated the levels of various cytochrome P450 isozymes, each of which exhibited different temporal characteristics. Yuan *et al*. (1997b) also evaluated the induction pattern of various cytochrome P450s with time following a single intraperitoneal injection of 10 mmol/kg bw ethylbenzene to male Holtzman rats. The forms found to be induced were CYP1A1, CYP2B1/2 and CYP2E1.

A 13-week inhalation study of ethylbenzene was conducted by exposing male and female Fischer 344/N rats and B6C3F$_1$ mice to 0, 100, 250, 500, 750 or 1000 ppm [0, 0.43, 1.1, 2.2, 3.3 or 4.3 g/m^3] ethylbenzene for 6 h per day for five days per week. No mortality was observed and the mean body weight gains of the exposed rats and mice did not differ from those of the respective controls. Signs of toxicity included increased absolute and relative liver, lung and kidney weights in exposed rats and an increase in liver weights in exposed mice. There was no evidence of histological changes in these studies (National Toxicology Program, 1992).

Chronic inhalation exposure to 0, 75, 250 or 750 ppm [0, 0.32, 1.1 or 3.3 g/m^3] ethylbenzene for 6 h per day on five days per week for 104 weeks caused an increased incidence of renal tubule hyperplasia in male Fischer 344/N rats and increased severity of spontaneous, age-related chronic progressive nephropathy in males and females. Male B6C3F$_1$ mice developed an increased incidence of alveolar epithelial metaplasia, syncytial alterations of hepatocytes, hepatocellular hypertrophy, hepatocyte necrosis and thyroid gland follicular-cell hyperplasia. Exposure to ethylbenzene also caused an

increase incidence of eosinophilic foci of the liver, pituitary gland hyperplasia and thyroid gland follicular-cell hyperplasia in female mice (National Toxicology Program, 1999).

(*b*) *In-vitro studies*

Neural membranes isolated from primary astrocyte cultures established from new-born Sprague-Dawley rat cerebella were exposed to 3, 6 or 9 mmol/L ethylbenzene for 1 h. ATPase activity decreased linearly with log concentration of ethylbenzene (Naskali *et al*., 1994). In the same astrocyte cultures, ethylbenzene (3, 6 or 9 mmol/L; 1-h exposure) decreased in a dose-dependent manner the activity of important membrane integral proteins such as Na^+/K^+-ATPase and Mg^{2+}-ATPase (Vaalavirta & Tahti, 1995).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

(*a*) *Developmental toxicity studies*

In an inhalation study, rabbits were exposed to 100 or 1000 ppm [0.43 or 4.3 g/m^3] ethylbenzene for 6–7 h per day on gestational days 1–24 and sacrificed on the day before term. A significantly reduced number of live fetuses per litter was found at both exposure levels, although the number of implantations per litter and the number of dead or resorbed fetuses per litter did not differ significantly from those of the controls. In rats (strain not specified) similarly exposed during gestational days 1–19, there was a significant increase in the incidence of extra ribs at both doses (Hardin *et al*., 1981).

An increased rate of anomalies (of uropoietic apparatus + extra ribs) and weight retardation were seen in CFY rats exposed to 2400 mg/m^3 ethylbenzene for 24 h per day during days 6–15 of gestation. Similar exposure to 600 or 1200 mg/m^3 ethylbenzene induced skeletal retardation in the fetuses. Maternal effects were moderate and dose-dependent (not specified further). In CFLP mice exposed to 500 mg/m^3 ethylbenzene intermittently 4 h three times per day on gestational days 6–15, increased rates of anomalies (the same as in rats) were found. In New Zealand White rabbits, inhalation exposure to 1000 mg/m^3 ethylbenzene for 24 h per day on gestational days 7–20 induced abortions (with decreased maternal weight gain). Exposure to 500 mg/m^3 led to lower fetal weight in female offspring (Ungváry & Tátrai, 1985).

(*b*) *Reproductive toxicity studies*

No studies of the effects of ethylbenzene on fertility were available.

No testicular abnormalities were reported in Fischer 344 rats and B6C3F$_1$ mice exposed to ethylbenzene concentrations of up to 782 ppm [3.40 g/m^3] and in New Zealand White rabbits exposed to ethylbenzene at concentrations of up to 1610 ppm [6.99 g/m^3] for 6 h per day on five days per week for four weeks (Crag *et al.*, 1989). [The Working Group noted the small number of animals (five per sex per group) used].

Sperm or vaginal cytological evaluations of Fischer 344/N rats and B6C3F$_1$ mice exposed to ethylbenzene concentrations of up to 1000 ppm [4.34 g/m^3] for 6 h per day on five days per week for 13 weeks revealed no changes from normal (National Toxicology Program, 1992).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 10 for references)

Ethylbenzene has been found consistently to be non-mutagenic in bacteria, yeast and insects. It did not cause chromosomal aberrations in mammalian cells. It was inactive in inducing sister chromatid exchanges in Chinese hamster embryo cells, but was very weakly positive in cultured human lymphocytes. It did not induce micronuclei in in-vivo test systems but, *in vitro*, it was positive in Syrian hamster embryo cells. It also caused cell transformation in these cells at the highest concentration tested. At the highest non-lethal concentration, an increase in mutant mouse lymphoma L5178Y cell colonies was induced by ethylbenzene in both the absence and presence of an exogenous metabolic system.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Ethylbenzene is a major industrial chemical produced by alkylation of benzene. The pure chemical is used almost exclusively for styrene production. It is also present at up to 25% in technical grades of mixed xylenes and up to 15% in gasoline.

Occupational exposure to ethylbenzene may occur by inhalation during its production and use. Most occupational exposures are related to technical grades of mixed xylenes used as solvents in various paints and coatings, inks, insecticides and in rubber and plastic production, as well as from the production and handling of gasoline and bitumen. Ethylbenzene from these sources as well as from vehicle emissions is ubiquitous at μg/m^3 levels in ambient air. It is a component of tobacco

Table 10. Genetic and related effects of ethylbenzene

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, TA1535, TA1537, TA98, reverse mutation	–	–	318 µg/plate	Florin *et al.* (1980)
Salmonella typhimurium TA100, TA1535, TA1537, TA1538, TA98, reverse mutation	–	–	400 µg/plate	Nestmann *et al.* (1980)
Salmonella typhimurium TA100, TA1535, TA1537, TA1538, TA98, reverse mutation	–	–	2000 µg/plate	Dean *et al.* (1985)
Salmonella typhimurium TA100, TA1535, TA98, TA97, reverse mutation	–	–	1000 µg/plate	Zeiger *et al.* (1992); National Toxicology Program (1999)
Escherichia coli, WP2 and WP2 *uvrA*, reverse mutation	–	–	2000 µg/plate	Dean *et al.* (1985)
Pseudomonas putida, mutation	–		vapour; ≤ 40 d	Leddy *et al.* (1995)
Saccharomyces cerevisiae, mitotic gene conversion	–	–	NR	Dean *et al.* (1985)
Saccharomyces cerevisiae, mitotic gene conversion and reversion	–	NT	NR	Nestmann & Lee (1983)
Mutation, mouse lymphoma L5178Y cells *in vitro*	+	NT	80	McGregor *et al.* (1988); National Toxicology Program (1999)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	–	100	National Toxicology Program (1999)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	–	125	National Toxicology Program (1999)
Chromosomal aberrations, rat liver epithelial cells *in vitro*	–		NG	Dean *et al.* (1985)
Micronucleus formation, Syrian hamster embryo cells *in vitro*	+		25	Gibson *et al.* (1997)
Cell transformation, Syrian hamster embryo cells *in vitro*	+		200	Kerckaert *et al.* (1996)
Sister chromatid exchange, human lymphocytes *in vitro*	(+)		1060	Norppa & Vainio (1983)

Table 10 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus formation, male mouse bone-marrow erythrocytes *in vivo*	–		650 ip × 2	Mohtashamipur *et al.* (1985)
Micronuclei, male and female B6C3F$_1$ mouse peripheral blood erythrocytes *in vivo*	–		1000 ppm inh, × 6 h/d, 5 d/w, 13 w	National Toxicology Program (1999)

[a] +, positive; (+), weak positive; –, negative
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; ip, intraperitoneal; inh, inhalation; d, day; w, week

smoke and of several household products. These various sources contribute to indoor air levels that are often higher than adjacent outdoor levels. Ethylbenzene is only rarely found in drinking-water but is found at μg/kg levels in a variety of foodstuffs.

5.2 Human carcinogenicity data

Two studies of workers potentially exposed to ethylbenzene in a production plant and a styrene polymerization plant were available. In the first study, no excess of cancer incidence was found but the description of methods was insufficient to allow proper evaluation of this finding. In the second study, no cancer mortality excess was observed during the follow-up of 15 years.

5.3 Animal carcinogenicity data

Ethylbenzene was tested by inhalation exposure in single experiments in mice and rats. In mice, it increased the incidence of lung adenomas in males and of liver adenomas in females. In male rats, it increased the incidence of renal tubule adenomas and carcinomas. An increase in the incidence of renal adenomas was seen in females only after step-sectioning. A study in rats by oral administration could not be evaluated. A metabolite of ethylbenzene, 1-phenylethanol, increased the incidence of renal tubule adenomas in male rats.

5.4 Other relevant data

Ethylbenzene is well absorbed from the skin, lungs and gastrointestinal tract. It is virtually completely metabolized, the primary pathways being hydroxylation of the two carbons of the side-chain, followed by further oxidation to a range of metabolites that are excreted principally in the urine. The fate of ethylbenzene is similar in animals and humans.

Limited data were available to evaluate the toxic effects of ethylbenzene in humans. Liver and kidney weights were increased in rats following exposure to ethylbenzene with no signs of hepatic necrosis. Cytochrome P450 enzymes were induced in both liver and kidney of ethylbenzene-exposed rats. Ethylbenzene caused changes in dopamine levels in brain and prolactin secretion in rats exposed for three to seven days. In rat brain cell cultures, ethylbenzene decreased the activity of several integral membrane enzymes.

No data on reproductive or developmental effects of ethylbenzene in humans were available. In rats and mice, developmental retardation and an increased incidence of variations were reported after inhalation exposure during pregnancy. Reduced numbers of live pups per litter or abortions were reported in rabbits exposed during pregnancy. No changes in sperm motility or estrous cyclicity were found in rats or mice exposed to ethylbenzene for 13 weeks.

Ethylbenzene was non-mutagenic in bacteria, yeast and insects. In mammalian cells, it was inactive in inducing sister chromatid exchanges in Chinese hamster embryo cells but very weakly positive in cultured human lymphocytes. It did not induce micronuclei *in vivo*, although it was positive in Syrian hamster embryo cells *in vitro*. It also caused cell transformation in these cells. Ethylbenzene induced mutations in the mouse lymphoma assay, but only at the highest non-lethal concentration tested.

5.5 Evaluation

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

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethylbenzene.

Overall evaluation

Ethylbenzene is *possibly carcinogenic to humans (Group 2B)*.

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