

FOREWORD

INTRODUCTION

ETHYLBENZENE
CAS N°:100-41-4

SIDS Initial Assessment Report

For

SIAM 14

March 26-28, 2002, Paris, France

- 1. Chemical Name:** Ethylbenzene
- 2. CAS Number:** 100-41-4
- 3. Sponsor Country:** United States and Germany

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4. Shared Partnership with:

5. Roles/Responsibilities of the Partners:

- Name of industry sponsor /consortium
- Process used

6. Sponsorship History

- How was the chemical or category brought into the OECD HPV Chemicals Programme ?
Documents were initially prepared for consideration at SIAM 11 however, additional review by sponsor countries and industry was necessary. Documents were prepared and reviewed by industry prior to submission to sponsor countries. Sponsor countries conducted reviews of submitted data and offered comments to industry. Data searches consisted of searching available literature, databases and internal consortia files.

7. Review Process Prior to the SIAM:

8. Quality check process:

9. Date of Submission: Deadline for circulation: February 1, 2002

Date of Circulation: February 1, 2002

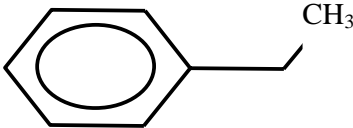
10. Date of last Update:

11. Comments:

Testing: No testing (X)

Testing ()

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-41-4
Chemical Name	Ethylbenzene
Structural Formula	
RECOMMENDATIONS	
The chemical is a low priority for further work.	
SUMMARY CONCLUSIONS OF THE SIAR	
Human Health	
<p>Ethylbenzene is readily absorbed following inhalation, oral, and dermal exposures, distributed throughout the body, and excreted primarily through urine. There are two different metabolic pathways for ethylbenzene with the primary pathway being the α-oxidation of ethylbenzene to 1-phenylethanol, mostly as the R-enantiomer. The pattern of urinary metabolite excretion varies with different mammalian species. In humans, ethylbenzene is excreted in the urine as mandelic acid and phenylglyoxylic acids; whereas rats and rabbits excrete hippuric acid and phenaceturic acid as the main metabolites. Ethylbenzene can induce liver enzymes and hence its own metabolism as well as the metabolism of other substances. Ethylbenzene has a low order of acute toxicity by the oral, dermal or inhalation routes of exposure. Studies in rabbits indicate that ethylbenzene is irritating to the skin and eyes. There are numerous repeat dose studies available in a variety of species, these include: rats, mice, rabbits, guinea pig and rhesus monkeys. In a 13 week inhalation repeat-dose study in male and female rats, mild body weight or organ weight (kidney, liver, lung) effects occurred at doses ≥ 250 ppm without any accompanying histopathological or clinical chemistry changes, as a result these findings were not considered toxicologically significant. In chronic toxicity/carcinogenicity studies, both rats and mice were exposed via inhalation to 0, 75, 250 or 750 ppm for 104 weeks. In rats, the kidney was the target organ of toxicity, with renal tubular hyperplasia noted in both males and females at the 750 ppm level only. In mice, the liver and lung were the principal target organs of toxicity. In male mice at 750 ppm, lung toxicity was described as alveolar epithelial metaplasia, and liver toxicity was described as hepatocellular syncytial alteration, hypertrophy and mild necrosis; this was accompanied by increased follicular cell hyperplasia in the thyroid. As a result the NOAEL in male mice was determined to be 250 ppm. In female mice, the 750 ppm dose group had an increased incidence of eosinophilic foci in the liver (44% vs 10% in the controls) and an increased incidence in follicular cell hyperplasia in the thyroid gland. In addition, female mice exposed to 250 ppm and 750 ppm had an increase in hyperplasia of the pituitary gland. As a result, the NOAEL for female mice was 75 ppm. Hearing loss has been reported in rats (but not guinea pigs) exposed to relatively high exposures (<i>400 ppm and greater</i>) of ethylbenzene. Ethylbenzene was negative in bacterial gene mutation tests and in a yeast assay on mitotic recombination. In mouse lymphoma assays, positive responses were only observed at doses with excess cytotoxicity. No clear conclusion can be drawn from the chromosomal aberration tests <i>in vitro</i>. A single <i>in vitro</i> micronucleus test without S-9 mix was positive. An <i>in vitro</i> SCE test was clearly negative with and without S-9 mix. With <i>in vivo</i> tests, negative findings were obtained in micronucleus tests and in a mouse liver UDS test. In studies conducted by the U.S. National Toxicology Program, inhalation of ethylbenzene at 750 ppm resulted in increased lung tumors in male mice, liver tumors in female mice, and increased kidney tumors in male and female rats. No increase in tumors was reported at 75 or 250 ppm. Ethylbenzene is considered to be an animal carcinogen, however, the relevance of these findings to humans is currently unknown. Although no reproductive toxicity studies have been conducted on ethylbenzene, repeated-dose studies indicate that the reproductive organs are not a target for ethylbenzene toxicity. Furthermore, in the 13-week NTP studies with rats and mice, no effects were observed for</p>	

sperm, testicular morphology, spermatid counts, sperm motility, caudal or epididymal weights, or length of estrous cycle. Developmental toxicity studies have been conducted in the rabbit and rat with developmental effects (14% increase in incidence in pups with supernumerary ribs) observed in the rat only at 1,000 ppm ethylbenzene. Maternal effects in the dams at this dose consisted of increases in liver (approximately 22%), kidney (approximately 10%), and spleen (approximately 10%) weights in the absence of histopathology changes.

Environment

Ethylbenzene has the following physical chemical properties: molecular weight, 106.2; Log Kow, 3.15; water solubility, 169 mg/l at 25°C ; vapor Pressure, 1270 Pa (1.27 kPa); melting point, -95°C; Henry's Law Constant, 798.1 Pa.m³/mol. Ethylbenzene partitions to air from water and soil, and is degraded in air. Ethylbenzene is volatile and when released will quickly vaporize. Photodegradation is the primary route of removal in the environment. Photodegradation is estimated with a half-life of 1 day. Ethylbenzene is considered inherently biodegradable and removal from water occurs primarily by evaporation but in the summer biodegradation plays a key role in the removal process. Level I and Level III fugacity modeling indicate that partitioning is primarily to the air compartment, 98 and 96%, respectively. Ethylbenzene is inherently biodegradable in water and in soil under aerobic conditions, and not rapidly biodegradable in anaerobic conditions. Ethylbenzene is expected to be moderately adsorbed to soil. In acute aquatic toxicity testing LC₅₀ values range approximately between 1 and 10 mg/l. In acute aquatic fish tests (fresh water species), the 96-hr LC₅₀ for *Pimphales promelas* and *Oncorhynchus mykiss* are 12.1 and 4.2 mg/L, respectively. Data are available in the saltwater species *Menidia menidia* and give results within the same range as for the fresh water species with a 96-hr LC₅₀ = 5.1 mg/L. In fresh water invertebrate species *Daphnia magna* and *Ceriodaphnia dubia*, 48-hr LC₅₀ values were 1.81 and 3.2 mg/L, respectively. Additional data is available in the saltwater species *Crangon franciscorium* (96-hr LC₅₀ = 0.49 mg/L) and *Mysidopsis bahia* (96-hr LC₅₀ = 2.6 mg/L). In 96-hr algal toxicity testing, results indicate that ethylbenzene inhibits algae growth in *Selenastrum capricornatum* at 3.6 mg/L and in *Skeletonema costatum* at 7.7 mg/L. Based on measured data, ethylbenzene is not expected to bioaccumulate (BCF 1.1 – 15).

Exposure

Ethylbenzene is an industrial chemical that is primarily produced and further reacted to make styrene in a closed continuous process; thus, occupational exposures are expected to be very low. In addition, ethylbenzene occurs in crude oil and as a component of mixed xylenes, which is used in gasoline or as a solvent. Emissions and exposures from solvent use are not well characterized. Ethylbenzene has been detected in urban and rural air and water samples at ppt to low ppb concentrations. Exposure to the general population is possible through extremely low ambient air concentrations, primarily due to gasoline and automobile emissions.

NATURE OF FURTHER WORK RECOMMENDED

Regional and national exposure and risk assessments are ongoing. This chemical is a substance of the 1st EU Priority List. An in-depth risk assessment will be performed within the framework of the EU Risk Assessment Programme under Regulation 793/93. This chemical is also to undergo review in the US Voluntary Children's Chemical Evaluation Programme and additional testing of reproductive toxicity (two generation study), adult neurotoxicity, and immunotoxicity is planned.

FULL SIDS SUMMARY

STUDY (CAS NO.: 100-41-4)	SPECIES	PROTOCOL	RESULTS
PHYSICAL CHEMISTRY			
2.1	Melting Point		-95° C
2.2	Boiling Point		136.25° C
2.3	Density		0.867 g/mL @ 20° C
2.4	Vapor Pressure		1.27 kPa (9.53 mmHg) at 25° C
2.5	Partition Coefficient		log Pow = 3.13 – 3.15
2.6	Water Solubility		140 mg/l at 15° C, 152 mg/l at 20° C 169 mg/l at 25° C
	pKa		
ENVIRONMENTAL FATE AND PATHWAY			
3.1.1	Photodegradation		T _{1/2} = 1 day (OH) T _{1/2} = 1400 days (O ₃)
3.1.2	Stability in Water	Estimated	T _{1/2} = 13 days (winter) T _{1/2} = 20 days (spring) T _{1/2} = 0.1 day (summer)
3.2	Monitoring Data		<p>There were a total of 1727 personal monitoring samples (8-hour time-weighted averages) representing exposures of process operators, maintenance workers, loading/unloading, quality laboratory workers and supervisory/professional workers. Of these data, approximately 71% of the exposures were either non-detectable or less than 0.1 ppm, 25% were between 0.1 ppm to 1.0 ppm, 4% were greater than 1.0 ppm and less than 5 ppm, and 0.4% were greater than 5 ppm (4 of 6 samples were less than 9 ppm, 2 samples unspecified). Thus, worker exposure during production of ethylbenzene is consistently very low.</p> <p>In the U.S., ambient air concentrations of ethylbenzene are generally less than 1 - 2 ppb. Ethylbenzene has been found in U.S. municipal drinking water supplies at levels up to 4 ppb (µg/l).</p>
3.3	Environmental fate & distribution	Estimate Level III	Air – 96.10 Water – 0.89% Soil – 2.99%
3.5	Biodegradation	OECD 302C	81% after 14 days
3.7	Bioaccumulation	Measured	BCF = 1.1 - 15
ECOTOXICOLOGICAL DATA			
4.1	Acute Fish	<i>Menidia menidia</i> <i>Pimephales promelas</i> <i>Oncorhynchus mykiss</i>	flow-through, TSCA 797.1440 flow-through static, OECD 203
			96 hr LC50 = 5.1 mg/l ^a 96 hr LC50 = 12.1 mg/l ^a 96 hr LC50 = 4.2 mg/l ^b

STUDY (CAS NO.: 100-41-4)		SPECIES	PROTOCOL	RESULTS
4.2	Acute Daphnid	<i>Mysidopsis bahia</i> <i>Daphnia magna</i> <i>Crago franciscorium</i> <i>Ceriodaphnia dubia</i>	flow-through EPA Method F static static static EPA Whole Effluent Testing Program method	96 hr LC50 = 2.6 mg/l ^a 48 hr EC50 = 1.81-2.38 mg/l ^a 96 hr EC50 = 0.49 mg/l ^a 48 hr LC50=3.2 mg/l ^a
4.3	Acute Aquatic Plant	<i>Selanastrum capricornatum</i> <i>Skeletonema costatum</i>	growth rate, TSCA 797.1050 growth rate, TSCA 792.1050	96 hr EC50 = 3.6 mg/l ^a 96 hr EC50 = 7.7 mg/l ^a
4.4	Toxicity to Bacteria			
4.5.	Chronic Toxicity (Invertebrates)	<i>Ceriodaphnia dubia</i>	static EPA Whole Effluent Testing Program method	7 day LC50=3.6 mg/l ^a 7 day IC50 (repro)= 3.3 mg/l ^a 7 day LOEL (repro)= 1.7 mg/l ^a 7day NOEL (repro) =1.0 mg/l ^b
4.6.2	Toxicity to Terrestrial Plants	<i>Phaseolus multiflorus</i>	leaf kill	EC50 ~ 27 mg/l, vapor in air, 1 hour
TOXICOLOGICAL DATA				
5.1.1	Acute Oral	rat		LD50 = 3.5 to 4.7g/kg
5.1.2	Acute Inhalation	rat		4 hr LC50 = 17.4 mg/l (4000 ppm)
5.1.3	Acute Dermal	rabbit		LD50 = 15.4 g/kg
5.1.4	Acute Other Routes			
5.2.1	Skin Irritation	rabbit		irritating
5.2.2	Eye Irritation	rabbit		irritating
5.2.3	Skin Sensitization	Human	patch test	Negative
5.4	Repeated Dose	F344 Male and Female Rats B6C3F1 mice, male and female Rats (F344) and mice (B6C3F1) Rabbits F344 rats, male and female B6C3F1 mice, male B6C3F1 mice, female	13 weeks (OECD 413) 13 weeks (OECD 413) 28-days 28 day 2-years 2-years 2-years	NOAEL = 1000 ppm (4335 mg/m ³) NOAEL = 1000 ppm or 4335 mg/m ³ (study did not actually assign a NOAEL) NOAEL = 382 ppm (1656 mg/m ³) NOAEL = 728 ppm (3390 mg/m ³) NOAEL = 250 ppm (1084 mg/m ³) NOAEL = 250 ppm (1084 mg/m ³) NOAEL = 75 ppm (325 mg/m ³)
5.5	Genetic Toxicity In Vitro			
A	Bacterial	<i>S. typhimurium</i> <i>S. Cervisae</i> <i>E. coli</i>	Ames Assay With and w/out activation	Negative Negative Negative

B	Non-Bacterial	Mouse	Mouse lymphoma Assay	Positive at 80 µg/ml
		Mouse	Mouse lymphoma Assay (3 trials) with and w/out activation	1 st Trial: (w/out), definitive positive at 34 and 69 µg/ml; (with activation), limited positive at 825 µg/ml. 2 nd and 3 rd trials: Inconclusive negative.
		Rat liver cells	Chromosome Aberration	Negative
		Chinese Hamster Ovary Cells	Chromosome Aberration	Negative
		Chinese Hamster Ovary Cells	Sister Chromatid Exchange	Negative
		Syrian Hamster Embryo	Micronucleus	Positive
		Syrian Hamster Ovary Cells	Cell Transformation	24 hr: Negative up to 500µg/ml 7-days: Positive at 150 and 200 µg/ml
5.6	Genetic Toxicity In vivo	B6C3F1 mice	Micronucleus (inhalation)	Negative
		NMRI mice	Micronucleus (i.p)	Negative
		B6C3F1 mice	UDS (inhalation)	Negative
5.7	Carcinogenicity	F344/N rats, male and female	Inhalation, 104 weeks at 0, 75, 250 or 750 ppm (0, 325, 1084, or 3252 mg/m ³)	750 ppm, there was an increased incidence of renal tubule adenomas and combined renal tubule adenoma/carcinomas based on combined original kidney sections and additional step-sectioning of the kidneys. The incidence of renal tubule carcinomas was not significantly elevated. In females, no renal tubule carcinomas were found. However, at 750 ppm, there was an increased incidence of renal tubule adenomas. In males exposed to 750 ppm, there was a slight, but significant, increase in the incidence of testicular interstitial cell adenoma. However, these slides were re-examined along with the 13-week study and it was determined that the apparent increase in renal tumors was strongly associated with Chronic Progressive Nephropathy or CPN, a spontaneous age-related disease of rodents with no identical counterpart in humans. CPN occurred in the 750 ppm animals, markedly so in the male rats, and modestly so in the females. In addition, there was a high incidence of high-dose rats that had end-stage CPN, a terminal condition where

		B6C3F1 mice, male and female	Inhalation, 103 weeks at 0, 75, 250 or 750 ppm (0, 325, 1084, or 3252 mg/m ³)	<p>the kidneys are so morphologically altered that renal failure (as well as secondary hyperthyroidism) occurs.</p> <p>Exposure to ethylbenzene had no meaningful effect on survival or body weight gain. In the lung at 750 ppm, male rats exhibited increased alveolar epithelial metaplasia, but there was no increase in alveolar hyperplasia. There was increased incidence of alveolar/bronchiolar adenomas and of combined alveolar/bronchiolar adenoma/carcinomas in male mice exposed to 750 ppm. Incidences of lung tumors at 75 and 250 ppm were not significantly different from the control incidence and were within the historical control range. In the liver, females, exposed to 750 ppm had an increased incidence of eosinophilic foci, a lesion which is judged to be a precursor of hepatocellular adenomas. The incidence of eosinophilic foci in either males or females exposed to 250 or 75 ppm were not significantly different from the control incidences. However, increased incidences of syncytial alteration, hypertrophy and necrosis in the liver of males exposed to 750 ppm ethylbenzene. There was a significantly increased incidence of hepatocellular adenomas in females at 750 ppm and combined hepatocellular adenoma/carcinomas. The incidence of tumors in females exposed to 75 and 250 ppm were not significantly different from the control incidences. In males there was no increase in liver tumors at any exposure concentration.</p> <p>The lung and liver sections of mice from the National Toxicology Program (NTP) two-year bioassay were re-evaluated. This re-evaluation revealed an increased incidence of male and female mice of the 750 ppm exposure group with decreased eosinophilia of the terminal bronchiolar epithelium. Also, a dose-related increased incidence in multifocal hyperplasia of the bronchiolar epithelium with extension to the peribronchiolar alveolar epithelium was observed in all male treated groups and mid- and high-exposure females. The author noted that the necrotic hepatocytes in the high-dose males were usually that of a coagulation-type necrosis of single or small groups of cells, usually the enlarged, hypertropied centrilobular hepatocytes. The morphology of this necrosis was histomorphologically different from</p>
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				<p>“apoptosis.” Also, the syncytial cells were not the predominant cell type with necrosis.</p> <p>There were also increased follicular cell hyperplasia in the thyroid gland in both the 750 ppm males and females; and hyperplasia in the pituitary gland in the 250 and 750 ppm females.</p>
5.8	Reproductive Toxicity	F344 Fischer Rats and B6C3F1 mice	Inhalation, 13 weeks at 100, 500, or 1000 ppm (0, 434, 2168, or 4335 mg/m ³)	There were no treatment-related effects on sperm, testicular morphology, length of estrus cycle, spermatid counts, sperm motility, caudal or epididymal weights.
5.9	Developmental Toxicity/Teratogenicity	Female, Wistar Rats Rabbits	Inhalation, 1-19 days gestation at 0, 100, or 1000 ppm (0, 434, or 4335 mg/m ³) Inhalation, 1-24 days gestation at 0, 100 or 1000 ppm	<p>Developmental effects were limited to increased incidence (14%) of skeletal variations (supernumerary ribs) at 1000 ppm. Maternal toxicity was observed only at 1000 ppm, and included increased liver, kidney, and spleen weight changes (approximate change of 22%, 10%, and 10%, respectively), with no accompanying histopathological effects. NOAEL (maternal and developmental toxicity) is considered to be 100 ppm(434 mg/m³).</p> <p>No developmental effects; maternal toxicity (increased liver weights) was observed in the 1000 ppm only. The NOAEL for both maternal and developmental toxicity is considered to be 100 ppm (434 mg/m³) and 1000 ppm (4335 mg/m³), respectively</p>
5.10	Toxicokinetics			<p>The principal route of excretion from both oral and inhalation exposure is through urine. Two very different metabolic pathways for ethylbenzene have been cited in the literature through the alpha- or omega-oxidation of the side chain by various cytochrome P450 isozymes to 1- and 2-phenylethanol, respectively. The major pathway is the alpha-oxidation of ethylbenzene to 1-phenylethanol, mostly as the R-enantiomer. The subsequent intermediates are acetophenone, omega-hydroxyacetophenone, phenylglyoxal, phenylglyoxylic acid, and finally hippuric acid and mandelic acid. The omega-oxidation of ethylbenzene to 2-phenylethanol leads to phenylacetic acid, which is conjugated with glycine to phenacetic acid. The pattern of urinary metabolite excretion seems to vary with different mammalian species. Humans mainly excrete ethylbenzene in the urine as mandelic acid and phenylglyoxylic acids; whereas rats and</p>

				rabbits excrete hippuric acid and phenaceturic acid as the main metabolites of ethylbenzene.
5.11	Human Experience:			

SIDS Initial Assessment Report

1. IDENTITY

1.1 Identification of the Substance

Commercial ethylbenzene (CAS # 100-41-4; $(C_6H_5)CH_2CH_3$) is more than 99.7% pure. It is manufactured in a closed continuous process by reacting ethylene and benzene with an aluminum chloride or zeolite catalyst. Ethylbenzene also occurs at 15 to 20% in the “mixed xylenes” stream isolated at some petroleum refineries for use as a solvent. Ethylbenzene is also present in crude oil and several refinery streams that are blended in gasoline and aviation fuels.

At room temperature ethylbenzene is a liquid (density 0.867 g/ml at 20°C) with a vapor pressure of 1.27 kPa (9.53 mm Hg) at 25°C and a boiling point of 136 °C. It has low water solubility (169 mg/l at 25°C) and a moderate octanol/water partition coefficient ($\text{Log } K_{ow} = 3.13$ to 3.15).

2. GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Manufacturing capacities of 6,738,000 metric tons in the United States, 1,020,000 metric tons in Canada, and 176,000 metric tons in Mexico have been reported for the production of ethylbenzene (DeWitt, 1999). In Germany, more than 1,200,000 metric tons of ethylbenzene were produced (four producers) in 2000. The total production volume in the EU (including Germany) can be estimated to be about 5,700,000 tons per year based on data from 13 producers (German UBA, personal communication).

More than 99% of the ethylbenzene produced via the reaction of ethylene and benzene is used as a precursor in the production of styrene (ATSDR, 1999). Ethylbenzene is also present in refinery products such as mixed xylenes, which are used as solvents and in gasoline and other fuels. Mixed xylenes contain about 80% o-, m-, and p-xylene and 15 to 20% ethylbenzene. Mixed xylenes (also called xylene-range aromatic solvent) are used largely as solvents for spray paints, primers, paint removers, thinners, wood stains, varnishes and other finishes, and cleaners for automotive and household uses. Ethylbenzene is also present in several refinery streams that are blended into gasoline and aviation fuels (Cannella, 1998).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

United States Toxic Release Inventory (TRI) data indicates that greater than 99% of releases are anticipated to be to the air compartment. Please see Table 1.

Table 1: TRI on-site and off-site reported release (in pounds) in United States, 1998, all industries.

Emission Rate	Lbs.	Kg	%
Total to Air	8,499,147	3,855,148	99.5
Total to Water	10,408	4,721	0.1
Total to Soil	32,863	14,906	0.4
to Sediment	0	0	0

2.2.2 Photodegradation

Due to its volatility, most ethylbenzene releases will quickly vaporize. Thus photodegradation is the most important means of removing ethylbenzene from the environment. Photodegradation is rapid, with an estimated half-life of 1 day and reaction rates of $7-8 \times 10^{-12} \text{ cm}^3/\text{mol} \cdot \text{sec}$ for reaction with hydroxyl radicals.

2.2.3 Stability in Water

No data is available.

2.2.4 Terrestrial Fate

No data is available.

2.2.5 Environmental Distribution

Removal of ethylbenzene from surface water is mostly by evaporation but biodegradation plays an important role during summer months. However, it is not possible to differentiate between volatilization and degradation. Half-life in water was estimated at 13 days for winter, 20 days for spring, and 0.1 day in summer.

The results of Mackay Level I and Level III fugacity multimedia modeling (Dow, 2000) are presented below. Primary input values for Level I and Level III modeling are: Molecular weight, 106.2; Log Kow, 3.15; Water solubility, 169 g/m³; Vapor Pressure, 1270 hPa; Melting point, -95C; Henry's Law Constant, 798.1 Pa.m³/mol.

When performing Level I modeling the default emission values of 10,000 kg/yr were used, assuming equal distribution to all compartments. Results of Level I modeling indicate that the majority of ethylbenzene will partition to the air compartment (98.6%) with only 0.6% to the water, 0.8% to the soil, 0.02% to the sediment compartments. The high proportion in the air phase reflects the relatively large Henry constant of ethylbenzene.

For the Mackay Level III (Equilibrium Criterion) Model, the information in Tables 1 and 2 were used (Dow, 2000) to determine appropriate emission rates of ethylbenzene to each individual compartment.

Results of the Mackay Level III Model are presented in Table 3. The Level III model calculation constrains the chemical of interest to steady state concentrations in each media. The chemical of interest is released into the individual compartments and can degrade within compartments. Based on the U.S. 1998 Toxic Release Inventory Data (Table 1), emissions are primarily to air. The ultimate partitioning of ethylbenzene in the environment is expected to be in air, with minor partitioning to other compartments.

Table 2: Emission input values for Level III

Emission Rate	Kg/h (%)	mol/h
to Air	2985 (99.5)	28107
to Water	3.5 (0.1)	33
to Soil	11.5 (0.4)	108
to Sediment	0 (0)	0

Table 3: Results of Level III Modeling

MEDIA	AMOUNT	HALF-LIFE (h)
Air: Bulk	96.10%	-
Pure Air	96.10%	36
Aerosol	0.00%	360
Water: Bulk	0.89%	-
Water	0.89%	360
Sus. Sediment	0.00%	850
Fish	0.00%	850
Soil: Bulk	2.99%	360
Air	0.01%	
Water	0.06%	
Solid	2.91%	
Sediment: Bulk	0.01%	1440
Water	0.00%	
Solid	0.01%	

2.2.6 Biodegradation

Based on a test using OECD method 302C, 81% degradation of ethylbenzene was observed after 14 days. Based on results of this study, ethylbenzene is inherently biodegradable under aerobic conditions (CITI, 1992). This finding is supported by a number of other studies, which show that ethylbenzene is biodegradable. The OECD 302 MITI II test is designed to evaluate inherent biodegradation. However, in the CITI 1992 study volatilization cannot be discounted as a removal mechanism since it is not clear as to whether the study was conducted in an open or closed system. Under anaerobic conditions, ethylbenzene is not considered readily biodegradable (7 studies).

2.2.7 Abiotic Degradation

No data is available.

2.2.8 Bioaccumulation

Tests in four species of fish and two studies in clams indicate ethylbenzene has a low potential for bioaccumulation; bioaccumulation factors (BCF) of 1.1 to 15 were measured (Ogata et al., 1984; Roubal et al., 1978; Howard, 1989; Nunes and Benville, 1979). Based on log Pow, a theoretical BCF of approximately 100 was calculated (Yoshida et al., 1983; Mackay et al., 1980); however, this degree of bioaccumulation did not occur in the tests on aquatic organisms.

2.3 Human Exposure

2.3.1 Occupational Exposure

U.S. ethylbenzene producers recently compiled worker exposure data collected over the past 10 years (ACC Ethylbenzene Panel, 2000). There were a total of 1727 personal monitoring samples (8-hour time-weighted averages) representing exposures of process operators, maintenance workers, loading/unloading, quality laboratory workers and supervisory/professional workers. Of these data, approximately 71% of the exposures were either non-detectable or less than 0.1 ppm (0.4 mg/m³), 25% were between 0.1 ppm to 1.0 ppm (4 mg/m³), 4% were greater than 1.0 ppm and less than 5 ppm (22 mg/m³), and 0.4% were greater than 5 ppm (4 of 6 samples were less than 9 ppm (39 mg/m³), 2 samples unspecified). Thus, worker exposure during production of ethylbenzene is consistently very low. Both the U.S. OSHA Permissible Exposure Level and the ACGIH Threshold Limit Value are 100 ppm (434 mg/m³, 8-hour time-weighted average).

The use of solvents containing ethylbenzene result in worker exposures ranging up to 29 ppm (125 mg/m³), in individual measurements. Time weighted average exposures are less than 5 ppm (Medinilla et al, 1988, Verhoeff et al., 1988, Whitehead et al., 1984).

2.3.2 Consumer Exposure

Ethylbenzene is contained as part of the solvent package in consumer products such as paints and finishes, cleaners, etc. The emissions from solvent uses are not available. Atmospheric ethylbenzene concentrations have not been estimated or measured during consumer uses of products containing ethylbenzene. Ethylbenzene is also present in several refinery streams that are blended into gasoline and aviation fuels. Thus consumers may be exposed to ethylbenzene during gasoline refueling; average levels have been measured at around 0.01 ppm (0.04 mg/m³), during refueling (API, 1991).

2.3.3 Indirect

In the U.S., ambient air concentrations of ethylbenzene are generally less than 1 - 2 ppb (0.004 – 0.008 mg/m³). For example, extensive monitoring in Texas during 1992 to 1997 revealed mean ambient concentrations nearly all less than 1 ppb at monitoring stations near industrial sites, with an overall mean of 0.33 ppb (0.001 mg/m³, TNRCC, 1997). Extensive monitoring during 1999 and 2000 in Texas City and LaMarque, Texas, down wind of an industrial complex with three refineries and three chemical plants, found ambient concentrations of 0.34 ppb (0.002 mg/m³), or less at each monitoring site. The mean concentration at all sites in 1999 was 0.16 ppb (0.007 mg/m³, Texas City/LaMarque Community Air Monitoring Network, 2000). Concentrations in rural and remote areas are also very low.

Ethylbenzene has been found in U.S. municipal drinking water supplies at levels up to 4 ppb (µg/l) (Howard, 1989). In Canada, it has been found at up to 7 ppb (µg/l) (ECETOC, 1986).

One paper estimated that the daily ethylbenzene exposure for the general population was approximately 130 µg/person or approximately 1.8 µg/kg/day, corresponding to an annual intake of approximately 46 mg/person (Tang et al., 2000). The majority (up to 99%) of ethylbenzene exposure was due to inhalation.

3. HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Ethylbenzene can be absorbed following inhalation or oral exposure (Gromiec and Piotrowski, 1984; Bardodej and Bardodejova, 1970; Astrand et al., 1978; Chin et al., 1980; Climie et al., 1983). Liquid ethylbenzene is also rapidly absorbed through the skin if volatilization is impeded; but dermal absorption of ethylbenzene vapor appears to be minimal (Gromiec and Piotrowski, 1984; Dutkiewicz and Tyras, 1967; Susten et al., 1990). Ethylbenzene is distributed throughout the body, and the principal route of excretion from both oral and inhalation exposure is through urine. The amount of ethylbenzene taken up by the human body has been correlated with the amount of body fat (Chin et al., 1980; Susten et al., 1990; Engstrom and Bjustrom, 1978; Astrand et al., 1978). Two very different metabolic pathways for ethylbenzene have been cited in the literature through the alpha- or omega-oxidation of the side chain by various cytochrome P450 isozymes to 1- and 2-phenylethanol, respectively. The major pathway is the alpha-oxidation of ethylbenzene to 1-phenylethanol, mostly as the R-enantiomer (McMahon and Sullivan, 1966). The subsequent intermediates are acetophenone, omega-hydroxyacetophenone, phenylgloxal, phenylglyoxylic acid, and finally hippuric acid and mandelic acid (McMahon and Sullivan, 1966). The omega-oxidation of ethylbenzene to 2-phenylethanol leads to phenylacetic acid, which is conjugated with glycine to phenacetic acid (Kiese and Lenk, 1974). The pattern of urinary metabolite excretion seems to vary with different mammalian species. Humans mainly excrete ethylbenzene in the urine as mandelic acid and phenylglyoxylic acids; whereas rats and rabbits excrete hippuric acid and phenacetic acid as the main metabolites of ethylbenzene (Bardodej and Bardodejova, 1970; Astrand et al., 1978; Gromiec and Piotrowski, 1984; Engstrom and Bjustrom, 1978; Kiese and Lenk, 1974; Engstrom, 1984). Cytochrome P450 induction by ethylbenzene can result in changes in metabolism of other chemicals (Sequeira et al., 1992). Also, exposure of rats to very high doses of ethylbenzene can either induce or inhibit a number of cytochrome P450 isozymes over different time courses (Backes et al., 1993; Bergeron et al., 1999; Gut et al., 1993; Koop and Laetham, 1992; Sequeira et al., 1992, Sequeira et al., 1994; Yuan et al., 1995; Yuan et al., 1997).

3.1.2 Acute Toxicity

Ethylbenzene has a low order of acute toxicity by the oral, inhalation or dermal routes of exposure. Result of various acute studies may be found in Table 4.

3.1.3 Irritation

Studies in rabbits indicate that ethylbenzene is irritating to the skin and slightly eyes (see Table 4).

3.1.4 Sensitisation

There was no evidence of skin sensitization when ethylbenzene (10% in petrolatum) was applied to the skin of humans; this study is not considered suitable for classification and labeling purposes (see Table 4).

Table 4 : Acute toxicity, Irritation, and Sensitization

Acute oral	rat	LD50 = 3.5 to 4.7g/kg (5.4 ml/kg)	Wolf et al., 1956 Smyth et al., 1962
Acute inhalation	rat	4 hr LC50 = 17.4 mg/l (4000 ppm)	Smyth et al., 1962
Acute dermal	rabbit	LD50 = 15.4 g/kg	Smyth et al., 1962
Dermal irritation	rabbit	irritating	Smyth et al., 1962 Opdycke, 1975
Eye irritation	rabbit	irritating	Wolf et al., 1956 Smyth et al., 1962
Sensitization	Human, patch test	Negative	Kligman, 1975

3.1.5 Repeated Dose Toxicity

In a four-week study, F344 rats and B6C3F₁ mice (five/sex/group) were exposed by inhalation to 0, 99, 382, or 782 ppm (0, 429, 1656, or 3390 mg/m³) ethylbenzene, six hours/day, five days/week (Cragg et al., 1992). There were no effects on survival, body weight gain, clinical chemistry, gross or microscopic pathology. For the rats, exposure to 782 ppm resulted in an approximate 20% and 13% increase ($p < 0.001$) in relative (to body weight) liver weights in females and males, respectively. Female rats that received 382 ppm ethylbenzene exhibited about a 7% increase ($p < 0.05$) in relative liver weight; whereas, the male relative liver weights were not significantly different from controls. In the mice that received 782 ppm ethylbenzene, liver weights relative to body weight were not statistically significantly different in males or females; but absolute liver weight was increased in females (about 15%; $p < 0.05$), and liver weights relative to brain weights were increased in males (about 17%; $p < 0.05$) and females (about 15% at $p < 0.01$). The authors interpreted the liver changes as probably metabolic adaptation, due to the absence of liver histopathology or abnormal clinical chemistry. The authors concluded the study indicated a subchronic NOAEL of 382 ppm for rats and mice.

In rabbits (five/sex/group), effects were limited to a transient initial decrease in body weights following exposure to 1610 ppm (6991 mg/m³), six hrs/day, five days/week for four weeks (Cragg et al, 1989), with a NOAEL of 782 ppm for rabbits.

The U.S. National Toxicology Program (NTP, 1992) conducted 13-week inhalation studies in rats and mice. Male and female F344 rats were exposed up to 1000 ppm (4335 mg/m³) ethylbenzene six hrs/day, five days/week for 13 weeks (NTP, 1992). There was a slight decrease (5-7%) in body weight in both sexes, which was not statistically significant. Absolute and/or relative liver, kidney, and lung weights occurred at 250 ppm (1086 mg/m³), and higher. Chemically-related histopathological changes were not observed in any tissues. Since the organ weight changes occurred in the absence of histopathological changes, these findings were not considered adverse and the NOAEL was considered to be 1000 ppm (4335 mg/m³).

Male and female B6C3F₁ mice were exposed up to 1000 ppm (4335 mg/m³) ethylbenzene six hrs/day, five days/week for 13 weeks. No adverse effects were reported for survival, body weights, or treatment-related pathological findings (NTP, 1992). Increased liver weights occurred in both sexes in exposed groups at 750 and 1000 ppm, and increased kidney weights in females at 1000 ppm. Since the organ weight changes occurred in the absence of histopathological changes, these findings are not considered adverse and the NOAEL is 1000 ppm or 4335 mg/m³ (the NTP report did not actually specify either a NOEL or NOAEL).

In chronic toxicity/carcinogenicity studies (NTP, 1999), both rats and mice were exposed via inhalation to 0, 75, 250 or 750 ppm (0, 325, 1084, or 3251 mg/m³) for 104 weeks. In rats, the kidney was the target organ of toxicity, with renal tubular hyperplasia noted in both males and females at the 750 ppm level only. In mice, the liver and lung were the principal target organs of toxicity. In male mice at 750 ppm, lung toxicity was described as alveolar epithelial metaplasia, and liver toxicity was described as hepatocellular syncytial alteration, hypertrophy and mild necrosis; this was accompanied by increased follicular cell hyperplasia in the thyroid. As a result the NOAEL for systemic effects in male mice was determined to be 250 ppm. In female mice, the 750 ppm dose group had an increased incidence of eosinophilic foci in the liver (44% vs 10% in the controls) and an increased incidence in follicular cell hyperplasia in the thyroid gland. In addition, female mice exposed to 250 ppm and 750 ppm had an increase in hyperplasia of the pituitary gland. As a result, the NOAEL for female mice was 75 ppm (325 mg/m³).

In an experiment to evaluate the effect of hearing following exposure of Wag/Rij rats to 800 ppm (3468 mg/m³) ethylbenzene 8 hr/day for five days, there was increased auditory thresholds for startle response at one and four weeks after the end of the exposure (Cappaert et al., 1999). A shift in the electrocochleography was seen at eight and 11 weeks after exposure. Three to six weeks after exposure to 300, 400, or 550 ppm (1300, 1734, or 3468 mg/m³) ethylbenzene (eight hr/day) for five days, mid-frequency hearing region (8-12 kHz) and auditory thresholds were increased in the 400 and 550 ppm groups. A dose-related outer hearing cell loss was found in two of the five examined regions (11 and 21 kHz) in the cochlea (Cappaert et al., 2000). In a follow-up study, hearing parameters (as measured by distortion product otoacoustic emissions (DPOAEs) and compound action potentials (CAPs) were altered by noise alone (105 dB) and with noise in combination with ethylbenzene (105 dB + 300 or 400 ppm ethylbenzene). However, the amount of loss after exposure to the combination did not exceed the loss after noise alone. In this study, ethylbenzene alone (300 or 400 ppm) did not cause significant hearing loss (Cappaert et al., 2000).

No hearing loss was reported in guinea pigs exposed to 2500 ppm (10,838 mg/m³) ethylbenzene eight hours on the first day, and six hours/day for an additional four days (Cappaert et al., 2000).

3.1.6 Mutagenicity

In vivo genotoxicity studies with ethylbenzene are all negative and *in vitro* genotoxicity studies are predominantly negative.

In vitro Studies

Bacterial Test: Four *Salmonella typhimurium*/mammalian microsomal (Ames) assays and three other bacterial mutagenicity assays (2 in *Saccharomyces cerevisiae* and 1 in *E. coli*) with and without activation at dose levels up to 2000 µg/plate were all negative (Dean et al., 1985; Florin et al., 1980; Nestmann et al., 1980; Zeiger et al., 1992; Nestmann and Lee, 1983).

Non-Bacterial: In the mouse lymphoma forward mutation assay, ethylbenzene was mutagenic only at the highest non-lethal concentration (80 µg/ml). At this concentration there was significant cytotoxicity, with the relative total growth in two trials being 34 or 13% of the control level (McGregor et al., 1988). Ethylbenzene was not tested in the presence of S9. In a follow-up study (Wollny, 2000) three trials were performed with and without activation. In the first trial without activation, the results indicate a definitive positive at 34 and 69 µL/mg. In the same trial with activation there was a limited positive response at 825 µL/mg in which the relative growth (RTG: an indicator of cytotoxicity) of one culture was above the 20% level, which indicates a “definitive positive”, and one result was below. However, both results from this dose level were above 10% RTG indicating a “limited positive” response. In addition, positive responses were obtained in both large and small colonies, and thus both gene and chromosome mutations contribute to the

response. In the second and third trials both with and without activation, the results were determined to be inconclusive or negative, due either to insufficiently high dose levels or to an inadequate positive control response. Overall the experiments of McGregor et al. (1988) and Wollny (2000) indicate a positive mutagenic effect of ethylbenzene in L5178Y tk⁺/tk⁻ mouse lymphoma cells.

Negative results were reported in an *in vitro* study of chromosome aberrations in rat liver cells (Dean et al., 1985) and in Chinese Hamster Ovary (CHO) cells in the absence or presence of metabolic activation were negative (NTP, 1999).

An *in vitro* sister chromatid exchange assay using Chinese hamster ovary cells was negative in the presence or absence of metabolic activation (NTP, 1999). Norppa and Vainio (1983) reported a marginally positive response in human whole blood lymphocytes at the highest toxic dose (10 mM) after incubation with ethylbenzene for 48 hours (concentrations ranged from 0.1 to 10 mM). However, this study cannot be considered reliable since the study protocol has not been validated.

An *in vitro* Syrian hamster embryo micronucleus assay was positive. (Gibson et al., 1997; Hazelton, 1996).

In Syrian hamster ovary cells, ethylbenzene (up to 500 µg/ml) did not induce cell transformations in a 24-hr period. But cell transformations did occur after a 7-day incubation period at ethylbenzene concentrations of 150 to 200 µg/ml. It was suggested by the authors that chemicals that are positive at 7 days, but negative after 24 hours act by (or through) a promotion-like mechanism (Kerckaert et al., 1996; Hazleton, 1995a,b).

In vivo Studies

Two *in vivo* micronucleus studies in B6C3F1 mice (by inhalation, up to 1000 ppm (4335 mg/m³) for 13 weeks; NTP, 1999) and NMRI mice (intraperitoneal injections, 2 daily doses up to 645 mg/kg; Mohtashampur et al., 1985) were negative.

Ethylbenzene did not induce DNA repair as measured by unscheduled DNA synthesis (UDS) in liver cells following a single 6-hour inhalation exposure of ethylbenzene vapor to male B6C3F1 mice (500 and 1000 ppm; 2168 and 4335 mg/m³) and female B6C3F1 mice (375 and 750 ppm; 1626 and 3251 mg/m³) (Clay, 2001). The exposure levels for each sex were based on a preliminary study which determined these exposure levels to be the maximum tolerated dose (MTD) based on observed patterns of clinical signs and lethality.

Ethylbenzene did not induce recessive lethal mutations in *Drosophila melanogaster* (Donner et al., 1980). This study is considered “invalid” since the study details are poorly reported; therefore, it should not be used for hazard identification.

3.1.7 Carcinogenicity

The U.S. National Toxicology Program conducted inhalation carcinogenicity studies in F344/N rats and B6C3F1 mice (NTP, 1999).

Rats

F344/N rats were exposed by inhalation to 0, 75, 250 or 750 ppm (0, 325, 1084, or 3251 mg/m³) ethylbenzene, 6 hours/day, 5 days/week for 104 weeks (NTP, 1999). At 750 ppm, survival in males was significantly reduced, while in females survival was increased (not significant). No adverse clinical findings were attributed to the ethylbenzene exposure. In males exposed to 250 or 750 ppm, body weights were reduced (up to 5 and 15%, respectively) from week 20 to the end of the study. In females all exposed groups weighed up to 5% less than the controls during the second year, but

there was no dose-response. In both males and females exposed to 750 ppm, but not to 75 or 250 ppm, there was increased renal tubule hyperplasia and increased severity of nephropathy. In males exposed to 750 ppm, there was an increased incidence of renal tubule adenomas and combined renal tubule adenoma/carcinomas based on combined original kidney sections and additional step-sectioning of the kidneys. The incidence of renal tubule carcinomas was not significantly elevated. In females, no renal tubule carcinomas were found. However, at 750 ppm, there was an increased incidence of renal tubule adenomas. In males exposed to 750 ppm, there was a slight, but significant, increase in the incidence of testicular interstitial cell adenoma (88% vs. 72% in controls; historical control range 54 to 83%) (NTP, 1999).

The kidney slides from this study, as well as the NTP 13-week study were re-examined (Hard, 2000). It was concluded that the apparent increase in renal tumors was strongly associated with Chronic Progressive Nephropathy or CPN, a spontaneous age-related disease of rodents with no identical counterpart in humans. CPN occurred in the 750 ppm animals, markedly so in the male rats, and modestly so in the females. In addition, there was a high incidence of high-dose rats that had end-stage CPN, a terminal condition where the kidneys are so morphologically altered that renal failure (as well as secondary hyperthyroidism) occurs. Although there some evidence of a dose-related increase in hyaline droplet formation in the 13-week NTP study, it was not considered to be of the magnitude indicative of an α_2 -globulin associated mechanism of renal carcinogenesis (Hard, 2000).

B6C3F1 mice were exposed by inhalation to 0, 75, 250 or 750 ppm (0, 325, 1084, or 3251 mg/m³) ethylbenzene, 6 hours/day, 5 days/week for 103 weeks (NTP, 1999). Exposure to ethylbenzene had no meaningful effect on survival or body weight gain. In the lung at 750 ppm, male rats exhibited increased alveolar epithelial metaplasia, but there was no increase in alveolar hyperplasia. In females, no significant increase in the incidence of either hyperplasia or metaplasia was observed. There was increased incidence of alveolar/bronchiolar adenomas and of combined alveolar/bronchiolar adenoma/carcinomas in male mice exposed to 750 ppm. Incidences of lung tumors at 75 and 250 ppm were not significantly different from the control incidence and were within the historical control range. In females, there was no significant increase in the incidence of lung tumors. In the liver, females (but not males) exposed to 750 ppm had an increased incidence of eosinophilic foci, a lesion which is judged to be a precursor of hepatocellular adenomas. The incidence of eosinophilic foci in either males or females exposed to 250 or 75 ppm were not significantly different from the control incidences. There were, however, increased incidences of syncytial alteration, hypertrophy and necrosis in the liver of males exposed to 750 ppm ethylbenzene. There was a significantly increased incidence of hepatocellular adenomas in females exposed to 750 ppm and combined hepatocellular adenoma/carcinomas. The incidence of tumors in females exposed to 75 and 250 ppm were not significantly different from the control incidences. In males there was no increase in liver tumors at any exposure concentration.

The lung and liver sections of mice from the National Toxicology Program (NTP) two-year bioassay were re-evaluated by Brown (2000). This re-evaluation revealed an increased incidence of male and female mice of the 750 ppm exposure group with decreased eosinophilia of the terminal bronchiolar epithelium. Also, a dose-related increased incidence in multifocal hyperplasia of the bronchiolar epithelium with extension to the peribronchiolar alveolar epithelium was observed in all male treated groups and mid- and high-exposure females. The author noted that the necrotic hepatocytes in the high-dose males were usually that of a coagulation-type necrosis of single or small groups of cells, usually the enlarged, hypertropied centrilobular hepatocytes. The morphology of this necrosis was histomorphologically different from "apoptosis." Also, the syncytial cells were not the predominant cell type with necrosis.

There were also increased follicular cell hyperplasia in the thyroid gland in both the 750 ppm males and females; and hyperplasia in the pituitary gland in the 250 and 750 ppm females.

A study of Sprague-Dawley rats dosed orally with 500 and 800 mg/kg/day, 4 to 5 days/week for 104 weeks, followed by observation until death (at 141 weeks) was reported to result in a larger percentage of the animals with total malignant tumors (not defined) in both dose groups (no dose response) and head cancers at 800 mg/kg/day (Maltoni et al., 1985; 1997). The studies were incompletely reported and no statistical analyses were presented.

Medical records of 200 males involved in the production of ethylbenzene in Czechoslovakia from 1964 to 1985 did not show any increased incidence of cancer, or any adverse health effects on the liver and/or the hematopoietic system, based on hematological and serum enzyme assays. The mandelic acid urine concentration in these workers never exceeded 3.25 mmol/l (Bardodej and Círek, 1988).

Potential factors underlying the tumorigenic activity of ethylbenzene (EB) were examined in F344 rats and B6C3F1 mice inhaling nontumorigenic (75 ppm) or tumorigenic (750 ppm) levels of EB vapor 6 hours/day, 5 days/week, for one and/or four weeks [Stott, et al., 1999, Stott, et al., 2001]. Kidneys of rats exposed to 750 ppm EB for one or four weeks weighed slightly more than controls. In males, this was accompanied by focal deposition of hyaline droplets (one-week), slight tubular degeneration, increased immunohistochemically-identified $\alpha_2\mu$ -globulin, and S-phase DNA synthesis in proximal tubules. Elevations in enzyme activities suggested an adaptive metabolic response. In females, decreased renal S-phase synthesis (one-week) and decreases in the MFO activities (four weeks) suggested an alteration or loss of MFO competent cells with increasing exposure period. Liver weights of mice exposed to 750 ppm EB vapor were elevated, and accompanied by histopathological changes (four week), increases in mitotic figures and increased S-phase synthesis, primarily in centrilobular and midzonal regions of hepatic lobules. Changes in enzyme activities indicative of hepatic adaptation were also noted. No changes in lung weights or histopathology were noted in exposed mice at either time point, but S-phase synthesis rates in terminal bronchiolar epithelium were elevated in both sexes of mice and were accompanied by a significant loss of whole lung MFO activity. Increased rates of S-phase synthesis persisted at four weeks in both sexes while decreased MFO activity remained in females. Few changes were observed in rats or mice exposed to a nontumorigenic exposure level of 75 ppm EB vapor for one week. Stott et al., [1999, 2001] concluded that exposure to 750 ppm EB vapor causes biochemical, histopathological and cytological effects that may promote tumor formation in rat kidney and mouse liver and lung."

3.1.8 Toxicity for Reproduction

Effects on Fertility

No reproductive toxicity studies conducted according to or equivalent to current testing guidelines were found.

In a developmental toxicity study, female Wistar rats were exposed to 0, 100, or 1000 ppm (0, 434, or 4335 mg/m³) ethylbenzene 7 hr/day, 5 days/week for 3 weeks; mated with unexposed males; and pregnant females were further exposed to 0, 100, or 1000 ppm (0, 434, or 4335 mg/m³) 7 hr/day through Gestational Day 19. Maternal effects (increased organ weights) occurred in the 1000 ppm-exposed group. A higher percentage of ethylbenzene exposed females mated (were sperm positive) than the controls (67, 78 and 74% for 0, 100 and 1000 ppm, respectively) and a slightly smaller percentage of ethylbenzene-exposed females that mated were pregnant at gestation day 21 (89, 77 and 77%, respectively). When expressed on the basis of total females per group, 56, 60, and 57% of the females exposed to 0, 100, or 1000 ppm were pregnant at gestation day 21. Thus exposure of female rats to ethylbenzene at 100 or 1000 ppm for three weeks did not decrease fertility (Andrew et al, 1981; Hardin et al, 1981).

No effects on reproductive organs have been reported in rats, mice, or rabbits exposed to ethylbenzene for up to 13 weeks in repeated dose studies (Cragg et al, 1989; NTP, 1992). In the 13-week NTP study (1992), there were no treatment-related effects on sperm, testicular morphology, length of estrus cycle, spermatid counts, sperm motility, caudal or epididymal weights in rats exposed to 100, 500, or 1000 ppm (0, 434, 2168, or 4335 mg/m³) ethylbenzene.

Developmental Toxicity

In female Wistar rats exposed by inhalation to 0, 100, or 1000 ppm (0, 434, or 4335 mg/m³) ethylbenzene, 7 hours/day for three weeks prior to mating, then 7 hours/day during 1-19 days of gestation, developmental effects were limited to increased incidence (14%) of skeletal variations (supernumerary ribs) at 1000 ppm. Maternal effects were observed only at 1000 ppm, and included increased liver, kidney, and spleen weight changes (approximate change of 22%, 10%, and 10%, respectively), with no accompanying histopathological effects. The NOAEL for both maternal toxicity and developmental toxicity is considered to be 100 ppm or 434 mg/m³ (Andrew et al, 1981; Hardin et al., 1981).

In the same study, rabbits exposed by inhalation to 0, 100 or 1000 ppm (0, 434, or 4335 mg/m³) ethylbenzene during days 1-24 of gestation had no developmental effects; maternal effects (increased liver weights) were observed in the 1000 ppm only. The NOAEL for both maternal and developmental toxicity is considered to be 100 and 1000 ppm, respectively. (Andrew et al., 1981; Hardin et al., 1981).

In poorly-reported studies, CFY rats were exposed to 600, 1200, 2400 mg/m³ (138, 277, 554 ppm) ethylbenzene 24 hours/day or 600 mg/m³ 6 hours/day during gestation days 7-15 of gestation. No developmental effects were reported in animals exposed 6 hours/day to 600 mg/m³. However, increased percentage of dead or resorbed fetuses and fetuses with retarded skeletal development were noted in all of the exposed 24-hour group. At 2400 mg/m³, increased malformations were observed. Maternal toxicity was reported to be "moderate" and dose-dependent (Ungvary and Tátrai, 1985). Malformations, but no other developmental effects, were observed in CFLP mice exposed by inhalation to 500 mg/m³ ethylbenzene for 3-4 hours/day during days 6-15 of gestation. Maternal toxicity was not reported (Ungvary and Tátrai, 1985). Rabbits exposed to 500 mg/m³ ethylbenzene for 24 hours/day during days 7-20 of gestation had mean maternal and fetal body weight gain, with no other maternal or developmental toxicity (Ungvary and Tátrai, 1985). These studies are of limited usefulness since they do not provide characterization of the test material, inhalation methods, definitions of malformations or numbers of animals or litters affected.

3.2 Initial Assessment for the Human Health

Ethylbenzene is an industrial chemical that is primarily produced and further reacted to make styrene in a closed continuous process: thus, occupational exposures are expected to be very low. In addition, ethylbenzene occurs in crude oil and as a component of mixed xylenes, which are used in gasoline or as a solvent. Emissions and exposures from solvent use are not well characterized. Exposure to the general population is possible through extremely low ambient air concentrations, primarily due to gasoline and automobile emissions.

Ethylbenzene is readily absorbed following inhalation, oral, and dermal exposures, distributed throughout the body, and excreted primarily through urine. There are two different metabolic pathways for ethylbenzene with the primary pathway being the alpha-oxidation of ethylbenzene to 1-phenylethanol, mostly as the R-enantiomer. The pattern of urinary metabolite excretion varies with different mammalian species. In humans, ethylbenzene is excreted in the urine as mandelic acid and phenylglyoxylic acids; whereas rats and rabbits excrete hippuric acid and phenaceturic acid as the main metabolites. Ethylbenzene can induce liver enzymes and hence its own metabolism as

well as the metabolism of other substances. Ethylbenzene has a low order of acute toxicity by the oral, dermal or inhalation routes of exposure. Studies in rabbits indicate that ethylbenzene is irritating to the skin and eyes. Repeat-dose studies have been conducted in rats, mice, and rabbits. In a four-week inhalation study, absolute and/or relative liver weights were observed in rats and mice at 782 ppm (but not at 382 ppm), with no accompanying histopathology or clinical chemistry changes; a four-week NOAEL of 382 ppm was determined for the rat and mouse. Other than a transient initial decrease in body weight, no adverse effects were observed in rabbits that were exposed up to 1610 ppm, and a NOAEL of 782 was determined. In a 13 week inhalation repeat-dose study in male and female rats, mild body weight or organ weight (kidney, liver, lung) effects occurred at doses ≥ 250 ppm without any accompanying histopathological or clinical chemistry changes, as a result these findings were not considered toxicologically significant. In chronic toxicity/carcinogenicity studies, both rats and mice were exposed via inhalation to 0, 75, 250 or 750 ppm for 104 weeks. In rats, the kidney was the target organ of toxicity, with renal tubular hyperplasia noted in both males and females at the 750 ppm level only. In mice, the liver and lung were the principal target organs of toxicity. In male mice at 750 ppm, lung toxicity was described as alveolar epithelial metaplasia, and liver toxicity was described as hepatocellular syncytial alteration, hypertrophy and mild necrosis; this was accompanied by increased follicular cell hyperplasia in the thyroid. As a result the NOAEL in male mice was determined to be 250 ppm. In female mice, the 750 ppm dose group had an increased incidence of eosinophilic foci in the liver (44% vs 10% in the controls) and an increased incidence in follicular cell hyperplasia in the thyroid gland. In addition, female mice exposed to 250 ppm and 750 ppm had an increase in hyperplasia of the pituitary gland. As a result, the NOAEL for female mice was 75 ppm. Hearing loss has been reported in rats (but not guinea pigs) exposed to relatively high exposures (*400 ppm and greater*) of ethylbenzene. Ethylbenzene was negative in bacterial gene mutation tests and in a yeast assay on mitotic recombination. In mouse lymphoma assays, positive responses were only observed at doses with excess cytotoxicity. No clear conclusion can be drawn from the chromosomal aberration tests *in vitro*. A single *in vitro* micronucleus test without S-9 mix was positive. An *in vitro* SCE test was clearly negative with and without S-9 mix. With *in vivo* tests, negative findings were obtained in micronucleus tests and in a mouse liver UDS test. In studies conducted by the U.S. National Toxicology Program, inhalation of ethylbenzene at 750 ppm resulted in increased lung tumors in male mice, liver tumors in female mice, and increased kidney tumors in male and female rats. No increase in tumors was reported at 75 or 250 ppm. Ethylbenzene is considered to be an animal carcinogen, however, the relevance of these findings to humans is currently unknown. Although no reproductive toxicity studies have been conducted on ethylbenzene, repeated-dose studies indicate that the reproductive organs are not a target for ethylbenzene toxicity. Furthermore, in the 13-week NTP studies with rats and mice, no effects were observed for sperm, testicular morphology, spermatid counts, sperm motility, caudal or epididymal weights, or length of estrous cycle. Developmental toxicity studies have been conducted in the rabbit and rat with minor developmental effects (14% increase in incidence in pups with supernumerary ribs) observed in the rat only at 1,000 ppm ethylbenzene. Maternal effects in the dams at this dose consisted of increases in liver (approximately 22%), kidney (approximately 10%), and spleen (approximately 10%) weights in the absence of histopathology changes.

Ethylbenzene has the following physical chemical properties: molecular weight, 106.2; Log Kow, 3.15; water solubility, 169 mg/l at 25°C ; vapor Pressure, 1270 Pa (1.27 kPa); melting point, -95°C; Henry's Law Constant, 798.1 Pa.m³/mol. Ethylbenzene partitions to air from water and soil, and is degraded in air. Ethylbenzene is volatile and when released will quickly vaporize. Photodegradation is the primary route of removal in the environment. Photodegradation is estimated with a half-life of 1 day. Ethylbenzene is considered inherently biodegradable and removal from water occurs primarily by evaporation but in the summer biodegradation plays a key role in the removal process. Level I and Level III fugacity modeling indicate that partitioning is primarily to the air compartment, 98 and 96%, respectively. Ethylbenzene is inherently

biodegradable in water and in soil under aerobic conditions, and not rapidly biodegradable in anaerobic conditions. Ethylbenzene is expected to be moderately adsorbed to soil. Ethylbenzene exhibits toxicity to aquatic organisms with LC₅₀ and EC₅₀ values ranging between 1 and 10 mg/L. In acute aquatic toxicity testing LC₅₀ values range approximately between 1 and 10 mg/l. In acute aquatic fish tests (fresh water species), the 96-hr LC₅₀ for *Pimphales promelas* and *Oncorhynchus mykiss* are 4.2 and 12.1 mg/L, respectively. Data are available in the saltwater species *Menidia menidia* and give results within the same range as for the fresh water species with a 96-hr LC₅₀ = 5.1 mg/L. In fresh water invertebrate species *Daphnia magna* and *Ceriodaphia dubia*, 48-hr LC₅₀ values were 1.81 and 3.2 mg/L, respectively. Additional data is available in the saltwater species *Crangon franciscorium* (96-hr LC₅₀ = 0.49 mg/L) and *Mysidopsis bahia* (96-hr LC₅₀ = 2.6 mg/L). In 96-hr algal toxicity testing, results indicate that ethylbenzene inhibits algae growth in *Selanastrum capricornatum* at 3.6 mg/L and in *Skeletonema costatum* at 7.7 mg/L. Based on measured data, ethylbenzene is not expected to bioaccumulate (BCF 1.1 – 15).

4. HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Studies using flow-through or closed systems demonstrates that ethylbenzene exhibits toxicity to aquatic organisms with LC50 and EC50 values ranging between 1 and 10 mg/L. Other acute studies using static testing methods without supporting analytical measurements of ethylbenzene concentrations were not used in this assessment. Results of aquatic effects may be found in Table 5.

Acute Toxicity Test Results

Acute Toxicity to Fish

Based on studies with analysis of ethylbenzene concentrations, LC50s of 4.2 to 12.1 mg/l were obtained for fish species. See Table 5.

Acute Toxicity to Invertebrates

Based on studies with supporting analytical data on test concentrations, acute EC50 and LC50 values for aquatic invertebrates ranged from 0.49 to 3.2 mg/l. See Table 5.

Acute Toxicity to Algae

Studies of the inhibition of growth of algae with analytical data gave acute EC50s of 3.6 mg/l for *Selenastrum capricornutum* and 7.7 mg/l for *Skeletonema costatum*. See Table 5

Chronic Toxicity Test Results

Toxicity studies in *Ceriodaphnia dubia* found essentially identical values for the 48 hour LC50 value and 7 day LC50 value, and the 7 day IC50 value for inhibition of reproduction. This lack of differences between acute and repeated exposure toxicity indicates additional testing is not a priority.

Table 5: Aquatic Effects

Acute toxicity - fish	<i>Menidia menidia</i>	flow-through, TSCA 797.1440	96 hr LC50 = 5.1 mg/l ^a	Boeri, 1987a
	<i>Pimephales promelas</i> <i>Oncorhynchus mykiss</i>	flow-through static, OECD 203	96 hr LC50 = 12.1 mg/l ^b 96 hr LC50 = 4.2 mg/l ^a	Geiger et al., 1986 Galassi et al., 1988
Acute toxicity-invertebrates	<i>Mysidopsis bahia</i>	flow-through EPA Method F static	96 hr LC50 = 2.6 mg/l ^a	Boeri, 1988
	<i>Daphnia magna</i>	static	48 hr EC50 = 1.81-2.38 mg/l ^a	Vigano, 1993
	<i>Crangon franciscorium</i>		96 hr EC50 = 0.49 mg/l ^a	Benville and Korn, 1977
	<i>Ceriodaphnia dubia</i>	static EPA Whole Effluent Testing Program method	48 hr LC50=3.2 mg/l ^a	Neiderlehner et al., 1998
Acute toxicity-aquatic plants	<i>Selanastrum capricornatum</i>	growth rate, TSCA 797.1050	96 hr EC50 = 3.6 mg/l ^a	Boeri, 1987b
	<i>Skeletonema costatum</i>	growth rate, TSCA 792.1050	96 hr EC50 = 7.7 mg/l ^a	Boeri, 1987c
Other toxicity-invertebrates	<i>Ceriodaphnia dubia</i>	Static (ethylbenzene renewed every 24 hr) EPA Whole Effluent Testing Program method	7 day LC50=3.6 mg/l ^a 7 day IC50 (repro)= 3.3 mg/l ^a 7 day LOEL (repro)= 1.7 mg/l ^a 7day NOEL (repro) =1.0 mg/l ^a	Neiderlehner et al., 1998
Terrestrial plants	<i>Phaseolus Multiflorus</i>	leaf kill	EC50 ~ 27 mg/l ^b , vapor in air, 1 hour	Ivens, 1952

^a Measured concentrations ^b Nominal concentrations

Toxicity to Microorganisms

Ethylbenzene exhibited limited toxicity to microorganisms responsible for the treatment of wastewater. An EC₅₀ of 130 mg/l (oxygen uptake) was reported for activated sludge while the EC₅₀ for anaerobic sludge was similar (EC₅₀ of 160 mg/l based on inhibition of gas production).

4.2 Terrestrial Effects

Limited data indicate that exposure to high ethylbenzene vapour concentrations results in toxic effects to terrestrial plants.

5. RECOMMENDATIONS

The chemical is currently of low priority for further work.

Regional and national exposure and risk assessments are ongoing. This chemical is a substance of the 1st EU Priority List. An in-depth risk assessment will be performed within the framework of the EU Risk Assessment Programme under Regulation 793/93. This chemical is also to undergo review in the US Voluntary Children's Chemical Evaluation Programme and additional testing of reproductive toxicity (two generation study), adult neurotoxicity and immunotoxicity is planned. For the SIDS program specifically, this chemical is a low priority for further work.

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SIDS DOSSIER

Name of Sponsor Country: United States of America

Contact point: Richard Hefner
EPA/Office of Toxic Substances (TS-778)
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Name of Lead Organization: U.S. Environmental Protection Agency

REVISED: January 24, 2002

1.0 Chemical Identity

1.1 CAS-No.: 100-41-4

1.2 Name: ethylbenzene

1.3 Common synonyms: phenylethane

1.4 Empirical formula: C₈H₁₀

1.5 Structural formula: C₆H₅-CH₂-CH₃

1.6 Purity of industrial product:

1.6.1 Degree of purity (percentage by weight): > 99.7 %

1.6.2 Identity of major impurities:

Benzene	<0.1 wt%
Toluene	<0.2 wt%
Xylenes	<0.2 wt%
Cumene	<0.02 wt%
Diethylbenzenes	<0.001 wt%

1.6.3 Essential additives (stabilizing agents, inhibitors, other additives), if applicable:

None

1.7 Use Patterns

1.7.1 Technology Production and Use

Commercial ethylbenzene (CAS # 100-41-4; (C₆H₅)CH₂CH₃) is more than 99.7% pure. It is manufactured in a closed continuous process by reacting ethylene and benzene with an aluminum chloride or zeolite catalyst (Chen, 1998). Ethylbenzene also occurs at 15 to 20% in the "mixed xylenes" stream isolated at some petroleum refineries for use as a solvent (Cannella, 1998). Ethylbenzene is also present in crude oil and several refinery streams that are blended in gasoline and aviation fuels (Cannella, 1998).

Manufacturing capacities of 6,738,000 metric tons in the United States, 1,020,000 metric tons in Canada, and 176,000 metric tons in Mexico have been reported for the production of ethylbenzene (DeWitt, 1999). In Germany, more than 1,200,000 metric tons of ethylbenzene were produced (four producers) in 2000.

The total production volume in the EU (including Germany) can be estimated to be about 5,700,000 tons per year based on data from 13 producers (German UBA, personal communication).

1.8 Occupational Exposure Limit Values

U.S. OSHA Permissible Exposure Level and the ACGIH Threshold Limit Value are 100 ppm (8-hour time-weighted average).

1.9 Sources of Exposure

More than 99% of the ethylbenzene produced via the reaction of ethylene and benzene is used as a precursor in the production of styrene (ATSDR, 1999). Ethylbenzene is also present in refinery products such as mixed xylenes, which are used as solvents and in gasoline and other fuels. Mixed xylenes contain about 80% o-, m-, and p-xylenes and 15 to 20% ethylbenzene. Mixed xylenes (also called xylene-range aromatic solvent) are used largely as solvents for spray paints, primers, paint removers, thinners, wood stains, varnishes and other finishes, and cleaners for automotive and household uses. Ethylbenzene is also present in several refinery streams that are blended into gasoline and aviation fuels (Cannella, 1998).

In Germany, 6 metric tons per year are discharged during production and 8 metric tons are discharged during processing at 3 sites (German UBA, personal communication).

2.1 Melting or Decomposition Point:

Method (e.g., OECD, others): Not specified

-95 degree C

GLP: YES []
NO []
NO DATA [x]

Reference: Weast, RC ed, CRC Handbook of Chemistry and Physics. 60th ed. Boca Raton, FL, CRC Press Inc., C-269 (1988)

2.2 Boiling Point (including temperature of decomposition, if relevant)

Method (e.g., OECD, others): Not specified

136.25 degree C

GLP: YES []
NO []
NO DATA [x]

Reference: Windholz, M. ed., The Merck Index. 10th edition. Rahway, NJ, Merck & Co, Inc. 546-547 (1983)

2.3 A Density

Method (e.g., OECD, others): Not specified

0.867 g/mL @ 20 degree C

GLP: YES []
NO []
NO DATA [x]

Reference: Weast, RC, ed. CRC Handbook of Chemistry and Physics. 60th ed., Boca Raton, FL, CRC Press Inc., C-269 (1988)

2.3 B Density

Method (e.g., OECD, others): Not specified

0.866 g/mL @ 25 degree C

GLP: YES []
NO []
NO DATA [x]

Reference: Windholz, M, ed. The Merck index 10th ed. Rahway, NJ; Merck & Co., Inc., 546-547 (1983)

2.4 Vapor Pressure

Method (e.g., OECD, others): Not specified

1.27 kPa (9.53 mmHg) at 25 degrees C

GLP: YES []
NO []
NO DATA [x]

Comments: The CRC Handbook of Chem and Physics, 70th ed. 1989-1990, CRC Press lists the temperature at a range of vapor pressures as follows:

Temp deg C					
1 mmHg	10 mm	40 mm	100 mm	400 mm	760 mm
neg 9.8deg	25.9deg	52.8deg	74.1deg	113.8deg	136.2deg

Laboratory derived values determined by stripping a known concentration of ethylbenzene (EB) from solution at a predetermined gas flow rate. The Henry's law constant was determined by measuring (UV spectrophotometer) the concentration of EB in solution.

Reference: Mackay, D, Shiu, WY, A critical review of Henry's law constants for chemicals of environmental interest. J. Phys. Chem. Ref. Data 19:1175-1199 (1981)

2.5 A Partition Coefficient

Method (e.g., OECD, others): Not specified

log Pow = 3.13

GLP: YES []
NO []
NO DATA [x]

Comments:

Reference: Yalkowsky, SH, Valvani SC, Partition coefficients and surface areas of some alkylbenzenes. J. Med. Chem. 19:727-728 (1976)

2.5 B Partition Coefficient

Method (e.g., OECD, others): Not specified

log Pow = 3.15

GLP: YES []
NO []
NO DATA [x]

Reference: Hansch, C, Leo, A, Nikaitani, D, On the additive-constitutive character of partition coefficients. J. Org. Chem. 37:3090-3092 (1972)

2.6 A Water Solubility

Method (e.g., OECD, others): Not specified

140 mg/l at 15 degree C

152 mg/l at 20 degree C

GLP: YES []

NO []

NO DATA [x]

Reference: Verschueren, K, Handbook of Environmental Data on Organic Chemicals. 2nd ed. New York, NY, Van Reinhold Co., 628-630 (1983).

2.6 B Water Solubility

Method (e.g., OECD, others): Not Specified

169 mg/l at 25 degree C

GLP: YES[]

NO []

NO DATA [x]

Reference: Howard, PH. And Meylan, WM. 1997. *In Handbook of Physical Properties of Organic Chemicals*, Lewis Publisher, Boca Raton, FL
Sanema, I. Araki, M. Deguchi, T. Nagai, H. 1982. Solubility measurements of benzene and alkylbenzenes in water by making use of solubility vapor. Bull. Chem. Soc. Jpn. 55: 1054-1062

2.7 A Flash Point

Method (e.g., OECD, others): Not specified

18 degree C - closed cup

GLP: YES []

NO []

NO DATA [x]

Reference: Windholz, M, ed. The Merck index. 10th ed. Rahway, NJ; Merck & Co., Inc., 546-547 (1983)

2.7 B Flash Point

Method (e.g., OECD, others): Not specified

26.7 degree C open cup

GLP: YES []
NO []
NO DATA [x]

Reference: CHRIS (Chemical hazards response information system). US Department of Transportation , US Coast Guard, Washington, DC. (1985)

2.8 Auto Flammability

432 degree C

GLP: YES []
NO []
NO DATA [x]

Reference: Sax, NI, Lewis, RJ Sr., Dangerous Properties Industrial Materials. Vol. II. 7th ed, New York, NY: Van Nostrand Reinhold, 1601 (1989)

2.9 Flammability

flammable

GLP: YES []
NO []
NO DATA [x]

Comments: Flammability limits are 1.0%-6.7%.

Reference: CHRIS (Chemical Hazards Response Information System). US Department of Transportation , US Coast Guard, Washington, DC (1985)

2.10 Explosive Properties

no data

2.11 Oxidizing Properties

no oxidizing properties

2.12 Additional Remarks

Soluble in most organic solvents including ethyl alcohol and ethyl ether.

The color of ethylbenzene liquid is colorless.

The odor of ethylbenzene is sweet, gasoline like odor.

3.1.1 Photodegradation

3.1.1 A Sensitizer: NO_3^-

$K \leq 0.6 \cdot 10^{-15} \text{ cm}^3/\text{molecule} \cdot \text{sec}$ at 298 K (relative to propene)

GLP: YES []
NO []
NO DATA [x]

Reference: Atkinson, R, Aschmann, SM, Winer, AM, Kinetics of the reactions of NO_3 radicals with a series of aromatic compounds. Environ. Sci. Technol. 21(11), 1123-1126 (1987)

3.1.1 B Sensitizer: OH^-

$K = 0.00000000000068 \text{ cm}^3/(\text{molecule} \cdot \text{sec})$

GLP: YES []
NO []
NO DATA [x]

Reference: Ohta, T, Ohyama, T, A set of rate constants for the reactions of hydroxyl radicals with aromatic hydrocarbons. Bull. Chem. Soc. Japan. 58, 3029-3030 (1985)

3.1.1 C Sensitizer: OH^-

$k = (7.50 \pm 0.38) \cdot 10^{-12} \text{ cm}^3/\text{mol} \cdot \text{sec}$ at 3 torr He;
 $k = (7.06 \pm 0.26) \cdot 10^{-12} \text{ cm}^3/\text{mol} \cdot \text{sec}$ at 20 torr He;
 $k = (7.95 \pm 0.28) \cdot 10^{-12} \text{ cm}^3/\text{mol} \cdot \text{sec}$ at 200 torr He.
The rate constant in the lower troposphere:
 $k = 8.20 \cdot 10^{-12} \text{ cm}^3/\text{mol} \cdot \text{sec}$.

Comment: The reaction of hydroxyl radicals with ethylbenzene were studied utilizing the flash photolysis-resonance fluorescence technique. The rate constants were measured at 298 K using He as diluent gas.

GLP: YES []
NO []
NO DATA [x]

Reference: Ravishankara, AR, Wagner, S, Fischer, S, Smith, G, Schiff, R, Watson, RT, Tesi, G, Davis, DD, A kinetics study of the reactions of hydroxyl with several aromatic and olefinic compounds. Int. J. Chem. Kinet. 10, 783-804 (1978)

3.1.1 D Sensitizer: OH^-

Comment: Degradation was approximately 50% after 1 day

GLP: YES []

NO []
NO DATA [x]

Reference: ECETOC, Joint Assessment of Commodity Chemicals, No. 7, p.6, ISSN 0773-6339-7 (1986)

3.1.1 E Sensitizer: OH⁻

$k = 8 \cdot 10^{-12} \text{ cm}^3/\text{mol} \cdot \text{sec}$; 300 degree K

GLP: YES []
NO []
NO DATA [x]

Reference: Singh, HB, Salas, LJ, Smith, AJ, Shigeishi, H, Measurements of some potentially hazardous organic chemicals in urban environments. Atmosph. Environ.15, 601-602 (1981)

3.1.1 F Sensitizer: OH⁻

Comment: Degradation was approximately 50% after 1 day

GLP: YES []
NO []
NO DATA [x]

Reference: ECETOC, Joint Assessment of Commodity Chemicals, No. 7, p.6, ISSN 0773-6339-7 (1986)

3.1.1 G Sensitizer: OH⁻

Conc. of Sensitizer 500000 molecule/cm³

$k = 7.1 \cdot 10^{-12} \text{ cm}^3/\text{mol} \cdot \text{sec}$; 25 deg C

GLP: YES []
NO []
NO DATA [x]

Reference: Atkinson, R, J. Phys. Chem. Ref. Data, Monograph No. 1 (1989)

3.1.1 H Sensitizer: OH⁻

Conc. of Sensitizer 500000 molecule/cm³

$k = 7.9 \cdot 10^{-12} \text{ cm}^3/\text{molecule} \cdot \text{sec}$

Comment: Degradation = 100 % after 2.9 day

GLP: YES []
NO []

NO DATA [x]

Reference: Wagner, HG, Zellner, R, Erdoel und Kohle-Erdgas-Petrochemie vereinigt mit. Brennstoff-Chemie 37(5), 212-219 (1984)

3.1.1 I Sensitizer: RO₂⁻

k = 0.65 1/mol*sec (30 deg C)

Comment: H-atom transfer from Benzyl-CH

GLP: YES []

NO []

NO DATA [x]

Reference: Hendry, DG, , Mill, T, Piskiewicz, L, Howard, JA, Eigenmann, HK, Critical review of hydrogen-atom transfer in the liquid phase. Chlorine atom, alkyl, trichloromethyl, alkoxy, and alkylperoxy radicals. J. Phys. Chem. Ref. Data 3, 944-978 (1974)

3.1.1 J Sensitizer: not specified

K = 6.94 * 10⁻¹² cm³/mol*s; measured with AOP according to Meylan at 305 K

K = 7.95 * 10⁻¹² cm³/mol*s; measured with AOP according to Meylan at 298 K

K = 6.51 * 10⁻¹² cm³/mol*s; measured with AOP according to at room temperature.

Comment:

GLP: YES []

NO []

NO DATA [x]

Reference: Atkinson, R, J. Phys. Chem. Ref. Data; Monograph 1 (1989); Meylan, W; Howard, P, Atmospheric Oxidation Programme Version 1.5. Syracuse Research Corporation. New York (1993)

3.1.1 K Methanol Solution

Comment: Photolysis in air or surface water unlikely as no significant absorption over 290 nm (measured in methanol)

Comment: absorption coefficient (1/mol*cm)/wavelength (nm): 0.142*10³ at 269.5; 0.2*10³ at 260.5; 0.168*10³ at 254.5; 7.52*10³ at 208. Ethylbenzene does not significantly absorb light above 290 nm in methanol solution.

GLP: YES []

NO []

NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large production Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

Reference: Sadtler, N.A., Standard Spectra, UV No. 97, cited in HSDB (11/92)

3.1.2 Stability in Water

3.1.2 A Hydrolysis

Comment: Ethylbenzene is resistant to hydrolysis. This estimation was based upon professional judgement since ethylbenzene does not contain any hydrolysable functional groups.

Reference: Lyman, WJ, et al., Handbook of Chemical Property Methods, McGraw-Hill, NY, 7-1 to 7-4 (1982)

3.1.3 Stability in Soil

Soil Partition Coefficient

Method (e.g., OECD, others): Not specified

Log K_{oc} = 2.21

GLP: YES []
NO [X]
NO DATA []

Reference: Chiou, CT, Porter, PE, Schmedling, DW, Partition equilibria of nonionic organic compounds between soil organic matter and water. Environ. Sci. Technol. 17, 227-231 (1983)

Chiou et al. reported a log K_{om} NOT log K_{oc}. To convert one needs to divide by 0.58 (Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: large production Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2 Monitoring Data (Environment)

3.2.1 A Media: air : *Occupational Exposure*

U.S. ethylbenzene producers compiled worker exposure data collected over the past 10 years. There were a total of 1727 personal monitoring samples (8-hour time-weighted averages) representing exposures of process operators, maintenance workers, loading/unloading, quality laboratory workers and supervisory/professional workers. Of these data, approximately 71% of the exposures were either non-detectable or less than 0.1 ppm, 25% were greater than 0.1 ppm to 1.0 ppm, 4% were greater than 1.0 ppm and less than 5 ppm, and 0.4% were greater than 5 ppm (4 of 6 samples were less than 9 ppm, 2 samples unspecified). Thus, worker exposure during production of ethylbenzene is very low.

GLP: YES []
NO [x]

NO DATA []

Reference: ACC Ethylbenzene Panel. Worker exposures in U.S. ethylbenzene production (2000)

3.2.1 B Media: air : *Occupational Exposure*

Typical workplace exposure levels of ethylbenzene in styrene and ethylbenzene processing plants ranged from 0.1 to 1 ppm for an 8 hour time-weighted average. Exposure levels during routine operations were reported to be well below 1 ppm, ranging from 0.01 to 0.5 ppm.

GLP: YES []
NO [x]
NO DATA []

Reference: Helmes, CT. Data Submission to the Agency for Toxic Substances and Disease Registry Regarding Workplace Exposure Levels of Ethylbenzene. Synthetic Organic Chemical Manufacturers Association, Washington, DC (1990).

3.2.1 C Media: air : *Occupational Exposure*

Workers in paint spray booths: TWA ethylbenzene conc. 1.2 ppm (5.3 mg/m³)
Highest TWA exposure was 4.4 ppm (19 mg/ m³)

GLP: YES []
NO []
NO DATA [x]

Reference: Whitehead, LW, Ball, GL, Fine, LJ, Langolf, GD, Solvent vapor exposures in booth spray painting and spray glueing, and associated operations. Am. Ind. Hyg. Assoc. J. 45: 767-772 (1984)

3.2.1 D Media: air : *Occupational Exposure*

TWA exposures for pressroom and plate maker workers ranged from 0 to 36 mg/m³ (8.4 ppm)

GLP: YES []
NO []
NO DATA [x]

Reference: Ahrenholz, SH, Health Hazard Evaluation Determination Report No. HHE-80-18-691, Looart Press Incorporated, Colorado Springs, Colorado. Hazard Evaluation and Technical Assistance Branch, NIOSH, Cincinnati, Ohio (1980)

3.2.1 E Media: air : *Occupational Exposure*

Roofers exposed to ethylbenzene in solvents; exposure ranged from undetectable to 1.3 mg/m³ (0.3 ppm)

GLP: YES []
 NO []
 NO DATA [x]

Reference: Reed, L, Health Hazard Evaluation Determination Report No. HETA-83-380-1671, Roofing sites, Dayton, Ohio. Hazard Evaluation and Technical Assistance Branch, NIOSH, Cincinnati, Ohio (1986)

3.2.1 F Media: air : *Occupational Exposure*

Ethylbenzene conc. in 11 paint shops in Spain ranged from 0.5 to 125 mg/m³ (0.1 - 29 ppm). The median was 21.8 mg/m³ (4.9 ppm)

GLP: YES []
 NO []
 NO DATA [x]

Reference: Medinilla, J de, Espigares, M, Contamination by organic solvents in auto paint shops. Ann. Occup. Hyg. 32: 509-513 (1988)

3.2.1 G Media: air : *Occupational Exposure*

The maximum TWA conc. of ethylbenzene in 11 paint shops in the Netherlands ranged from 0.11 to 3.21 mg/m³ (0.03 - 0.75 ppm)

GLP: YES []
 NO []
 NO DATA [x]

Reference: Verhoeff, AP, Suk, J, van Wijnen, JH, Residential indoor air contamination by screen printing plants. Int. Arch. Occup. Environ. Health 60: 201-209 (1988)

3.2.1 H Media: air : *Occupational Exposure*

ethylbenzene concentration	(µg/m ³)	mean	range
indoor air in Milan, Italy:		21	2-40
outdoor air (traffic wardens) in Milan, Italy:		37	11-87
	(ng/l)	before shift	after shift
blood of indoor workers (means):		140	162
blood of traffic wardens (means):		158	184

GLP: YES []
 NO []
 NO DATA [x]

Reference: Fustinoni, S, Buratti, M, Giampiccolo, R and Colombi, A, Biological and environmental monitoring of exposure to airborne benzene and other aromatic hydrocarbons in Milan traffic wardens. Toxicol. Lett. 77: 387-392 (1995)

3.2.1 I Media: air : *Occupational Exposure*

Long-term exposure to ethylbenzene (8 hr TWA) ranged from < 0.01 ppm to <1 ppm for service station attendants and mechanics in 16 service stations nationwide. Short-term exposures (15 minutes) ranged from <0.07 ppm to 8.7 ppm

GLP: YES []
NO []
NO DATA [x]

Reference: API, Service Station Exposures to Oxygenated Fuel Components - 1994, API Publication 4625 (August 1995)

3.2.2 A Media: air

Consumers at gasoline service stations may be exposed to ethylbenzene levels of 0.01 ppm in ambient air.

GLP: YES []
NO []
NO DATA [x]

Reference: American Petroleum Institute, Gasoline vapor assessment at service stations. API Publication 4553, Washington, DC (1991).

3.2.2 B Media: air

Median air concentrations of ethylbenzene in the US have been measured to be 0.156 ppb for 6 remote locations, 0.013 ppb for 122 rural locations, 0.62 ppb for 886 suburban locations, and 0.62 ppb for 1532 urban locations.

GLP: YES []
NO []
NO DATA [x]

Reference: Shah, JJ and Heyerdahl, EK, National ambient volatile organic compounds (VOCs) data base update. Report by Nero and Associates, Inc. Portland, OR to Environmental Protection Agency, Atmospheric Sciences Research Laboratory, Research Triangle Park, NC. EPA 600/3-88/010(A) (1988), as cited in ATSDR (1997). Draft Toxicological Profile for Ethylbenzene. Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services.

3.2.2 C Media: air

Ethylbenzene in expired air from 54 humans: 16.5% positive for ethylbenzene; mean 1.8 mg/m³ (0.4 ppm)

GLP: YES []
NO []
NO DATA [x]

Reference: Krotoszynski, BK, Bruneau, GM, O'Neill, HJ, Measurement of chemical inhalation exposure in an urban population in the presence of endogenous effluents. *J. Anal. Toxicol.* 3: 225- 234 (1979)

3.2.2 D Media: air

Mean concentrations were 0.33, 0.26 and 0.17 ppb (n=38 of 38, 36 of 37 and 33 of 35, 24-h-measurements). Newark, Elizabeth, Camden (NJ, USA): July/August 1981:

GLP: YES []
NO []
NO DATA [x]

Reference: Harkov, R, Kebbekus, B, Bozzelli, JW, Liroy, PJ, Measurement of selected volatile organic compounds at 3 locations in New Jersey (USA) during the summer season. *J. Air Pollut. Control Assoc.* 33 (12), 1177-1183 (1983)

3.2.2 E Media: air

Portland, OR, USA, 1984: 0.78-2.8 $\mu\text{g}/\text{m}^3$ (0.18-0.65 ppb), mean value 1.3 $\mu\text{g}/\text{m}^3$ (n=7)

GLP: YES []
NO []
NO DATA [x]

Reference: Ligocki, MP, Leuenberger, C, Pankow, JF, Trace organic compounds in rain II. Gas scavenging of neutral organic compounds. *Atmos. Environ.* 19, 1609-1617 (1985)

3.2.2 F Media: air

Pacific Ocean (ca. 42 Grad N- 30 Grad S, 1983): northern hemisphere: mean = 7.6 +/- 3.7 ppt (n=35), southern hemisphere: mean = 3.7 +/- 1.6 ppt (n=21)

GLP: YES []
NO []
NO DATA [x]

Reference: Nutmagul, W, Cronn, D.R., Determination of selected atmospheric aromatic hydrocarbons at remote continental and oceanic locations using photionization/flame-ionization detection. *J. of Atmos. Chem.* 2, 415-433 (1985)

3.2.2 G Media: air

Ethylbenzene concentration in the air of flats of smokers and non-smokers in the USA (mean values): 3.5-8.3 $\mu\text{g}/\text{m}^3$ (smokers) resp. 3.5-5.1 $\mu\text{g}/\text{m}^3$ (non-smokers); 5.2 (smokers) resp. 4.6 $\mu\text{g}/\text{m}^3$ (non-smokers) (in the night; New Jersey, Los Angeles, Antioch)

GLP: YES []
NO []
NO DATA [x]

Reference: Wallace, L, Pellizzari, E, Hartwell, TD, Perritt, R, Ziegenfus, R, Exposures to benzene and other volatile compounds from active and passive smoking. Arch. Environ. Health 42: 272-279 (1987)

Reference: Wallace, LA, Pellizzari, ED, Personal air exposures and breath concentrations of benzene and other volatile hydrocarbons for smokers and nonsmokers. Toxicol. Lett., 35, 113-116 (1986)

3.2.2 H Media : air

Mean ethylbenzene concentration in clean air areas (Black Forest, FRG): 0.4 ug/m³ (0.1 ppb); no more details.

Reference: Juettner, F, Analysis of organic compounds (VOC) in the forest air of the Southern Black Forest. Chemosphere 15: 985-992 (1986)

Reference: Juettner, F, Motorboat-derived volatile organic compounds (VOC) in lakewater. Z. Wasser Abwasser Forsch., 21: 36-39 (1988)

3.2.2 I Media: air

Areas in the continental United States ranged between 0.5 to 2.2 ppb.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 J Media: air

Air in England - 0.011 ppb average

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 K Media: air

The Netherlands - 0.8 ppb average; and Belgium 0.01 to 15 ppb.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 L Media: air

Concentration at rural site in UK, May-Aug 1983, 204 samples, not detected - 0.7 ppb, 0.14 average; July 1982, 175 samples, not detected - 0.6, 0.12 average.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 M Media: air

Values for major western U.S. cities ranged from 0.1 to 27.7 ppb, average 2.68 ppb.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 N Media: air

Representative centers in New Jersey had a range of 0.17 to 0.33 ppb average, 107 to 110 sample pos.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 O Media: air

The Hague, Netherlands - 5 ppb

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 P Media: air

Frankfurt/Main - 1 ppb
Japan (urban/suburban) - 0.2 ppb

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 Q Media: air

Zurich, Switzerland - 8.7 ppb

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 R Media: air

3 sites in England away from traffic - 0.0161 to 0.0188 ppb average;
2 sites with heavy traffic 0.0287 to 0.0339 ppb average.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 S Media: air

669 samples from the United States had a median concentration of 1.2 ppb

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 T Media: air

Gas-phase concentration (ng/m^3) during 7 rain events, Portland, OR, Feb-Apr 1984, 100% pos., 780-2800, 1300 avg.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 U Media : air

Exhibition Road, London,
May-Aug 1983, 267 samples, 100% pos., 0.05-2.17 ppb, 0.78 ppb average
June-July 1982, 256 samples, not detected - 3.3 ppb, 0.88 ppb average

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 V Media: air

United States 1979-1984, 15 cities, 1-2 weeks of sampling/site, overall range not detected - 31.5 ppb; range of average 0.6-4.6 ppb, average of average 1.9 ppb

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.2 W Media: air

Ethylbenzene concentration in industrial air; air sample: medical solutions (mean values): 94 (Finland) resp. $2 \mu\text{g}/\text{m}^3$ (Chicago, USA); no further information.

GLP: YES []
NO []

NO DATA [x]

Reference: Kroneld, R, Volatile pollutants in suburban and industrial air. Bull. Environ. Contam. Toxicol. 42: 868-872 (1989)

3.2.2 X Media: air

Annual means (1989) of ethylbenzene concentration in the air of the FRG: Hamburg: suburb, periphery; municipal residential area: ca. 6-7 $\mu\text{g}/\text{m}^3$; municipal traffic resp. industrial area: ca. 10-22 $\mu\text{g}/\text{m}^3$; inner rooms, municipal area: 0 $\mu\text{g}/\text{m}^3$; probably Deuselbach: rural area: ca. 1 $\mu\text{g}/\text{m}^3$

GLP: YES []
NO []
NO DATA [x]

Reference: UBA, Daten zur Umwelt 1990/91. Umweltbundesamt, Erich Schmidt, Berlin (1992)

3.2.2 Y Media: air

Ethylbenzene concentration overall mean reported by Texas Natural Resource Conservation Commission (TNRCC) for 1992 to 1997 was 0.33 ppb from 43 monitoring Sites.

GLP: YES []
NO []
NO DATA [x]

Reference: TNRCC, Air Quality Assessment Program: Community Air Toxics Monitoring Program Report 1992 - 1997, Texas Natural Resource Conservation Commission, Austin, Texas (1998)

3.2.2 Z Media: air

Extensive monitoring during 1999 and 2000 in Texas City and LaMarque, Texas down wind of an industrial complex with three refineries and three chemical plants found ambient concentrations of 0.34 ppb or less at each monitoring site. The mean concentration at all sites in 1999 was 0.16 ppm.

GLP: YES []
NO []
NO DATA [x]

Reference: Texas City/La Marque Community Air Monitoring Network (2000)

3.2.2 AA Media: air

Modeled air concentrations in homes based on ethylbenzene volatilization from drinking water (showers, etc.), volatilization from household products, and from environmental

tobacco smoke. Estimated increments from each source was Household products - 7.9 $\mu\text{g}/\text{m}^3$, water use - 0.2 $\mu\text{g}/\text{m}^3$, ETS - 0.6 $\mu\text{g}/\text{m}^3$.

GLP: YES []
NO []
NO DATA [x]

Reference: Ligocki, MP, Stiefer, PS, Rosenbaum, AS, Atkinson, RD and Axelrad, D, Cumulative exposures to air toxics: Indoor sources. Air & Waste Management Association Meeting, 88: paper 95-TP33B.03, 1-16 (1995)

3.2.2 BB Media: air

Presents a national air toxics inventory based on 1990 data using VOC-derived toxic emissions and TRI data; poor agreement between two sources. For ethylbenzene, estimated emissions in tons/day are:

area sources - 69,
nonroad mobile - 99,
on-road mobile - 203,
manufacturing - 15,
other point sources - 11;
total - 395 tons/day

GLP: YES []
NO []
NO DATA [x]

Reference: Ligocki, MP, Gardner, L, Tunggal, HH, Heiken, JG, Atkinson, RD and Axelrad, D, Cumulative exposures to Air Toxics: Emission inventories for mobile and stationary sources. Air & Waste Management Association Meeting, 88: paper 95-RA110.01, 1-19 (1995)

3.2.2 CC Media: air: *Laboratory experiment*

Ethylbenzene concentration in gasoline vapors during refinery, transportation and fueling operations reviewed: values reported <0.1 % to 0.4 % of total vapor detected. In liquid light catalytically cracked naphtha sample 1.5%, in static headspace 0.1%; not detected in inhalation chamber during 13 week subchronic study in rats.

GLP: YES [x]
NO []
NO DATA []

Reference: Dalbey, WE, Feuston, MH, Yang, JJ, Kommineni, CV and Roy, TA, Light catalytically cracked naphtha: subchronic toxicity of vapors in rats and mice and developmental toxicity screen in rats. J. Toxicol. Environ. Health 47: 77-91 (1996)

3.2.3 A Media: soil

76 mg ethylbenzene/kg in the soil of a former asphalt production unit (Deventer, Netherlands)

GLP: YES []
NO []
NO DATA [x]

Reference: Van der Hoek, JP, Urlings, LGCM, Grobber, CM, Biological Removal of Polycyclic Aromatic Hydrocarbons, Benzene, Toluene, Ethylbenzene, Xylene and Phenolic Compounds from Heavily Contaminated Ground Water and Soil. Environ. Technol. Lett. 10: 185-194 (1989)

3.2.3 B Media: sediment

USEPA STORET database, 350 data points, 11% pos., 5.0 ppm median, dry wt.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.4 A Media: drinking water

Drinking water (USA): <0.5-1.1 ug/l, Median 0.74-0.95 ug/l (n=6 of 945)

GLP: YES []
NO []
NO DATA [x]

Reference: Westrick, JJ, Westrick JJ; Mello, JW, Thomas, RF, The groundwater supply survey. Journal American Water Works A. 76(5), 52-59 (1984)

3.2.4 B Media: drinking water

Untreated drinking water and drinking water (Canada, ca.1981): <1-7 ug/l

GLP: YES []
NO []
NO DATA [x]

Reference: ECETOC, Joint Assessment of Commodity Chemicals, No.7, p.8, ISSN 0773-6339-7 (1986)

3.2.4 C Media : drinking water

Drinking water from riverbank filtrate (Rhein, NL, ca.1982): 30 ppb

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ., Inc., Michigan (1989)

3.2.4 D Media: drinking water

Drinking water (Chicago, IL, USA, ca.1977): 4 ppb
Drinking water (New Orleans, LA, USA, prior to 1976): 1.6-2.3 ppb (n=3)
Drinking water from ground water (USA, 1982): <0.5-1.1 ppb
Median (of samples over the detection limit) 0.8 ppb (n=3 of 466)

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.5 A Media: other: *water*

Kawamura and Kaplan (1983) found 9 ng/l (ppt) of ethylbenzene in the rain water of Los Angeles. The Commission of the European Communities (CEC-1976) reported ethylbenzene levels which in most cases were less than 1 ug/l (ppb). This was also true in a more recent study of 30 Canadian water-treatment facilities where the average level of ethylbenzene was less than 1 ug/l, with a maximum in treated, potable water of 7 ug/l. Analysis of surface sea-water in the Gulf of Mexico showed levels of ethylbenzene from 0.5 to 4.4 ng/l.

GLP: YES []
NO []
NO DATA [x]

Reference: ECETOC, Joint Assessment of Commodity Chemicals, No.7, p.8, ISSN 0773-6339-7 (1986)

3.2.5 B Media: other: *running water*

Rhing (1986): South <500 ng/l; Middle <500 ng/l; North 160 ng/l.

GLP: YES []
NO []
NO DATA [x]

Reference: Report on water purity 1986, publisher: Landesamt fuer Wasser und Abfall [Regional authority for water and refuse] North Rhine-Westphalia, Duesseldorf (1987)

3.2.5 C Media : other: *running water*

Emscher (1986): max. 500 ng/l

Lippe (1986): <500 ng/l

GLP: YES []

NO []

NO DATA [x]

Reference: Report on water purity 1986, publisher: Landesamt Fuer Wasser und Abfall [Regional Authority for water and refuse] North Rhine-Westphalia, Duesseldorf (1987)

3.2.5 D Media: other: *running water*

Brazos River (Texas, USA, 1982-1988): <4-43 ng/l (n=4 of 5) At the mouth of the Brazos River (Texas, USA, 1982-1988): <4 and 50 ng/l (n=2 of 5)

GLP: YES []

NO []

NO DATA [x]

Reference: McDonald TJ; Kennicutt II, MC, Brooks, JM, Volatile organic compounds at a coastal Gulf of Mexico site. Chemosphere 17(1), 123-136 (1988)

3.2.5 E Media: other: *surface water*

Lower Tennessee River near Calvert City, KY reported 4.0 ppb

GLP: YES []

NO []

NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.5 F Media: other: *surface water*

North Sea, max. concentration 0.02 ppb

GLP: YES []

NO []

NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.5 G Media: other: *snow*

Duebendorf, CH, 1985: 130-2700 ng/l, mean value 1100 ng/l (n=5)

GLP: YES []
NO []
NO DATA [x]

Reference: Czuczwa, J, Leuenberger, C, Giger, W, Seasonal changes of organic compounds in rain and snow. *Atmos. Environ.* 22(5), 907-916 (1988)

3.2.5 H Media: other: *rainwater*

Portland, OR, USA, 1984: dissolved 6.9-72 ng/l, mean value 31 ng/l (n=7)

GLP: YES []
NO []
NO DATA [x]

Reference: Ligocki, MP, Leuenberger, C, Pankow, JF, Trace organic compounds in rain II. Gas scavenging of neutral organic compounds. *Atmos. Environ.* 19, 1609-1617 (1985)

3.2.5 I Media: other: *rainwater*

Duebendorf, CH, 1985: <15-440 ng/l, mean value 280, 35, 15 and 61 ng/l depending on time of year (n=13)

GLP: YES []
NO []
NO DATA [x]

Reference: Czuczwa, J, Leuenberger, C, Giger, W, Seasonal changes of organic compounds in rain and snow. *Atmos. Environ.* 22(5), 907-916 (1988)

3.2.5 J Media: other: *rainwater*

Concentration dissolved in rain, Portland, OR, Feb-April 1984, 7 rain events, 100% pos., 6.9-72 ppt, 34 ppt average.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.5 K Media: other: *seawater*

Gulf of Mexico, unpolluted areas - 0.4 to 5 ppb, an area of anthropogenic influence ranged from 5 to 15 ppb.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.5 L Media: other: *seawater*

North Sea (NL, 1980): <5-20 ppt, mean value 4 ppt (n=108)

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.5 M Media: other: *wastewater*

Ethylbenzene concentration in waste waters from various outlets (mean values): percolating filter: <0.1 ug/l (Stevenage, England); sewage sludge: 39 ug/l; percolation filter: 1.4 ug/l; pre-purification: 0.03-11 ug/l (all California, USA); 0.2-8.7/0.02-0.5 ug/l (inlet), <0.01 - 0.18/0.02-0.06 ug/l (outlet) (Orange County, California, USA)

GLP: YES []
NO []
NO DATA [x]

Reference: COST 64b, Concerted Action. - Analysis of Organic Micropollutants in Water, 4th ed., Vol. I (1984)

Reference: McCarty, PL, Reinhard, M, Trace organics removal by advanced wastewater treatment. J. Water Pollut. Control Fed. 52: 1907-1922 (1980)

3.2.6 A Media: *biota*

Ethylbenzene concentration in different parts of various plants:

Loquat and Curuba fruit: 10-100 µg/kg (Wuerzburg, FRG)
Centaurea calcitrapa: leaves 0.12 µg/g, flowers 0.56 µg/g (California, USA)
Centaurea solstitialis: flowers 0.04 µg/g; bud 0.05 µg/g (California, USA)

GLP: YES []
NO []
NO DATA [x]

Reference: Binder, RG, Turner, CE, Flath, RA, et al., Volatile components of purple star thistle. *J. Agric. Food Chem.*, 38, 1053-1055 (1990)

Reference: Binder, RG, Benson, ME, Flath, RA, Volatile components of Safflower. *J. Agric. Food Chem.*, 38 1245-1248 (1990)

Reference: Froehlich, O, Duque, C, Schreier, P, Volatile constituents of curuba passiflora-mollissima fruit. *J. Agric. Food Chem.* 37: 421-425 (1989)

Reference: Froehlich, O, Scheier, P, Volatile constituents of loquat eriobotrya-japonica lindl.fruit. *J. Food Sci.* 55, 176-180 (1990)

3.2.6 B Media: food

Ethylbenzene concentration in food: pork fat 31.3 µg/kg (California, USA);
skin of fried chicken 2 µg/kg (Vevy, Switzerland)

GLP: YES []
NO []
NO DATA [x]

Reference: Noleau, I, Toulemonde, B, Volatile components of roasted guinea hen. *Lebensm.-Wiss. Technol.*, 21, 195-197 (1988)

Reference: Yasuhara, A, Shibamoto, T, Headspace volatiles from heated pork fat. *Food Chem.* 37: 13-20 (1990)

3.2.6 C Media: food

Detected in dried legumes: beans, not detected - 11 ppb, 5 ppb average; split peas - 13 ppb;
lentils - 5 ppb.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.2.6 D Media: human blood

Ethylbenzene in blood samples of 250 humans ranged from not detectable to 59 ppb, with a mean level of 1 ppb.

GLP: YES []
NO []

NO DATA [x]

Reference: Antoine, SR, DeLeon, IR, O'Dell-Smith, RM, Environmentally significant volatile organic pollutants in human blood. Bull. Environ. Contam. Toxicol. 36: 364-371 (1986)

3.3.1 Transport between Environmental Compartments

3.3.1 A Comment: The sediment to water partition coefficients have been measured for ethylbenzene with HPLC. The sediment or soil-water partition coefficient is an important parameter - for ethylbenzene: $\log K_p = 1.01$

GLP: YES []
NO []
NO DATA [x]

Reference: Vowles, PD, Mantoura, RFC, Sediment-water partition coefficients and HPLC retention factors of aromatic hydrocarbons. Chemosphere 16: 109-116 (1987)

3.3.1 B Comment: Ethylbenzene has a moderate adsorption for soil. The measured K_{oc} for silt loam was 164. Its presence in bank infiltrated water suggests that there is a good probability of its leaching through soil. Using its octanol/water partition coefficient and using a recommended regression equation, one can calculate a $\log K_{oc}$ of 2.94.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989). Chiou, CT, Porter, PE, Schmedding, DW. 1983. Partition equilibria Of nonionic organic compounds between soil organic mater and water.

3.3.1 C Comment: A half-life for evaporation from water with 1 m/sec current, 3 m/sec wind, and 1 m depth is 3.1 h.

GLP: YES []
NO []
NO DATA [x]

Reference: Lyman, WJ, Reehl, WF, Rosenblatt DH, Handbook of Chemical Property Estimation Methods, Environmental Behaviour of Organic Compounds, New York, McGraw-Hill, p. 15-25 (1982)

3.3.1 D Comment: In a mesocosm experiment using simulated conditions for Narragansett Bay, MA, and seasonal conditions, the loss of ethylbenzene was primarily by evaporation in winter ($t_{1/2} = 13$ days).

GLP: YES []
NO []

NO DATA [x]

Reference: Wakeham, SG, Davis, AC, Karas, JL, Mesocosm Experiments to Determine the Fate and Persistence of Volatile Organic Compounds in Coastal Seawater. Environ. Sci. Technol. 17: 611-617 (1983).

3.3.1 E Comment: Henry's Law Constant: $6.44 \cdot 10^{-3}$ atm*m³/mol at 298 K.

GLP: YES []
NO []
NO DATA [x]

Reference: Shen, TT, Estimation of organic compound emissions from waste lagoons. J. Air Poll. Cont. Assoc. 32: 79-82 (1982)

3.3.1 F Comment: Henry's Law Constant: 0.37 (measured)

GLP: YES []
NO []
NO DATA [x]

Reference: Lyman, WJ, Reehl, WF, Rosenblatt DH, Handbook of Chemical Property Estimation Methods, Environmental Behavior of Organic Compounds, New York, McGraw-Hill, p. 9-60 (1982)

3.3.1 G Comment: Henry's Law Constant: $8.43 \cdot 10^{-3}$ atm*m³/mol (25 deg C)

GLP: YES []
NO []
NO DATA [x]

Reference: Mackay, D, Shiu, WY, Sutherland, RP, Determination of air-water Henry's Law constants for hydrophobic pollutants. Environ. Sci. Technol. 13: 333-336 (1979)

3.3.1.H Theoretical Distribution (Fugacity Calculations)

The Level I Model by Mackay (1,2) was used to evaluate the distribution of ethylbenzene between environmental compartments. Chemical-physical properties were used to quantify ethylbenzene's behavior.

Media: Air-biota []; Air-biota-soil-sediment-water [**X**]; Soil-biota []; Water-air []; Water-biota []; Water-soil []; Other []

Method: Fugacity level I [**X**]; Fugacity level II []; Fugacity level III []; Fugacity level IV []; Other (calculation) []; Other (measurement) []

Results:

TABLE 1: RESULTS OF LEVEL I MODELING

MEDIA	AMOUNT
Air:	98.6%
Water:	0.6%
Soil:	0.8%
Sediment:	0.02%
Biota:	0.0004%

1998 TRI data base (Table IV).

Table 2. The required input values for Level I & Level III modeling of ethylbenzene.

Property	Value
Chemical Type	1
Molecular Mass (g/mol)	106.2
Data Temperature (Degrees Celsius)	25
LogKow	3.15
Water Solubility (g/m ³)	169
Vapor Pressure (Pa)	1270
Melting Point (Degrees Celsius)	-95
Amount of Chemical Released to Each Compartment (kg/yr)	10,000
Henry's Law Constant (Pa.m ³ /mol)	798.1

References: Mackay D, Paterson, S., Kicsi, G., Di Guardo, A., Cowan, C.E. "Assessing the Fate of New and Existing Chemicals: A Five Stage Process". Environ. Toxicol. Chem. 15 No.9 , 1618-1626, 1996.

Mackay D, Paterson, S., Di Guardo, A., Cowan, C.E. "Evaluating the Environmental Fate of a Variety of Types of Chemicals Using the EQC Model", Environ. Toxicol. Chem. 15 No.9, 1627- 1637, 1996.

Dow Chemical Company. Assessment of Ethyl benzene's transport and partitioning in the environment using the EQC Model, Internal Dow Report, 2000.

3.3.1. I Theoretical Distribution (Fugacity Calculations)

The EQC (Equilibrium Criterion) Model by Mackay (1,2) was used to evaluate the distribution of ethyl benzene between environmental compartments. Chemical-physical properties were used to quantify ethyl benzene's behavior.

The level III calculation has the environmental matrices and the chemical of interest flowing through the system. The level III model calculation constrains the chemical of interest to

steady state concentrations in each media. The chemical of interest is released into the individual compartments and can degrade within compartments. The results of modeling are presented in Table 1. The required input values for level III modeling of ethyl benzene are listed in Tables 2, 3, and 4. The Mackay level III was used to calculate the transport between environmental compartments.

Media: Air-biota []; Air-biota-soil-sediment-water [**X**]; Soil-biota []; Water-air []; Water-biota []; Water-soil []; Other []

Method: Fugacity level I []; Fugacity level II []; Fugacity level III [**X**]; Fugacity level IV []; Other (calculation) []; Other (measurement) []

Results:

TABLE 1: RESULTS OF LEVEL III MODELING

MEDIA	AMOUNT	HALF-LIFE (h)
Air: Bulk	96.10%	-
Pure Air	96.10%	36
Aerosol	0.00%	360
Water: Bulk	0.89%	-
Water	0.89%	360
Suspended Sediment	0.00%	850
Fish	0.00%	850
Soil: Bulk	2.99%	360
Air	0.01%	
Water	0.06%	
Solid	2.91%	
Sediment: Bulk	0.01%	1440
Water	0.00%	
Solid	0.01%	

Based on the TRI release data, the emissions of ethylbenzene in the U.S. are primarily to air. The ultimate partitioning of ethylbenzene in the environment is expected to be to air, with very minor partitioning to other compartments. The half-life of vapor in air is estimated to be 36 hours.

Remarks: Default volumes for mass of chemical released into air-soil water were based on the percentages reported in the 1998 TRI data base.

Table 2. The required input values for Level I & Level III modeling of ethyl benzene.

Property	Value
Chemical Type	1
Molecular Mass (g/mol)	106.2
Data Temperature (Degrees Celsius)	25
LogKow	3.15
Water Solubility (g/m ³)	169
Vapor Pressure (Pa)	1270
Melting Point (Degrees Celsius)	-95
Henry's Law Constant (Pa.m ³ /mol)	798.1

Table 3: Emission input values for Level III

Emission Rate	kg/h (%)	mol/h
to Air	2985 (99.5)	28107
to Water	3.5 (0.1)	33
to Soil	11.5 (0.4)	108
to Sediment	0 (0)	0

Table 4: TRI on-site and off-site reported release (in pounds) in United States, 1998, all industries. (U.S. Environmental Protection Agency, 1998)

Emission Rate	Lbs.	Kgs	%
Total to Air	8,499,147	3,855,148	99.5
Total to Water	10,408	4,721	0.1
Total to Soil	32,863	14,906	0.4
To Sediment	0	0	0

References: Mackay D, Paterson, S., Kicsi, G., Di Guardo, A., Cowan, C.E. "Assessing the Fate of New and Existing Chemicals: A Five Stage Process". Environ. Toxicol. Chem. 15 No.9, 1618-1626, 1996.

Mackay D, Paterson, S., Di Guardo, A., Cowan, C.E. "Evaluating the Environmental Fate of a Variety of Types of Chemicals Using the EQC Model", Environ. Toxicol. Chem. 15 No.9, 1627- 1637, 1996.

Dow Chemical Company. Assessment of Ethyl benzene's transport and partitioning in the environment using the EQC Model, Internal Dow Report, 2000.

U.S. Environmental Protection Agency. 1998. Toxics Release Inventory (TRI) Public Data Release Report (EPA 745-R-00-007), <http://www.epa.gov/tri/tri98/>

3.3.1 J

Half-lives of TS:	Initial conc. (ug/l)	Half-life (d)
winter (3-7 degree C)	2.5	13
spring (8-16 degree C)	3.3	20
summer (20-22 degree C)	2.4	.1

Comment: Batch-tests in experimental marine ecosystems (mesocosms: tanks containing 13 m³ of Seawater); ethylbenzene concentrations in the water columns followed for up to 2 months, under experimental conditions simulating winter, spring, and summer; analysis of TS by GC. Volatization appears to be the major process removing TS during all seasons; although biodegradation of ethylbenzene may account for some of the loss.

Reference: Wakeham, SG, Davis, AC, Karas, JL, Mesocosm Experiments to Determine the Fate and Persistence of Volatile Organic Compounds in Coastal Seawater. Environ. Sci. Technol. 17, 611-617 (1983).

3.3.2 Distribution

3.3.2 A Comment: On the basis of the physicochemical properties, the following is the likely relative compartmentalization of ethylbenzene emissions:

air	98%
water	1.5%
ground/sediment	0.5%

GLP: YES []
NO []
NO DATA [x]

Reference: Koch, R, Umweltchemikalien, VCH Weinheim, 235-236 (1991)

3.3.2 B Comment: Atmospheric fate: If ethylbenzene is released to the atmosphere, it will exist predominantly in the vapor phase based on its vapor pressure.

GLP: YES []
NO []
NO DATA [x]

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.3.2 C Media: other: *sediment - water*

Sediment-water partition coefficient = 10.2

Comment: Surface sediment from the central Tamar estuary (Australia), mixed with water and ethylbenzene solution (in acetone), was incubated for 2 hours; analyses of ethylbenzene by GC.

Test condition 18.5 degree C, stirred

GLP: YES []
NO []
NO DATA [x]

Reference: Vowles, PD, Mantoura, RFC, Sediment-water partition coefficients and HPLC retention factors of aromatic hydrocarbons. Chemosphere 16: 109-116 (1987)

3.5 Biodegradation

3.5.1 A Test type: aerobic

Inoculum Adapted [] non-adapted [x]

Test substance, purity: 99.5%

Concentration of chemical....related to COD []; DOC [x]; Test substance [x];

Method: OECD Guidelines for Testing of Chemicals, "Ready Biodegradability: Modified OECD Screening Test", Procedure 301E, adopted draft ENV/EPOC(92)15, March 1992

Medium water [x]; water-sediment []; soil []; sewage-treatment [];

GLP Yes [] No [x]

Results: 100% degradation after 6 days
(see OECD Guidelines) ready biodeg. []; inherently biodeg. [x];
Under test conditions no biodeg. Observed []; other []

Comment: Volatilisation cannot be discounted as a removal mechanism in tests conducted in open systems.

Reference: Dow Chemical Company. Evaluation of the biodegradation of ethylbenzene in the Modified OECD Screening test, Internal Dow Report, 1994.

3.5.1 B Test type: aerobic

Test medium: A. water, acclimated activated sludge seed
B. water, activated sludge

ethylbenzene concentration not given

Test Method: Screening-Test (BOD of THOD); Acclimation period: 16 +/- 2 days; 20 deg C

GLP: YES []
NO []

NO DATA [x]

Test Results: A. 2.7 % degradation after 5 days
 B. 8.2 % degradation after 5 days

Reference: Bogan, RH, Sawyer, CN, Biochemical degradation of synthetic detergents. II. Studies on the relation between chemical structure and biochemical oxidation. Sewage Industrial Wastes 27: 917-928 (1955)

3.5.1 C Test type: aerobic

Test medium: water, phenol-acclimated microorganisms in activated sludge
(microbial pop.: 5230 mg/l)

500 ppm ethylbenzene

Test Method: Other

GLP: YES []
 NO []
 NO DATA [x]

Test Results: 27 % degradation after 12 hours

Reference: McKinney, RE, Tomlinson, HD, Wilcox, RL, Metabolism of aromatic compounds by activated sludge. Sewage Industrial Wastes 28: 547-557 (1956)

3.5.1 D Test type: aerobic

Test medium: aged sterilized seawater, distilled water, aerobic microorganisms from mud samples, developed in seawater medium enriched with mineral oil;

2 mg/l ethylbenzene

Test Method: Static test at 25 degree C; pH ca. 7.8; ethylbenzene was dispersed in the medium adsorbed on a mixture of ignited asbestos fibers and sand; dissolved oxygen content determined by iodometric titration method (ALPHA, 1965); degradation calculated as % of ThOD.

GLP: YES []
 NO []
 NO DATA [x]

Test Results: 54 % degradation after 35 day

Reference: ZoBell, CE, Prokop, JF, Microbial oxidation of mineral oils in Barataria Bay bottom deposits. Z. Allg. Mikrobiol. 6: 143-162 (1966)

3.5.1 E Test type: aerobic

Test medium: water, activated sludge

ethylbenzene conc. not reported

Test Method: Removal in sewage plant (laboratory standard activated sludge system)

GLP: YES []

NO []

NO DATA [x]

Test Results: 78 % biodegradation; 22% by stripping out

Reference: Gibson, DJ, Gschwendt, B, Yeh, WK, Kobal, VM, Initial reactions in the oxidation of ethylbenzene by *Pseudomonas putida*. *Biochemistry* 12(8), 1520-1528 (1973)

3.5.1 F Test type: aerobic

Test medium: water, *Pseudomonas* sp.

ethylbenzene conc. not reported

Test Method: Four *Pseudomonas* species 39D and the fungi *Nocardia tartaricans* ATCC3119, grown in the presence of ethylbenzene at 10 deg C

GLP: YES []

NO []

NO DATA [x]

Test Results: 100 % degradation after 12 days

Reference: Gibson, DJ, Gschwendt, B, Yeh, WK, Kobal, VM, Initial reactions in the oxidation of ethylbenzene by *Pseudomonas putida*. *Biochemistry* 12(8), 1520-1528 (1973)

Reference: Kappeler, T, Wuhrmann, K, Microbial degradation of the water soluble fraction of gas oil part 1. *J. Water Research* 12: 327-333 (1978)

Reference: Marion, CV, Malaney, GW, Ability of activated sludge microorganisms to oxidize aromatic organic compounds. *Purdue University, Proceeding of 8th Industrial Waste*

3.5.1 G Test type: aerobic

Test medium: seawater

Test Method:

GLP: YES []

NO []

NO DATA [x]

Test Results: 100% after 10 days

Reference: Van der Linden, AC, Degradation of oil in the marine environment. Dev. Biodeg. Hydrocarbons 1, 165-200 (1978)

3.5.1 H Test type: aerobic

Test medium: water, activated sludge (industrial, adapted)

0.029 mg/l ethylbenzene

Test Method: Degradation of ethylbenzene in a wastewater treatment plant of an organic chemical manufacturing site by a combined powdered carbon-biological process; 23 degree C; pH 6.8 analysis of ethylbenzene by GC/MS.

GLP: YES []
NO []
NO DATA [x]

Test Results: 78 % degradation

Reference: Hutton, DG, Removal of priority pollutants. Ind. Wastes 22: 22-29 (1980)

3.5.1 I Test type: aerobic

Test medium: water, inoculum from domestic waste water

10 mg/l ethylbenzene

Test Method: static screening flask-test; substance removal established by total organic carbon (TOC) loss and GC analysis

GLP: YES []
NO []
NO DATA [x]

Test Results: 69 % degradation after 7 days

Reference: Tabak, HH, Quave, SA, Mashni, CI, Barth, EF, Biodegradability studies with organic priority pollutant compounds. J. Water Pollut. Control Fed. 53(10): 1503-1518 (1981)

3.5.1 J Test type: aerobic

Test medium: Simulated Narragansett Bay water

Test Method: Mesocosm experiment using simulated Narragansett Bay conditions; lag-phases: 2 weeks in spring and 2 days in summer

GLP: YES []
NO []
NO DATA [x]

Test Results: 100 % degradation after 2 days

Reference: Wakeham, SG, Davis, AC, Karas, JL, Mesocosm Experiments to Determine the Fate and Persistence of Volatile Organic Compounds in Coastal Seawater. Environ. Sci. Technol. 17: 611-617 (1983).

3.5.1 K Test type: aerobic

Test medium: sewage treatment plants

29-882 mg/l ethylbenzene

Test Method: 4 tests sewage treatment plants

GLP: YES []
NO []
NO DATA [x]

Test Results: 78 - 99 % removal

Reference: Ghisalba, O, Chemical wastes and their biodegradation--an overview. Experientia 39: 1247-1257 (1983)

3.5.1 L Test type: aerobic

Test medium: Continuous-flow laboratory biofilm column

ethylbenzene conc. not reported

Test Method: Continuous-flow, laboratory biofilm column; 20 min. detention time

GLP: YES []
NO []
NO DATA [x]

Test Results: 99 +/-1% removal

Reference: Bouwer, EJ, McCarty, PL, Modeling of trace organics biotransformation in the subsurface. Ground Water 22(4): 433-440 (1984)

3.5.1 M Test type: aerobic

Test medium: six wastewater treatment processes

0.1 mg/l ethylbenzene

Test Method: Elimination of ethylbenzene by adapted microorganisms in six different wastewater treatment processes (conventional and alternative systems).

GLP: YES []
NO []
NO DATA [x]

Test Results: An activated sludge process provided best removal rates (93%), ethylbenzene concentration in activated sludge was very low, a sign of probable biodegradation.

Reference: Hannah, SA, Austern, BM, Eralp, AE, Wise, RH, Comparative removal of toxic pollutants by six wastewater treatment processes. J. Water Pollut. Control Fed. 58:27-34 (1986)

3.5.1 N Test type: aerobic

Test medium: water, activated sludge (communal)

ethylbenzene conc. not reported

Test Method: BOD-Test (BOD of THOD)

GLP: YES []
NO []
NO DATA [x]

Test Results: BOD of THOD: 32% after 6 days; 36% after 9 days, 45 % after 20 days

Reference: ECETOC, Joint Assessment of Commodity Chemicals, No. 7, p.6, ISSN 0773-6339-7 (1986)

3.5.1 O Test type: aerobic

Test medium: water, adapted bacteria

ethylbenzene conc. not reported

Test Method: BSB-Test; (BSB des THSB)

GLP: YES []
NO []
NO DATA [x]

Test Results: 13 % degradation after 5 days

Reference: Niemi, GJ, Veith, GD, Regal, RR, Vaishnav, DD, Structural features associated with degradable and persistent chemicals. Environ. Toxicol. Chem. 6: 515-528 (1987).

3.5.1 P Test type: aerobic

Test medium: river water with microbial filter with/without reeds (*Phragmites communis*)

430 µg/l ethylbenzene

Test Method: other

GLP: YES []

NO []

NO DATA [x]

Test Results: transformation in 24 h: 66% without reeds, 88% with reeds.

Reference: Wolverton, BC, McDonald-McCaleb, RC, Biotransformation of priority pollutants using biofilms and vascular plants. *Journal of Mississippi Academy of Sciences* 31: 79-89 (1986)

3.5.1 Q Test type: aerobic

Test medium: water, activated sludge (communal)

Test Method: Static Screening Flask Test

GLP: YES []

NO []

NO DATA [x]

Test Results: 87% transformation in the original culture,
100% in third culture.

Reference: Richards, DJ, Shieh, WK, Biological Fate of Organic Priority Pollutants in the Aquatic Environment. *Water Research* 20: 1077-1099 (1986)

3.5.1 R Test type: aerobic

Test medium: 25 sewage treatment plants

148-882 mg/l ethylbenzene

Test Method: sewage treatment plants

GLP: YES []

NO []

NO DATA [x]

Test Results: 83-100% removed

Reference: Richards, DJ, Shieh, WK, Biological Fate of Organic Priority Pollutants in the Aquatic Environment. *Water Research* 20: 1077-1099 (1986)

3.5.1 S Test type: aerobic

Test medium: aerated ponds at three sewage treatments plants

45 mg/l ethylbenzene

Test Method: other

GLP: YES []

NO []

NO DATA [x]

Test Results: > 78 % removal

Reference: Richards, DJ, Shieh, WK, Biological Fate of Organic Priority Pollutants in the Aquatic Environment. Water Research 20: 1077-1099 (1986)

3.5.1 T Test type: aerobic

Test medium: sewage treatment plants

Test Method: 2 sewage treatment plants

GLP: YES []

NO []

NO DATA [x]

Test Results:	Plant A	Plant B
total removal	97.7%	97.5%
biodegradation	94.7%	94.1%
stripping out	2.9%	3.2%
adsorption	0.1%	0.1%

Reference: Namkung, E, Rittmann, BE, Estimating volatile organic compound emissions from publicly owned treatment works. J. Water Pollut. Control Fed. 59(7): 670-678 (1987)

3.5.1 U Test type: aerobic

Test medium: water, acclimated mixed microbial cultures

0.4-3.2 ppm ethylbenzene

Test Method: Screening-Test (BOD of THOD); 21 degree C

GLP: YES []

NO []

NO DATA [x]

Test Results: 29 % degradation after 5 days

Reference: Vaishnav, DD, Babeu, L, Comparison of Occurrence and Rates of Chemical Biodegradation in Natural Waters. Bull. Environ. Contam. Toxicol. 39: 237-244 (1987)

3.5.1 V Test type: aerobic

Test medium: water, activated sludge (adapted)

82 mg/l ethylbenzene

Test Method: Completely mixed batch reactor; analysis of ethylbenzene by GC.
Second test with completely mixed flow reactor (bench-scale) with following operating conditions: synthetic wastewater, 100 ug/l ethylbenzene influent, 5.5 hr hydraulic retention time, 6 day solids residence time;

GLP: YES []
NO []
NO DATA [x]

Test Results: elimination of ethylbenzene (percent of influent):

biodegradation	78%
volatilization	22%
biosorption	0%
in effluent	<1%

Reference: Weber, WJ Jr, Jones, BE, Katz, LE, Fate of toxic organic compounds in activated sludge and integrated pac systems. Water Sci. Technol. 19: 471-482 (1987)

3.5.1 W Test type: aerobic

Test medium: water, activated sludge (communal)

87 mg/l ethylbenzene

Test Method: Directive 84/449/EEC, C.7

GLP: YES []
NO []
NO DATA [x]

Test Results: 50% degradation after 28 days
69% degradation after 33 days

Reference: BASF AG, Labor Okologie [Ecology laboratory]; unpublished investigation (1988)

3.5.1 X Test type: aerobic

Test medium: water, activated sludge (100 mg/l)

30 mg/l ethylbenzene

Test Method: MITI II test (OECD 302C)

GLP: YES []
NO []
NO DATA [x]

Test Results: 81 % degradation after 14 days

Reference: Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan), edited by Chemicals Inspection & Testing Institute Japan, Published by Japan Chemical Industry Ecology-Toxicology & Information Center (CITI) October 1992.

3.5.1 Y Test type: aerobic

Test medium: water, *Mycobacterium vaccae*.

A. 50 mg/l ethylbenzene in a mixture of pollutants

B. 100 mg/l ethylbenzene alone

Test Method: batch test; analysis of ethylbenzene by GC/FID.
30 degree C

GLP: YES []
NO []
NO DATA [x]

Test Results: A. 60% degradation after 24 hours when ethylbenzene in a mixture of multiple pollutants; 4-ethylphenol identified as degradation product.

B. 0% degradation after 48 hours when ethylbenzene sole carbon source

Reference: Burback, BL, Perry, JJ, Biodegradation and biotransformation of groundwater pollutant mixtures by *Mycobacterium vaccae*. Appl. Environ. Microbiol. 59: 1025-1029 (1993)

3.5.1 Z Test type: aerobic

Test medium: water, fungi (*Phanerochaete chrysosporium*)

0.25-20 mg/l ethylbenzene

Test Method: Other: 25 degree C; 8 nM total N; cultures shaken; all values corrected for the sorption values obtained with heat-killed controls. Analysis of ethylbenzene by GC. Tests also performed with low-N (2.4 nM total N) or high-N (24 mM total N).

GLP: YES []
NO []
NO DATA [x]

Test Results: degradation after 5 days

normal nitrogen	89 %
low nitrogen	48.3%
high nitrogen	27.7 %

Reference: Yadav, JS, Reddy, CA, Degradation of benzene, toluene, ethylbenzene, and xylenes (BTEX) by the lignin-degrading basidiomycete *Phanerochaete chrysosporium*. *Appl. Environ. Microbiol.* 59: 756-762 (1993)

3.5.1 AA Test type: aerobic

Test medium: water, *Methylococcus capsulatus*

ethylbenzene conc. not reported

Test Method: Directive 84/449/EEC, C.7

GLP: YES []
NO []
NO DATA [x]

Test Results: *Methylococcus capsulatus* oxidized ethyl benzene to 1-phenyl-ethanol and p-ethylphenol in 15 min. to 1 hour at 45 degree C (no other details regarding quantities or conditions given).

Reference: Dalton, H, Golding, BT, Waters, BW, Higgins, R, Taylor, JA, Oxidations of cyclopropane, methylcyclopropane and arenes with the mono-oxygenase system from *Methylococcus capsulatus*. *J. Chem. Soc. Chem. Commun.* 10: 482-482 (1981)

3.5.2 A Test type: anaerobic

Test medium: anaerobic reactor with acetate cultures

Test Method: anaerobic reactor with acetate cultures and 110 days acclimation,

GLP: YES []
NO []
NO DATA [x]

Test Results: No degradation; not toxic to cultures.

Reference: Chou, WL, Speece, RE, Siddiqi, RH, Acclimation and degradation of petrochemical wastewater components by methane fermentation. *Biotechnol. Bioeng. Symp.*8: 391-414 (1979)

3.5.2 B Test type: anaerobic

Test medium: water, active denitrifying bacterial culture

41 to 114 ug/l. ethylbenzene

Test Method: Batch reactor; denitrifying conditions;

GLP: YES []
NO []
NO DATA [x]

Test Results: < 1% degradation after 77 days

Reference: Bouwer, EJ, McCarty, PL, Transformations of halogenated organic compounds under denitrification conditions. Appl. Environ. Microbiol. 45: 1295-1299 (1983)

3.5.2 C Test type: anaerobic

Test medium:

Test Method: Continuous-flow, laboratory biofilm column; 2 days detention time.

GLP: YES []
NO []
NO DATA [x]

Test Results: 7 +/- 26% removal

Reference: Bouwer, EJ, McCarty, PL, Modeling of trace organics biotransformation in the subsurface. Ground Water 22(4): 433-440 (1984)

3.5.2 D Test type: anaerobic

Test medium: unsterile methanogenous aquifer material (269 ug/l in pore water).

Test Method: Directive 84/449/EEC, C.7

GLP: YES []
NO []
NO DATA [x]

Test Results: 17% transformation in 12 weeks, 74% in 40 weeks, 99.5% in 120 weeks

Reference: Wilson, BH, Smith, GB, Rees, JF, Biotransformations of selected alkylbenzenes and halogenated aliphatic hydrocarbons in methanogenic aquifer material: a microcosm study. Envir. Sci. Technol. 20(10): 997-1002 (1986)

3.5.2 E Test type: anaerobic

Test medium: water, activated sludge (communal)

0.23 mg/l ethylbenzene

Test Method: laboratory aquifer column (length: 25 cm) operated under continuous-flow conditions at 30 degree C; pH 7.5 with nitrate as sole electron acceptor; aquifer material from the interface of a river-groundwater infiltration site, adapted to m-xylene for at least one week; medium contained mineral salts, supplemented with ethylbenzene, flow velocity:

2.6 cm/h; concentrations determined 2 to 6 days after medium was supplemented with ethylbenzene at a distance of 11.8 cm from the inlet; analysis of ethylbenzene by HPLC.

GLP: YES []
NO []
NO DATA [x]

Test Results: 23 % removal

Reference: Kuhn, EP, Zeyer, J; Eicher, P, Schwarzenbach, RP, Anaerobic degradation of alkylated benzenes in denitrifying laboratory aquifer columns. Appl. Environ. Microbiol. 54: 490-496 (1988)

3.5.2 F Test type: anaerobic

Test medium: anaerobic sludge (undiluted)

ethylbenzene conc. not reported

Test Method: other (35 degree C)

GLP: YES []
NO []
NO DATA [x]

Test Results: 1% degradation within 5 hours

Reference: Marion, CV, Malaney, GW, Ability of activated sludge microorganisms to oxidize aromatic organic compounds. Purdue University, Proceeding of 8th Industrial Waste

3.5.2 G Test type: anaerobic

Test medium: anaerobic reactor

Test Method: Other

GLP: YES []
NO []
NO DATA [x]

Test Results: No transformation after 110 days

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.5.3 A Test type: not specified

Test medium: ground water ethylbenzene conc. not reported

Test Method: Microbial degradation in ground water; lag-phase: 3-4 days; 10 deg C.

GLP: YES []
NO []
NO DATA [x]

Test Results: 100 % degradation after 8 days

Reference: Kappeler, T, Wuhrmann, K, Microbial degradation of the water soluble fraction of gas oil part 1. J. Water Research 12: 327-333 (1978)

3.5.3 B Test type: not specified

Test medium: sewage

ethylbenzene conc. not reported

Test Method: Screening-Test (Die-Away-Test); Refinery wastewater samples collected from final effluent discharged into Ismailia Canal, Egypt, sterile control; 24 deg C; analytical method: GC

GLP: YES []
NO []
NO DATA [x]

Test Results: 100 % degradation

Reference: Moursy, AS, El-Abagy, MM, Biodegradability of hydrocarbons in the refinery wastewater from Moustorod Oil Refinery; in: Manage Ind. Wastewater Dev. Nations Proc., Stucky, D & Harnza, A, eds, Oxford, U.K., Pergamon, 453-466 (1982)

3.5.3 C Test type: not specified

Test medium: seawater

Test Method: other

GLP: YES []
NO []
NO DATA [x]

Test Results: As a component of gas oil, it is completely degraded in seawater in 10 days. In a mesocosm experiment using simulated Narraganset Bay conditions, complete biodegradation occurred in approx 2 days after a 2-week lag in spring and a 2-day lag in summer.

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.5.3 D Test type: not specified

GLP: YES []
NO []
NO DATA [x]

Comment: Degradation in the ground: presumed slow transformation after acclimatization.

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.5.3 E Test type: not specified

Test medium: ground water

300 µg/l fuel

Test Method: Degradation in ground water: in aquifer contaminated with fuel; with addition of nutrient

GLP: YES []
NO []
NO DATA [x]

Test Results: 90% microbial transformation after 3 weeks,
> 90% in less than 1 week with addition of nutrient.

In uncontaminated aquifer, microbial transformation ca. 85% after 1 week, complete after 3 weeks

Reference: Thomas, JM, Gordy, VR, Fiorenza, S, Ward, CH, Biodegradation of BTEX in subsurface materials contaminated with gasoline: Granger, Indiana. Wat. Sci. Tech. 22(6):53-62 (1990)

3.5.3 F Test type: not specified

Comment: It has been shown that several species of soil (including pseudomonas and achromobacter) are capable of utilizing ethylbenzene as a sole carbon source and that the fungus Nocardia tartaricans AT CC 31190 can convert ethylbenzene into 1-phenylethanol and acetophenone under certain conditions.

Reference: ECETOC, Joint Assessment of Commodity Chemicals, No. 7, p.7. ISSN 0773-6339-7 (1986)

3.6 BOD5, COD or BOD5/COD Ratio

3.6 A BOD5/COD Ratio

Test Method: Standard Dilution B.O.D. technique according to APHA, 1946; 20 degree C inoculum: domestic sewage, non-adapted; ethylbenzene - 1000 mg/l

GLP: YES []
NO []
NO DATA [x]

Test Results: BOD5 = 2.8% of ThOD

Reference: Bogan, RH, Sawyer, CN, Biochemical degradation of synthetic detergents. II. Studies on the relation between chemical structure and biochemical oxidation. Sewage Industrial Wastes 27: 917-928 (1955)

3.6 B BOD5/COD Ratio

Test Method: Standard Dilution B.O.D. technique according to APHA, 1946; 20 degree C inoculum: domestic sewage, non-adapted; ethylbenzene - 1000 mg/l

GLP: YES []
NO []
NO DATA [x]

Test Results: BOD5 = 2.7% of ThOD

Reference: Bogan, RH, Sawyer, CN, Biochemical degradation of synthetic detergents. II. Studies on the relation between chemical structure and biochemical oxidation. Sewage Industrial Wastes 27: 917-928 (1955)

3.6 C COD

Test Method: AIChE DIPPR 911 project, Michigan Tech, Houghton, Michigan

GLP: YES []
NO []
NO DATA [x]

Test Results: COD = 2.38 g O₂/g chem

Reference: Janicke, W, Wasser-Boder-und Lufthyggen Des Bandes-Gasundheits. Dietrich Riemer Verlag, Berlin (1983)

3.6 D COD

Test Method:

GLP: YES []

NO []
NO DATA [x]

Test Results: ThOD = 3.17 g O₂/g chem.

Reference: Mihelcic, J, (JR. Baker) Paper #269, 270. AIChE DIPPR 911 project. Michigan Tech, Houghton, Michigan (1992)

3.7 Bioaccumulation

3.7 A Species: *Carassius auratus*

Test Method:

GLP: YES []
NO []
NO DATA [x]

Test Results: BCF = 15; log BCF = 1.9

Reference: Ogata, M, Fujisawa, K, Ogino, Y, Mano, E, Partition coefficients as a measure of bioconcentration potential of crude oil compounds in fish and shellfish. Bull. Environ. Contam. Toxicol. 33: 561-577 (1984)

3.7 B Species: *Oncorhynchus kisutch*

Test Method: Fish were exposed to 0.9±0.1 mg/l of a water-soluble fraction of crude oil (concentration of ethylbenzene: 0.005±0.002 mg/l) in flowing sea water for 42 days; analysis of ethylbenzene and C₂-substituted benzenes in tissues by GLC; bioconcentration = mg C₂-substituted benzenes in dry weight muscle tissue/mg in water.

GLP: YES []
NO []
NO DATA [x]

Test Results: bioconcentration values after 2, 3, and 5 weeks are 1.1, 2.4, and 2 resp.; after one week of depuration, C₂-substituted benzenes not detectable (limit of detection: 0.05 mg/kg). BCF = 1

Reference: Roubal, WT, Stranahan, SI, Malins, DC, The accumulation of low molecular weight aromatic hydrocarbons of crude oil by coho salmon (*Oncorhynchus kisutch*) and starry flounder (*Platichthys stellatus*). Arch. Environ. Contam. Toxicol. 7: 237-244 (1978)

3.7 C Species: *Platichthys stellatus*

Test Method: Starry flounder were exposed to 0.9±0.1 mg/l of a water-soluble fraction of crude oil (concentration of ethylbenzene: 0.005±0.002 mg/l) in flowing sea water for 14 days; analysis of ethylbenzene and C₂-substituted benzenes in tissues by GLC; bioconcentration = mg C₂-benzenes in dry weight muscle tissue/mg in water.

GLP: YES []
NO []
NO DATA [x]

Test Results: BCF = 4 bioconcentration values:
after one week: 20 (muscle tissue), 6 (liver), 7 (gills);
after two weeks: 4 (muscle tissue), 10 (liver), 4 (gills);

after 2 weeks of depuration, C2-Substituted benzenes not detectable in muscle tissue (limit of detection: 0.05 mg/kg) and gills (limit of detection: 0.1 mg/kg).

Reference: Roubal, WT, Stranahan, SI, Malins, DC, The accumulation of low molecular weight aromatic hydrocarbons of crude oil by coho salmon (*Oncorhynchus kisutch*) and starry flounder (*Platichthys stellatus*). Arch. Environ. Contam. Toxicol. 7: 237-244 (1978)

3.7 D Species: *Bottomfish*

Test Method:

GLP: YES []
NO []
NO DATA [x]

Test Results: Commencement Bay and adjacent waterways, Tacoma, WA, 1982:
highest average level 0.01 ppm.

Reference: Howard, PH, Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume I: Large Production and Priority Pollutants, Lewis Publ. Inc., Michigan (1989)

3.7 E Species: *clam (Tapes semidecussata)*

Test Method: Clams were exposed to a continuous-flow (3% salinity) of the water-soluble fraction of Cook Inlet crude oil for 8 days; concentration of ethylbenzene = 0.08 mg/l; analysis of ethylbenzene by GC/FID.

GLP: YES []
NO []
NO DATA [x]

Test Results: ethylbenzene concentrations in clam tissues:
at day 2 = 0.34 mg/kg wet weight,
at day 9 = 0.5 mg/kg;
depuration within 7 days (detection limit = 0.13 mg/)

Reference: Nunes, P, Benville, PE, Uptake and depuration of petroleum hydrocarbons in the Manila clam, *Tapes semidecussata* Reeve. Bull. Environ. Contam. Toxicol. 21: 719-726 (1979)

3.7 F

Comment: Yoshida et al. (1983) and McKay et al. (1980) measured the octanol/water partition coefficients and found log P_{ow}s of 3.15 and 3.11 respectively, which suggest that ethyl benzene has a moderate potential to bioaccumulate, corresponding to a bioconcentration factor of about 100. However, in the tests so far performed on living organisms such a degree of bioconcentration did not occur.

GLP: YES []
NO []
NO DATA [x]

Reference: ECETOC, Joint Assessment of Commodity Chemicals, No. 7, p. 7, ISSN 0773-6339-7 (1986)

4.1 Acute Toxicity to Fish

4.1 A Test Species: *Menidia menidia*

Test Substance: Ethylbenzene

Test Method: USEPA. 1985 Test Guidelines TSCA 797.1440. Fish Acute Toxicity Test.

duration: 96 hrs

type of test: Flow through

GLP: YES [x]
NO []
NO DATA []

Test Results: NOEC ca. 3.3; LC50 is between 5.1 and 5.7; LC100 ca. 7.3 ppm.

Reference: EB analysis: U.S. EPA. 1984, Method 602. Purgeable Aromatics. Federal Register 49 (209), Friday, October 26, 1984.

Reference: Study Report: Robert L. Boeri, Flow-through, Acute Toxicity of Ethyl Benzene to the Atlantic Silverside, *Menidia menidia*. Enseco Incorporated, Marblehead, MA, December 22, 1987a.

4.1 B Test Species: *Pimephales promelas*

Test Substance: Ethylbenzene

Test Method: Other; 26 deg C, pH 7.4, 45.6 mg CaCO₃/l; 02 7.0 mg/l.; based on analytical data. Ethylbenzene purity = 99%

duration: 96 hrs

type of test: Flow through

GLP: YES []
NO []
NO DATA [x]

Test Results: LC50 = 12.1 (95% confidence intervals 11.5-12.7) mg/l

Reference: Geiger, DL, Poirer, SH, Brooke, LT, Call, DJ (eds.), Acute toxicity of organic chemicals to fathead minnows (*Pimephales promelas*). Vol. III, Center for Lake Superior Environmental Studies, University of Wisconsin-Superior, Superior, WI (1986)

4.1 C Test Species: *Pimephales promelas*

Test Substance: Ethylbenzene

Test Method:

duration: 96 hrs

type of test: Static; no analytical data

GLP: YES []
NO []
NO DATA [x]

Test Results: hard water: LC50 = 42.33 (95% confidence limits 33.52-53.47) mg/l
soft water: LC50 = 48.51 (95% confidence limits 38.90-62.83) mg/l

Reference: Pickering, QH, Henderson, C, Acute Toxicity of Some Important Petrochemicals to Fish. J. Water Poll. Cont. Fed. 39: 1419-1429 (1966).

4.1 D Test Species: *Oncorhynchus kisutch*

Test Substance: Ethylbenzene

Test Method: Ethylbenzene introduced via pulse dosing to simulate a spill. Ethylbenzene probably volatilized in this study due to aeration.

duration: 96 hrs

type of test: static

GLP: YES []
NO [x]
NO DATA []

Test Results: LC50 not reported in article; between 10 and 50 ppm.
Mortality: 0 ppm = 0%; 10 ppm = 13%; 50 ppm = 100%

Reference: Morrow, JE, Gritz RL and Kirton, MP, Effects of Some Components of Crude Oil on Young Coho Salmon. Copeia 2: 326-331 (1975)

4.1 E Test Species: *Oncorhynchus mykiss*

Test Substance: Ethylbenzene

Test Method: Other; 12 deg C, pH 7.2-7.5, 40-50 mg CaCO₃/l; no analytical data

duration: 96 hrs

type of test: Static

GLP: YES [x]
NO []
NO DATA []

Test Results: LC50 = 14 (LC50 95% confidence intervals 11-18 mg/l.)

Reference: Johnson, WW and Finley, MT, Handbook of acute toxicity of chemicals to fish and aquatic invertebrates, US Dept. Interior, Fish and Wildlife Service, Resource Publication 137, Washington, DC (1980).

4.1 F Test Species: *Oncorhynchus mykiss*

Test Substance: Ethylbenzene

Test Method: OECD Guide-line 203; 12 deg C; analytical data

duration: 96 hrs

type of test: Static

GLP: YES [x]
NO []
NO DATA []

Test Results: LC50 = 4.2mg/l

Reference: Galassi, S, Mingazzini, M, Vigano, L, Cesareo, D, Tosato, ML, Approaches to modeling toxic responses of aquatic organisms to aromatic hydrocarbons. Ecotoxicol. Environ. Safety 16: 158-169 (1988).

4.1 G Test Species: *Lepomis macrochirus*

Test Substance: Ethylbenzene

Test Method: This test was conducted using soft water. No analytical data.

duration: 96 hrs

type of test: Static

GLP: YES [x]
NO []
NO DATA []

Test Results: LC50 = 32 mg/l (95% confidence intervals 32.00-32.00 mg/l).

Reference: Pickering, QH and Henderson, C, Acute Toxicity of Some Important Petrochemicals to Fish, J. Water Pollut. Control Fed. 39: 1419-1429 (1966).

4.1 H Test Species: *Lepomis macrochirus*

Test Substance: Ethylbenzene

Test Method: other; a series of chemicals was tested; some were mixed with a solvent (1,6-hexanediol, acetone, dimethylformamide, or ethanol) if insufficiently soluble. The paper does not indicate which solubilizer if any was used with ethylbenzene. It does report that undissolved chemical was noted. No analytical data

duration: 96 hrs

type of test: static

GLP: YES []
NO [x]
NO DATA []

Test Results: LC50 = 150 mg/l; 95% confidence interval 130-200 mg/l.

Reference: Buccafusco, RJ, Ells, SJ, LeBlanc, GA, Acute Toxicity of Priority Pollutants to Bluegill (*Lepomis macrochirus*). Bull. Environm. Contam. Toxicol. 26: 446-452 (1981).

4.1 I Test Species: *Leuciscus idus melanotus*

Test Substance: Ethylbenzene

Test Method: Semistatic conditions consisted of replacement of ethylbenzene to insure that ethylbenzene concentration was relatively constant. No analytical data.

duration: 48 hrs

type of test: semistatic

GLP: YES []
NO [x]
NO DATA []

Test Results: LC0 26; LC50 = 44; LC100 = 70 mg/l

Reference: Juhnke, VI, and Ludemann, D, Ergebnisse der Untersuchung von 200 chemischen Verbindungen auf akute Fischtoxizität mit dem Goldorfentest, Z.F. Wasser- und Abwasser-Forschung 11 (5): 161-164 (1978).

4.1 J Test Species: *Cyprinodon variegatus*

Test Substance: Ethylbenzene

Test Method: A series of chemicals was tested using seawater. Some were mixed with a solvent (triethylene glycol, acetone, or deionized water) if insufficiently soluble. The paper does not indicate which solubilizer if any was used with ethylbenzene. No analytical data

duration: 96 hrs

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: NOEC 88; LC50 = 280 (95% confidence limits 260-290) mg/l.

Reference: Heitmuller, PT, Hollister, TA and Parrish, PR, Acute Toxicity of 54 Industrial Chemicals to Sheepshead Minnows (*Cyprinodon variegatus*), Bull. Environm. Contam. Toxicol. 27: 596-604 (1981).

4.1 K Test Species: *Carassius auratus*

Test Substance: Ethylbenzene

Test Method: Other

duration: 96 hrs

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: LC50 = 94.44 (95% confidence intervals 79.62-110.1) mg/l.

Reference: Pickering, QH and Henderson, C, Acute Toxicity of Some Important Petrochemicals to Fish, J. Water Pollut. Control Fed. 39: 1419-1429 (1966).

4.1 L Test Species: *Lebistes reticulatus*

Test Substance: Ethylbenzene

Test Method: This test was conducted using soft water. No analytical data.

duration: 96 hrs

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: LC50 = 97.1 (95% confidence intervals 81.45-114.58) mg/l.

Reference: Pickering, QH and Henderson, C, Acute Toxicity of Some Important Petrochemicals to Fish, J. Water Pollut. Control Fed. 39: 1419-1429 (1966).

4.1 M Test Species: *Morone saxatilis*

Test Substance: Ethylbenzene

Test Method: Based on analytical results, > 99% of the ethylbenzene in the test system was lost in less than 24 hours. No attempt was made to supplement this chemical.

duration: 96 hrs

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: LC50 = 4.3 (95% confidence intervals 3.9-4.7) mg/l..

Reference: Benville, PE Jr., and Korn, S, The acute toxicity of six monocyclic aromatic crude oil components to striped bass (*Morone saxatilis*) and bay shrimp (*Crago Franciscorum*). Calif. Fish and Game 63(4): 204-209 (1977).

4.1 N Test Species: *Ictalurus punctatus*

Test Substance: Ethylbenzene

Test Method: Other; 22 deg C, pH 7.2-7.5, 40-50 mg CaCO₃/l.; no analytical data

duration: 96 hrs

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: LC50 = 210 (LC50 95% confidence intervals 134-330) mg/l..

Reference: Johnson, WW and Finley, MT, Handbook of acute toxicity of chemicals to fish and aquatic invertebrates. US Dept. Interior, Fish and Wildlife Service, Resource Publication 137, Washington, DC (1980)

4.1 O Test Species: *Poecilia reticulata*

Test Substance: Ethylbenzene

Test Method: Other; analytical data

duration: 96 hrs

type of test: Static

GLP: YES [x]
NO []
NO DATA []

Test Results: LC50 = 97.1 (95% confidence intervals 81.5-115) mg/l.

Reference: Pickering, QH and Henderson, C, Acute toxicity of some important petrochemicals to fish, J. Water Poll. Control Fed. 38: 1419-1429 (1966).

4.1 P Test Species: *Poecilia reticulata*

Test Substance: Ethylbenzene

Test Method: OECD Guide-line 203; analytical data

duration: 96 hrs

type of test: Flow through

GLP: YES []
NO []
NO DATA [x]

Test Results: EC50 = 9.9 mg/l

Reference: Galassi, S, Mingazzini, M, Vigano, L, Cesareo, D, Tosato, ML, Approaches to modeling toxic responses of aquatic organisms to aromatic hydrocarbons. Ecotoxicol. Environ. Safety 16: 158-169 (1988).

4.2 Acute Toxicity to Aquatic Invertebrates

4.2 A Test Species: *Daphnia magna*

Test Substance: Ethylbenzene

Test Method: Other; analytical data; daphnids were produced by parents fed five food levels.

duration: 48 hrs

type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: EC50 = 1.81 mg/l (EC50s for 5 food levels ranged from 1.81 to 2.38 mg/l)

Reference: Vigano, L, Reproductive strategy of *Daphnia magna* and toxicity of organic compounds. Wat. Res. 27: 903-909 (1993)

4.2 B Test Species: *Crangon franciscorium*, bay shrimp

Test Substance: Ethylbenzene

Test Method: Other. Based on analytic data collected in this study, under static conditions, > 99% of the EB concentration was lost within the first 24 hours. No attempt was made to supplement this chemical in the study.

duration: 96 hrs

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: EC50 = 0.49 (95% confidence limits 0.21-1.2) mg/l

Reference: Benville, PE and Korn, S, The acute toxicity of six monocyclic aromatic crude oil components to striped bass (*Morone saxatilis*) and bay shrimp (*Crango franciscorum*). Calif. Fish and Game 63(4): 204-209 (1977).

4.2 C Test Species: *Mysidopsis bahia*

Test Substance: Ethylbenzene

Test Method: USEPA. 1978. Bioassay procedure for the ocean disposal permit program. Method F. methods for acute static toxicity tests with Mysid shrimp. EPA-600/9-78-010.; analytical data

duration: 96 hrs

type of test: Flow-through

GLP: YES [x]
NO []
NO DATA []

Test Results: NOEC = 1; LC50 = 2.6 (95% confidence limits 2.0-3.3); LC100 > 5.2 mg/l

Reference: EB analysis: U.S. EPA. Method 602. Purgeable Aromatics. Federal Register 49(209), Friday, October 26, 1984.

Reference: Study Report: Robert L. Boeri, Flow-through, Acute Toxicity of Ethyl Benzene to the Mysid, *Mysidopsis bahia*. Enseco Incorporated, Marblehead, MA, September 13, 1988.

4.2 D Test Species: *Daphnia magna*

Test Substance: Ethylbenzene

Test Method: Other; no analytical data

duration: 48 hrs

type of test: Flow-through

GLP: YES []
NO [x]
NO DATA []

Test Results: LC50 = 20 (95% confidence limits 5-78) mg/l

Reference: Bobra, AM, Shiu, WY and Mackay, D, A Predictive Correlation for the Acute Toxicity of Hydrocarbons and Chlorinated Hydrocarbons to the Water Flea (*Daphnia magna*). Chemosphere, 12 (9): 1121-1129 (1983).

4.2 E Test Species: *Daphnia magna*

Test Substance: Ethylbenzene

Test Method: Other; diluent water had a mean hardness of 72 mg/l as CaCO₃; no analytical data.

duration: 48 hrs

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: NOEC = 6.8; LC50 = 75 mg/l

Reference: LeBlanc, GA, Acute Toxicity of Priority Pollutants to Water Flea (*Daphnia magna*). Bull. Environm. Contam. Toxicol. 24: 684-691 (1980).

4.2 F Test Species: *Daphnia magna*

Test Substance: Ethylbenzene

Test Method: Other; no analytical data

duration: 24 hrs

type of test: Flow-through

GLP: YES []
NO [x]
NO DATA []

Test Results: EC0 = 120; EC50 = 190 (95% confidence limits 2.0-3.3); LC100 = 200 mg/l

Reference: Bringmann, VG and Kuhn, R, Befunde der Schadwirkung wassergefährdender Stoffe gegen *Daphnia magna*, Z.F. Wasserund Abwasser-Forschung 10 (5): 161-166 (1977).

4.2 G Test Species: *Dicranophorus forcipatus* O.F. Muller.

Test Substance: Ethylbenzene

Test Method: Other; the concentration of EB used were 0.02, 0.20 and 2.00 % (v/v). No analytical data

duration: 6 days

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: After 6 days, the EC50 for growth of new individuals was approximately 0.02 % (v/v), i.e. the number of individuals was 54.2% of control. The two higher concentrations were associated with 36.1% and 21.7% of the increased number of individuals, respectively, when compared to the control group. The greatest effect of EB on growth was noted after 48 hours of exposure and recovery occurred later, in a dose related manner.

Reference: Erben, R, Effects of some petrochemical products on the survival of *Dicranophorus forcipatus* O.F. Muller (Rotataria) under laboratory conditions. Verh. Interna. Verein. Limnol. 20: 1988-1991 (1978).

4.2 H Test Species: the larvae of Dungeness crab, *Cancer magister*

Test Substance: Ethylbenzene

Test Method: Other; no analytical data

duration: 96 hrs
type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: LC50 = 13 mg/l (The 48 hour LC50 was 40 mg/l.)

Reference: Caldwell, RS, Caldarone, EM and Mallon, MH, Effects of a seawater-soluble fraction of Cook Inlet crude oil and its major aromatic components of larval stages of the

Dungeness crab, Cancer magister Dana. Chpt. 22, in Fate and Effects of Petroleum Hydrocarbons in Marine Ecosystems and Organisms, Proceedings of a Symposium, D.A. Wolfe, ed., Pergamon Press, Oxford (1977)

4.2 I Test Species: *Ceriodaphnia dubia*

Test Substance: Ethylbenzene (labeled as 99.8% purity)

Test Method: Other; Method from U.S.EPA's Whole Effluent Testing Program, modified to minimize volatilization. Analytical data from beginning and end of experiment (84.8% of material present at end of experiment). Initial concentration reported as exposure concentration.

duration: 48 hrs

type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: LC50 = 3.2 mg/l (30 µM)

Reference: Neiderlehner, B. R., Cairns, J., Smith, E.P. Modeling acute and chronic toxicity of nonpolar narcotic chemicals and mixtures to *Ceriodaphnia dubia*. Ecotox. and Environm. Safety 39:136-146. (1998)

4.3 Toxicity to Aquatic Plants (e.g. Algae)

4.3 A Test Species: *Selenastrum capricornutum*

Test Substance: Ethylbenzene

Test Method: USEPA. 1985 Test Guidelines. TSCA 797.1050. Algal acute toxicity; analytical data

endpoint: growth rate

type of test: Static

GLP: YES [x]
NO []
NO DATA []

Test Results: NOEC = ca. 3.4; EC50 = 3.6 (95% confidence interval 1.7-7.6);
EC100 > 12.5 mg/l

Reference: EB analysis: U.S. EPA. 1984, Method 602. Purgeable Aromatics. Federal Register 49 (209), Friday, October 26, 1984.

Reference: Study Report: Robert L. Boeri, Static Acute Toxicity of Ethyl Benzene to the Freshwater Algae, *Selenastrum capricornutum*. Enseco Incorporated, Marblehead, MA, December 18, 1987b.

4.3 B Test Species: *Selenastrum capricornutum*

Test Substance: Ethylbenzene

Test Method: Unspecified; analytical data

endpoint: growth rate

duration: 96 hrs

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: NOEC > 440 mg/l

Reference: U.S. Environmental Protection Agency, In-depth studies on health and environmental impacts of selected water pollutants. US EPA, Contract No. 68-01-4646 (1978)

4.3 C Test Species: *Skeletonema costatum*

Test Substance: Ethylbenzene

Test Method: Method. USEPA. 1985 Test Guidelines. TSCA 797.1050. Algal acute toxicity; analytical data.

endpoint: growth rate

duration: 96 hrs

type of test: Static

GLP: YES [x]
NO []
NO DATA []

Test Results: NOEC = 4.5; EC50 = 7.7 (95% confidence interval 1.7-7.6);
12.5 mg/l

Reference: EB analysis: U.S. Environmental Protection Agency. 1984, Method 602. Purgeable Aromatics. Federal Register 49 (209), Friday, October 26, 1984.

Reference: Study Report: Robert L. Boeri, Static Acute Toxicity of Ethyl Benzene to the Diatom, *Skeletonema costatum*. Enseco Incorporated, Marblehead, MA, December 22, 1987c.

4.3 D Test Species: *Skeletonema costatum*

Test Substance: Ethylbenzene

Test Method: Unspecified; analytical data

endpoint: growth rate

duration: 96 hrs

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: NOEC > 440 mg/l

Reference: U.S. Environmental Protection Agency, In-depth studies on health and environmental impacts of selected water pollutants. US EPA, Contract No. 68-01-4646 (1978)

4.3 E Test Species: *Microcystis aeruginosa*

Test Substance: Ethylbenzene

Test Method: Other; no analytical data.

endpoint: growth rate

duration: 8 days

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: LOEC = 33 mg/l

Reference: Bringmann, G and Kuhn, R, Testing of substances for their toxicity threshold: Model organisms *Microcystis* (*Diplocystis*) *aeruginosa* and *Scenedesmus quadricauda*. Mitt. Internat. Verein. Limnol. 21: 275-284 (1978)

4.3 F Test Species: *Scenedesmus quadricauda*

Test Substance: Ethylbenzene

Test Method: Other; no analytical data.

endpoint: growth rate

duration: 8 days

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: NOEC > 160 mg/l

Reference: Bringmann, G and Kuhn, R, Testing of substances for their toxicity threshold: Model organisms *Microcystis* (*Diplocystis*) *aeruginosa* and *Scenedesmus quadricauda*. Mitt. Internat. Verein. Limnol. 21: 275-284 (1978)

4.3 G Test Species: *Chlamydomonas sp.*

Test Substance: Ethylbenzene

Test Method: Other; no analytical data.

endpoint: 50% inhibition of photosynthesis

duration: 3 hrs

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: EC50 = 480 mmol/l

Reference: Hutchinson, TC, Hellebust, JA, Tam, D, Mackay, D, Mascarenhas, RA, Shiu, WY, The correlation of toxicity to algae of hydrocarbons and halogenated hydrocarbons with their physical-chemical properties, in Environ. Sci. Res. 16: 581-586 (1980)

4.3 H Test Species: *Chlorella vulgaris*

Test Substance: Ethylbenzene

Test Method: Other; no analytical data.

endpoint: inhibition of photosynthesis

duration: 3 hrs

type of test: Static

GLP: YES []
NO [x]
NO DATA []

Test Results: EC50 = 590 mmol/m³

Reference: Hutchinson, TC, et al., The correlation of toxicity to algae of hydrocarbons and halogenated hydrocarbons with their physical-chemical properties, in Environ. Sci. Res. 16: 581-586 (1980)

4.4 Toxicity to Microorganisms (e.g. Bacteria)

4.4 A Test Species: *Chilomonas paramecium*

Test Substance: Ethylbenzene

Test Method: Unspecified; analytical data

endpoint: growth rate

duration: 72 hrs

type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: NOEC > 56 mg/l

Reference: Bringmann, G and Kuhn, R, Vergleich der Wirkung von Schadstoffen auf flagellate sowie ciliate bzw. auf holozoische bakterienfressende sowie saprozoische Protozoen. gwf-wasser/abwasser 122 (7): 308-313 (1981).

4.4 B Test Species: *Entosiphon sulcatum*

Test Substance: Ethylbenzene

Test Method: Unspecified; analytical data

endpoint: growth rate

duration: 72 hrs

type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: EC0 = 1140 mg/l

Reference: Bringmann, G and Kuhn, R, Vergleich der Wirkung von Schadstoffen auf flagellate sowie ciliate bzw. auf holozoische bakterienfressende sowie saprozoische Protozoen. gwf-wasser/abwasser 122 (7): 308-313 (1981).

4.4 C Test Species: *Uronema parduzci*

Test Substance: Ethylbenzene

Test Method: Unspecified; analytical data

endpoint: growth rate

duration: 72 hrs

type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: NOEC > 110 mg/l

Reference: Bringmann, G and Kuhn, R, Vergleich der Wirkung von Schadstoffen auf flagellate sowie ciliate bzw. auf holozoische bakterienfressende sowie saprozoische Protozoen. gwf-wasser/abwasser 122 (7): 308-313 (1981).

4.4 D Test Species: *Pseudomonas fluorescens*

Test Substance: Ethylbenzene

Test Method: Unspecified field study; analytical data

endpoint: glucose utilization and turbidity

duration: 16 hrs

type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: EC0 = 12 mg/l

Reference: Bringmann, G, Bestimmung der biologischen Schädigung wassergefährdender Stoffe aus der Hemmung der Glucose-Assimilation des Bakterium *Pseudomonas fluorescens*. Gesundheits-Ingenieur 94(12): 366-369 (1973).

4.4 E Test Species: *Nitrosomonas* sp.

Test Substance: Ethylbenzene

Test Method: Culture fed with 1000 mg/l ammonia twice daily; water and solids retention time was 25 day; reactor temperature 25 deg. C; pH 6.5-8.0; N₂:O₂ = 1.6:1; analytical data endpoint: inhibition of ammonia consumption

duration: 96 hrs

type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: EC₅₀ = 96 mg/l

Reference: Blum, DJW and Speece, RE, A database of chemical toxicity to environmental bacteria and its use in interspecies comparisons and correlations. Res. J. Water Pollut. Control. Fed. 63: 198-207 (1991).

4.4 F Test Species: Activated sludge.

Test Substance: Ethylbenzene

Test Method: Feed complex carbon source; COD of feed solution 3800 g/l; 25 or 35 degrees C; pH 7; N₂:O₂ = 1:1 initial; data collection times 15, 27, 38 and 49h

Method: Inhibition of oxygen uptake determined; activated sludge of wastewater treatment plant, 1% nitrifier population

duration: data collection times 15, 27, 38 and 49 h

type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: EC₅ **EC₅₀** = 130mg/l

Reference: Blum, D.J.W.; Speece, R.E.: Res. J. Water Pollut. Control Fed. 63, 198-207 (1991)

4.4 G Test Species: Anaerobic bacteria.

Test Substance: Ethylbenzene

Test Method: Feed complex carbon source; COD of feed solution 3800 g/l; 25 or 35 degrees C; pH 7; N₂:O₂ = 1:1 initial; data collection times 15, 27, 38 and 49h

Method: Anaerobic toxicity assay for methanogens; inhibition of gas production determined

Reactor operated at 35 degrees C; solids and hydraulic retention times 50 d; acetate fed (sole organic carbon source); pH 7; N₂:CO₂ = 2:1

duration: 96 h

type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: EC₅₀ = 160mg/l

Reference: Blum, D.J.W.; Speece, R.E.: Res. J. Water Pollut. Control Fed. 63, 198-207 (1991)

4.5 Chronic Toxicity to Fish

4.5 A Test Species: *Pimephales promelas*

Test Substance: Ethylbenzene

Test Method: Other; analytical data

duration: not specified

type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: NOEC > 0.44 mg/l; no sign of adverse effects at concentration used

Reference: U.S. Environmental Protection Agency. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environmental Protection Agency Contract No. 68-01-4646 (1978), as presented in U.S. Environmental Protection Agency, Ambient water quality criteria for ethylbenzene. Washington, DC, PB81-117590 (1980)

4.6 Other Aquatic Effects

4.6 A Test Species: *Ceriodaphnia dubia*

Test Substance: Ethylbenzene (labeled as 99.8% purity)

Test Method: Other; Method from U.S.EPA's Whole Effluent Testing Program, modified to minimize volatilization. Analytical data from beginning and end of experiment (84.8% of

material present at end of experiment). Initial concentration reported as exposure concentration.

duration: 7 days

type of test: Static

GLP: YES []
NO []
NO DATA [x]

Test Results: 7 day LC50 = 3.6 mg/l (34 µM)
7 day IC50 (reproduction) = 3.3 mg/l (31 µM)
7 day LOEL (reproduction) = 1.7 mg/l (16 µM)
7 day NOEL (reproduction) = 1.0 mg/l (9 µM)

Reference: Neiderlehner, B. R., Cairns, J., Smith, E.P. Modeling acute and chronic toxicity of nonpolar narcotic chemicals and mixtures to *Ceriodaphnia dubia*. Ecotox. and Environm. Safety 39:136-146. (1998)

4.7 Toxicity to Soil Dwelling Organisms

4.7 A Test Species: *Eisenia fetida*, *Allolobophora tuberculata*, *Eudrilus eugeniae*, *Perionyx excavatus* (earthworms)

Test Substance: Ethylbenzene

Test Method: Other; contact test; no other description. No analytical data. 68 chemicals were tested in some of the earthworm species; the report does not specify which species were used for ethylbenzene.

duration: 2 days

type of test: not specified

GLP: YES []
NO []
NO DATA [x]

Test Results: LC50 = 0.0493 mg/l

Reference: Callahan, CA, Shirazi, MA and Neuhauser, EF, Comparative toxicity of chemicals to earthworms. Environ. Toxicol. Chem. 13: 291-298 (1994)

4.8 Toxicity to Terrestrial Plants

4.8 A Test Species: the runner bean, *Phaseolus multiflorus*

Test Substance: Ethylbenzene

Test Method: Other; analytical data

endpoint: capacity to kill leaves upon exposure to vapor concentrations
for 1 hour.

duration: 0.041 day

GLP: YES []
NO [x]
NO DATA []

Test Results: EC = ca. 27 mg/l in air

Reference: Ivens, GW, The phytotoxicity of mineral oils and hydrocarbons. Ann. Appl. Biol., 39: 418 (1952).

4.8 B Test Species: the parsnip, *Pasticana sativa*

Test Substance: Ethylbenzene

Test Method: Other; analytical data

endpoint: capacity to kill leaves upon exposure to vapor concentrations
for 1 hour.

duration: 0.041 day

GLP: YES []
NO [x]
NO DATA []

Test Results: EC = ca. 48 mg/l in air

Reference: Ivens, GW, The phytotoxicity of mineral oils and hydrocarbons. Ann. Appl. Biol., 39: 418 (1952).

4.9 Toxicity to Other Non-mammalian Terrestrial Species

No studies were located for this type of EB exposure.

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

5.1.1 A Test Species: rat, Carworth Wistar

Test Substance: Ethylbenzene

Test Method: Other; 5 non-fasted Carworth-Wistar male rats per group, 4-5 weeks old, 14 day observation period.

GLP: YES []
NO [x]
NO DATA []

Test Results: LD50 = 4.7 g/kg (equivalent to 5.4 ml/kg)

Reference: Smyth, Jr. HF, Carpenter, CP, Weil, CS, Pozzani, UC, and Striegel, JA, Range finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107 (1962)

5.1.1 B Test Species: rat

Test Substance: Ethylbenzene

Test Method: Other; young adult rats, both sexes, observed until recovery of survivors, usually 14 days.

GLP: YES []
NO [x]
NO DATA []

Test Results: LD50 = 3.5 g/kg, slight liver changes at necropsy

Reference: Wolf, MA, Rowe, VK, McCollister, DD, Hollingsworth, RL, and Oyen, F, Toxicological studies of certain alkylated benzenes and benzene. Amer. Med. Assoc. Arch. Ind. Health 14:387-398 (1956)

5.1.1 C Test Species: rat

Test Substance: Ethylbenzene

Test Method: Review of published data; analysis by solubility parameters; used LD50 of Wolf et al., 1956

Reference: Nishimura, H, Saito, S, Kishida, F and Matsuo, M, Analysis of acute toxicity (LD50 value) of organic chemicals to mammals by solubility parameter (1) Acute oral toxicity to rats. Sangyo Igaku 36: 314-323 (1994b)

5.1.2 Acute Inhalation Toxicity

5.1.2 A Test Species: rat, Carworth Wistar

Test Substance: Ethylbenzene

Test Method: Other; 4 hour exposure; single exposure level, nominal concentration was 4000 ppm, (17,400 mg/m³); concentration was not analytically confirmed; 14 day observation period.

GLP: YES []
NO [x]
NO DATA []

Test Results: LC50 = 4000 ppm (17,400 mg/m³)

Reference: Smyth, Jr. HF, Carpenter, CP, Weil, CS, Pozzani, UC, and Striegel, JA, Rangefinding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107 (1962)

5.1.2 B Test Species: rat, CFY male

Test Substance: Ethylbenzene

Test Method: Other; 4 hour exposure

GLP: YES []
NO []
NO DATA [x]

Test Results: narcotic effects as low as 2180 ppm (9450 mg/m³)

Reference: Molnár, J, Paksy, KÁ, and Náray, M, Changes in the rat's motor behavior during 4 hr inhalation exposure to pre-narcotic concentrations of benzene and its derivatives. Acta Physiol. Hung. 67: 349-354 (1986)

5.1.2 C Test Species: mouse, Swiss-Webster

Test Substance: Ethylbenzene

Test Method: sensory irritation; measurement of concentration necessary to depress the respiratory rate by 50%. Exposure was for 30 min, followed by a 20 min recovery period.

GLP: YES []
NO [x]
NO DATA []

Test Results: RD50 = 4060 ppm

Reference: Nielsen, GD and Alarie, Y, Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: Prediction of safe industrial exposure levels and correlation with their thermodynamic properties. Tox. Appl. Pharm. 65:459-477 (1982)

5.1.2 D Test Species: mouse

Test Substance: Ethylbenzene

Test Method: sensory irritation; measurement of concentration necessary to depress the respiratory rate by 50%.

GLP: YES []
NO [x]
NO DATA []

Test Results: RD50 = 1430 ppm (6199 mg/m³)

Reference: De Ceaurriz, J, Micillino, J, Bonnet, P, and Guenier, J, Sensory irritation caused by various airborne chemicals. Toxicol. Lett. 9: 137-143 (1981)

5.1.2 E Test Species: mouse, strain not specified

Test Substance: Ethylbenzene

Test Method: Other

GLP: YES []
NO []
NO DATA [x]

Test Results: 3500 ppm (1517mg/m³) caused prostration; 10,400 ppm (45,084 mg/m³) was minimal lethal concentration.

Reference: Gerarde, HW, Browning, E (ed.), Toxicology and biochemistry of aromatics hydrocarbons. Elsevier Monographs on Toxic Agents (1986) pp. 52-53.

5.1.2 F Test Species: mouse, CFW strain

Test Substance: Ethylbenzene

Test Method: Other

GLP: YES []
NO []
NO DATA [x]

Test Results: Acute, transitory central nervous system depression was observed in in adult male CFW mice exposed to 2000 to 8000 ppm (8670 to 34,680 mg/m³) ethylbenzene for 20 minutes based on a functional observational battery.

Reference: Tegeris, JS, and Balster, RL, (1994) A comparison of the acute behavioral effects of alkylbenzenes using a functional observational battery in mice. Fundam. Appl. Toxicol. 22: 240-250.

5.1.2 G Test Species: guinea pig

Test Substance: Ethylbenzene

Test Method: Other

GLP: YES []
NO [x]
NO DATA []

Test Results: 1000 ppm: nasal and eye irritation, no severe symptoms after several hours of exposure. 2000 ppm: all symptoms listed below, no serious symptoms after 1 hour of exposure.

5000 ppm: all symptoms listed below, fatal in 30-60 minutes.

10,000 ppm: all symptoms listed below, fatal in a few minutes.

Symptoms: eye and nasal irritation, unsteadiness, ataxia, tremors, narcosis and unconsciousness. Gross pathology findings: cerebral congestion, congestion and edema of the lungs, with signs of passive congestion throughout the abdominal viscera.

Reference: Yant, NP, Schrenk, HH, Waite, CP, and Patty, FA, Acute response of guinea pigs to vapors of some new commercial organic compounds. II. Ethylbenzene. Pub. Health Rep. 45:1241-1250 (1930)

5.1.3 Acute Dermal Toxicity

5.1.3 A Test Species: rabbit

Test Substance: Ethylbenzene

Test Method: Other; 4 male albino New Zealand rabbits per group, dose covered with plastic film. 24-hour exposure, 14-day observation.

GLP: YES []
NO [x]
NO DATA []

Test Results: LD50 = 15.4 g/kg

Reference: Smyth, Jr. HF, Carpenter, CP, Weil, CS, Pozzani, UC, and Striegel, JA, Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107 (1962)

5.1.3 B Test Species: rabbit

Test Substance: Ethylbenzene

Test Method: Review of published data; analysis by solubility parameters; source of LD50 value not found

Reference: Nishimura, H, Saito, S, Kishida, F and Matsuo, M, Analysis of acute toxicity (LD50 value) of organic chemicals to mammals by solubility parameter (3) Acute dermal toxicity to rabbits. Sangyo Igaku 36: 428-434 (1994)

5.1.4. Acute Intraperitoneal Toxicity

5.1.4 A Test Species: ddY mice

Test Substance: Ethylbenzene

Test Method: Mice were given ip dose of olive oil or CCl₄ in olive oil; 24 hours later ip dose of test material (one of 9 aromatic hydrocarbons). Mice were observed for 3 additional days.

GLP: YES []
NO []
NO DATA [x]

Test Results: LD50 = 19.7 mmol/kg; CCl₄-pretreated LD50 = 17.81 mmol/kg (attributed to reduced P450 metabolism of ethylbenzene due to carbon tetrachloride poisoning)

Reference: Tanii, H, Huang, J and Hashimoto, K, Structure-acute toxicity relationship of aromatic hydrocarbons in mice. Toxicol. Lett. 76: 27-31 (1995)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

5.2.1 A Test Species: rabbit

Test Substance: Ethylbenzene

Test Method: Other; 0.01 ml undiluted, uncovered application

GLP: YES []
NO [x]
NO DATA []

Test Results: moderate irritating; most severe irritation within 24 hours after application.

Reference: Smyth, Jr. HF, Carpenter, CP, Weil, CS, Pozzani, UC, and Striegel, JA, Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107 (1962)

5.2.1 B Test Species: rabbit

Test Substance: Ethylbenzene

Test Method: Other; Undiluted ethylbenzene applied to intact or abraded skin under occlusion for 24 hours.

GLP: YES []

NO
NO DATA

Test Results: moderate irritating.

Reference: Opdyke, DLJ, Monographs on fragrance raw materials. Ethylbenzene. Food Cosmet. Toxicol. 13:803-804 (1975)

5.2.1 C Test Species: rabbit

Test Substance: Ethylbenzene

Test Method: Other; 10-20 applications to ear and abdomen (bandaged) over 2-4 week period.

GLP: YES
NO
NO DATA

Test Results: moderate irritating (defined erythema) with moderate necrosis (development of edema and superficial necrosis, which resulted in a “chapped” appearance and exfoliation of large patches of skin. This study is of questionable reliability because it is an older study with limited information reported.

Reference: Wolf, MA, Rowe, VK, McCollister, DD, Hollingsworth, RL, and Oyen, F
Toxicological studies of certain alkylated benzenes and benzene. Amer. Med. Assoc. Arch. Ind. Health 14:387-398 (1956)

5.2.2 Eye Irritation

5.2.2 A Test Species: rabbit

Test Substance: Ethylbenzene

Test Method: Other; 2 drops of undiluted liquid applied to one eye.

GLP: YES
NO
NO DATA

Test Results: slight conjunctival irritation, with no corneal injury.

Reference: Wolf, MA, Rowe, VK, McCollister, DD, Hollingsworth, RL, and Oyen, F,
Toxicological studies of certain alkylated benzenes and benzene. Amer. Med. Assoc. Arch. Ind. Health 14:387-398 (1956)

5.2.2 B Test Species: rabbit

Test Substance: Ethylbenzene

Test Method: Other; amount of chemical applied to eye unknown.

GLP: YES []
NO [x]
NO DATA []

Test Results: slightly irritating. The authors reported a very small area of corneal injury resulting from 0.5 ml of undiluted chemical in the eye.

Reference: Smyth, Jr. HF, Carpenter, CP, Weil, CS, Pozzani, UC, and Striegel, JA, Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107 (1962)

5.3 Sensitization

5.3 A Test Species: human

Test Substance: Ethylbenzene

Test Method: Other; 25 volunteers, 10% ethylbenzene in petrolatum.

GLP: YES []
NO [x]
NO DATA []

Test Results: not sensitizing. However, this study is considered inadequate due to methodological limitations.

Reference: Kilgman, AM, Report to RIFM (1974) Cited in Opdyke, D. L. J. Ethylbenzene. Food Cosmet. Toxicol. 13:803-804 (1975)

5.4 Repeated Dose Toxicity

5.4 A Test Species: Fischer 344 rat male and female

Test Substance: Ethylbenzene (purity: 100%)

Test Method: Other; 12 per sex per group

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day

Duration of Exposure: 5 days

Post Exposure Observation Period: none

Doses: 0, 75 or 750 ppm (0, 325 or 3251mg/m³)

GLP: YES [x]
NO []
NO DATA []

Test Results: In the kidneys of high exposure males, there were increased hyaline droplet deposition and degeneration of cortical tubules, which correlated with increased cortical cell proliferation (1.4 fold). A three-fold increase in apoptosis of medullary cells were also noted; due to variability in these measurements, it was considered of unknown significance. No histopathological changes were seen in males exposed at 75 ppm or in females at 75 or 750 ppm. In females exposed at 750 ppm, there was a 50% decrease in cortical cell proliferation. A minimal induction of CYP2B and CYP2E1 was noted.

Reference: Stott, WT, Johnson, KA, Day, SJ, and McGuirk, RJ, Ethylbenzene: Mechanism of Tumorigenicity in Fischer 344 Rats and B6C3F1 Mice. Dow Chemical Company, Laboratory Project Study ID #981138 (1999).

5.4 B Test Species: Fischer 344 rat male and female

Test Substance: Ethylbenzene (purity: 99.7%)

Test Method: Other; 5 sex/group

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day, 5 days/week

Duration of Exposure: 4 weeks

Post Exposure Observation Period: none

Doses: 0, 99, 382, 782 ppm (0, 429, 1656, or 3390 mg/m³)

GLP: YES
NO
NO DATA

Test Results: There was no effect on survival, body, weight gain, clinical chemistry, gross or microscopic pathology. Exposure to 782 ppm resulted in an approximate 20% and 13% ($p < 0.01$) in relative (to body weight) liver weights of both sexes, respectively. Female rats that received 382ppm ethylbenzene exhibited about 7% increase ($p < 0.05$) in relative liver weights; whereas, the male relative liver weights were not significantly different from controls. The authors interpreted the liver changes as adaptive metabolic response, due to the absence of liver histopathology or abnormal clinical chemistry. The NOAEL is considered to be 382ppm (1656mg/m³).

Reference: Cragg, ST, Clarke, EA, Daly, IW, Miller, RR, Terrill, JB, and Ouellette, RE, Subchronic inhalation toxicity of ethylbenzene in mice, rats and rabbits. Fund. Appl. Tox. 13:399-408 (1989)

5.4 C Test Species: Fischer 344 rat male and female

Test Substance: Ethylbenzene (purity: 99.9%)

Test Method: Other; 16 per sex per group

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day

Duration of Exposure: 4 weeks

Post Exposure Observation Period: none

Doses: 0 or 750 ppm (0 or 3251 mg/m³)

GLP: YES []
NO []
NO DATA []

Test Results: There were no deaths and body weights were within 5% of the controls. There were no toxicologically significant effects on measured serum enzymes. In male and female rats, there was a 6-8% increase in kidney weights. In males, this was accompanied by an increase in the focal deposition of α 2u-globulin in the proximal tubule epithelial cells of the cortex extending to the capsule, proximal tubule degeneration, and a 79% increase in S-phase DNA synthesis. In females, neither histopathological changes nor increased S-phase DNA synthesis was noted. Changes *in vitro* enzyme activities were primarily restricted to females and consisted of decreases in mixed-function oxidase (MFO) activities suggesting the alteration or loss of cells. The authors concluded that the data in males were consistent with a treatment-related increased chronic progressive nephropathy. In females, the alteration and possible loss of kidney cell population(s) may also represent an early stage in ethylbenzene-induced acceleration of chronic progressive nephropathy.

Reference: Stott, WT, Day, SJ, McGuirk, RJ, Johnson, KA, and Bahnemann, R, Ethylbenzene: 4-Week Vapor Inhalation Toxicity Study in Fischer 344 Rats and B6C3F1 Mice. Dow Chemical Company, Laboratory Project Study ID #991224 (2001).

5.4 D Test Species: Fischer 344 rat, male and female

Test Substance: Ethylbenzene (purity: > 99%)

Test Method: meets the requirements of OECD Guideline 413: Subchronic Inhalation Toxicity: 90-Day Study with the following exceptions: food consumption not measured, ophthalmic examinations not conducted, and adrenals not weighed.

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day, 5 days/week

Duration of Exposure: 13 weeks

Post Exposure Observation Period: none

Doses: 0, 100, 250, 500, 750, 1000 ppm (0, 434, 1084, 2168, 3251, 4335 mg/m³)

GLP: YES []
NO []

NO DATA []

Test Results: There were no deaths or clinical signs. Male and rats at 1000 ppm had mild weight depression (5-7%) which was not statistically significant. There were no treatment-related effects on hematology, clinical pathology (except lower alkaline phosphatase), weights of heart, thymus or testis. Absolute and/or relative weights of kidney, liver, or lung were higher at 250 ppm and greater. There were no treatment-related histopathologic changes in any tissue. There were no effects on sperm, testicular morphology, or estrus cycle. The data were interpreted to indicate only minimal effects upon exposure of rats to up to 1000 ppm for 13 weeks.

The kidney slides from this study, as well as the NTP 2-year ethylbenzene study (see below) were re-examined. Kidney slides were evaluated for hyaline droplet accumulation and sustained cytotoxicity/cell regeneration. Although there was some evidence of a dose-related increase in hyaline droplet formation in the 13-week NTP study, it was not considered to be of the magnitude indicative of an α 2u-globulin associated mechanism of renal carcinogenesis, since pathological effects associated with α 2u-globulin were absent in the male rat kidneys. The author concluded that the re-evaluation of this study (as well as the NTP 2-year study; see 5.4_ below) provided persuasive evidence that the apparent increase in renal tumors was strongly associated with CPN, a spontaneous age-related disease of rodents with no identical counterpart in humans.

Reference: NTP. Toxicity studies of ethylbenzene (CAS No. 100-41-4) in F344/N rats and B6C3F1 mice (inhalation studies). NTP Tox. 10. NIH Publication No., 92-3129. PB93-149722. National Toxicology Program, U.S. Dept. of Health and Human Services. Research Triangle Park, NC (1992)

Hard, GC, Expert Report on Renal Histopathologic Changes in Rat Inhalation Studies with Ethyl Benzene. Report prepared for the American Chemistry Council Ethylbenzene Panel (2000).

5.4 E Test Species: Wistar rat, male and female

Test Substance: Ethylbenzene

Test Method: Other; 10-25 animals per sex per group

Route of Exposure: inhalation

Frequency of Exposure: 7 hours/day, 5 days/week

Duration of Exposure: 103 to 138 days (see below)

Post Exposure Observation Period: 41-76 days (see below)

Doses: 0, 400, 600, 1250, 2200 ppm (0, 1734, 2601, 5419, 953 mg/m³)
400 ppm for 130 exposures, then observed until day 136
600 ppm for 130 exposures, then observed until day 136
1250 ppm for 138 exposures, then observed until day 214
2200 ppm for 103 exposures, then observed until day 144

GLP: YES []
NO []
NO DATA [x]

Test Results: Growth depression was seen at 1250 and 2200 ppm. Liver and kidney weights were increased at all exposure levels. Cloudy swelling in the liver and in the kidney tubular epithelial cells were observed at 1250 and 2200 ppm. The NOAEL is 600 ppm (2601mg/m³).

Reference: Wolf, MA, Rowe, VK, McCollister, DD, Hollingsworth, RL, and Oyen, F, Toxicological studies of certain alkylated benzenes and benzene. Amer. Med. Assoc. Arch. Ind. Health 14:387-398 (1956)

5.4 F Test Species: Fischer 344 rat male and female

Test Substance: Ethylbenzene (purity: > 99%)

Test Method: National Toxicology Program carcinogenicity test

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day 5 days/week

Duration of Exposure: 104 weeks

Post Exposure Observation Period: none

Doses: 0, 75, 250, 750 ppm (0, 325, 1084, 3251mg/m³)

GLP: YES [x]
NO []
NO DATA []

Test Results: At 750 ppm, survival in males was significantly reduced, while in females survival was increased (not significant). No clinical findings were attributed to the ethylbenzene exposure. In males exposed to 250 or 750 ppm, body weights were reduced (up to 5 and 15%, respectively) from week 20 to the end of the study. In females all exposed groups weighed up to 5% less than the controls during the second year, but there was no dose-response. In both males and females exposed to 750 ppm, but not to 75 or 250 ppm, there was increased renal tubule hyperplasia and increased severity of nephropathy.

The kidney slides from this study, as well as the NTP 13-week study (see 5.4B above) were re-examined. Kidney slides were evaluated for hyaline droplet accumulation, sustained cytotoxicity/cell regeneration, interaction with chronic progressive nephropathy (CPN), and tumors. Ethylbenzene caused an exacerbation of age-related spontaneous renal disease, CPN, in the 750 ppm animals, markedly so in the male rats, and modestly so in the females. In addition, there was a high incidence of high-dose rats that had end-stage CPN, a terminal condition where the kidneys are so morphologically altered that renal failure (as well as secondary hyperthyroidism) occurs. Although there some evidence of a dose-related increase in hyaline droplet formation in the 13-week NTP study, it was not considered to be of the magnitude indicative of an α 2u-globulin associated mechanism of renal

carcinogenesis. Other pathological effects associated with α 2u-globulin were absent in the male rat kidneys from the 2-yr NTP study. The author concluded that the re-evaluation of this study provided persuasive evidence that the apparent increase in renal tumors was strongly associated with CPN, a spontaneous age-related disease of rodents with no identical counterpart in humans.

Reference: NTP. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ethylbenzene (CAS No. 100-41-4) in F344 Rats and B6C3F1 Mice (Inhalation Studies). NTP TR 466. NIH Publication 96-3956. US Department of Health and Human Services. Research Triangle Park, NC (1999)

Hard, GC, Expert Report on Renal Histopathologic Changes in Rat Inhalation Studies with Ethyl Benzene. Report prepared for the American Chemistry Council Ethylbenzene Panel (2000).

5.4 G Test Species: Wistar rat, female

Test Substance: Ethylbenzene

Test Method: Other. Ethylbenzene administered in an olive oil solution which was prepared monthly. No. of animals: 10/treatment group and 20 controls.

Route of Exposure: gavage

Frequency of Exposure: once/day, 5 days/week

Duration of Exposure: 6 months

Post Exposure Observation Period: 52 days

Doses: 0, 13.6, 136, 408, 680 mg/kg/day

GLP: YES []
NO [x]
NO DATA []

Test Results: Liver and kidney weights were higher, and minimal effects (cloudy swelling) were observed microscopically in the liver and kidney tubular epithelium cells at 408 and 680 mg/kg. NOAEL = 136 mg/kg/day.

Reference: Wolf, MA, Rowe, VK, McCollister, DD, Hollingsworth, RL, and Oyen, F, Toxicological studies of certain alkylated benzenes and benzene. Amer. Med. Assoc. Arch. Ind. Health 14: 387-398 (1956)

5.4 H Test Species: Wag/Rij rats

Test Substance: Ethylbenzene (purity: 99%)

Test Method: Other

Route of Exposure: inhalation

Frequency of Exposure: 8 hours/day

Duration of Exposure: 5 days

Post Exposure Observation Period: one and four weeks

Doses: 0 or 800 ppm (0 or 3468 mg/m³)

GLP: YES []
NO []
NO DATA [x]

Test Results: Auditory thresholds were increased for startle response one and four weeks after the end of the exposure by about 25 dB, irrespective of the stimulus frequency tested (4-24 kHz). A shift in the electrocochleography was seen at 8 and 11 weeks after exposure. The threshold for the compound action potential increased significantly by 10-30 dB at all frequencies tested (1-24 kHz). Histological examination of the cochlea showed outer hair cell loss (OHC), especially in the upper basal and lower middle turns (corresponding to the mid-frequency region) to an extent of 65%.e.

Reference: Cappaert, NLM, Klis, SFL, Muijser, H, deGroot, JCMJ, Kulig, GBM, and Smoorenburg, GF (1999) The ototoxic effects of ethyl benzene in rats. *Hearing Res.* 137: 91-102 (1999).

5.4 I Test Species: Wag/Rij rats (8/group)

Test Substance: Ethylbenzene (purity: 99%)

Test Method: Other; three to six weeks after the exposure, auditory function was tested by measuring compound action potentials (CAP) and 2f₁-f₂ distortion product otoacoustic emissions (DPOAEs). In addition, outer hair cell (OHC) loss was quantified by histological examinations.

Route of Exposure: inhalation

Frequency of Exposure: 8 hours/day

Duration of Exposure: 5 days

Post Exposure Observation Period: up to 11 weeks

Doses: 0, 300, 400, or 550 ppm (0, 1301, 1734, or 2384 mg/m³)

GLP: YES []
NO []
NO DATA [x]

Test Results: No effects were observed at 300 ppm. At 400 and 550 ppm, the mid-frequency hearing region (8-12 kHz) was affected. Auditory thresholds were increased in both the 400 and 550 ppm exposed rats, while DPOAE amplitude growth was increased

only in the 550 ppm group. A dose-related OHCs loss was found in two of the five examined locations (11 and 21 kHz) in the cochlea.

Reference: Cappaert, NLM, The Damaging Effects of Noise and Ethyl Benzene on Hearing. Thesis from University of Utrecht, Netherlands (2000).

5.4 J Test Species: Wag/Rij rats (8/group)

Test Substance: Ethylbenzene (purity: 99%)

Test Method: Other; the study examined noise levels and ethylbenzene concentrations for interaction effects on hearing as measured by the physiological measurements of distortion product otoacoustic emissions (DPOAEs) and compound action potentials (CAPs)

Route of Exposure: inhalation

Frequency of Exposure: 8 hours/day

Duration of Exposure: 5 days

Post Exposure Observation Period: one and four weeks

Doses: 0, 300, or 400 ppm ethylbenzene; 65 (background), 95 or 105 dB noise levels and all their combinations.

GLP: YES []
NO []
NO DATA [x]

Test Results: The hearing parameters (DPOAEs and CAPs) were altered by noise alone (105dB) and with noise in combination with ethylbenzene (105dB + 300 or 400 ppm ethylbenzene); however, the amount of loss after exposure to the combination did not exceed the loss induced after noise alone. At the concentrations tested, ethylbenzene alone did not cause significant DPOAE or CAP hearing loss. Hence these physiological measurements did not show any significant synergistic interactions between noise and ethylbenzene exposure.

Reference: Cappaert, NLM, The Damaging Effects of Noise and Ethyl Benzene on Hearing. Thesis from University of Utrecht, Netherlands (2000).

5.4 K Test Species: Sprague-Dawley rat, male and female

Test Substance: Ethylbenzene

Test Method: Other

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day

Duration of Exposure: 3 days

Post Exposure Observation Period: 16-18 hours after the last exposure

Doses: 0 or 2000 ppm (0 or 8670 mg/m³)

GLP: YES []
NO []
NO DATA [x]

Test Results: Increases in dopamine and noradrenaline levels and turnover in various parts of the hypothalamus and the median eminence were reported. Serum prolactin levels were also decreased. Ethylbenzene selectively increased dopamine turnover within the dopamine-cholecystokinin-8 immunoreactive nerve terminals of the nucleus accumbens (posterior part).

Reference: Andersson, K, Fuxe, K Nilsen, OG, Toftgård, R, Eneroth, P, and Gustafsson, J-A, Production of discrete changes in dopamine and noradrenalin levels and turnover in various parts of the rat brain following exposure to xylene, *ortho*-, *meta*-, and *para*-xylene, and ethylbenzene. *Tox. Appl. Pharmacol.* 60: 535-548 (1981)

5.4 L Test Species: B6C3F1 mouse, male and female

Test Substance: Ethylbenzene (purity: 100%)

Test Method: Other; 36 animals per sex per group

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day

Duration of Exposure: 5 days

Post Exposure Observation Period: none

Doses: 0, 75 or 750 ppm (0, 325, or 3251mg/m³)

GLP: YES [x]
NO []
NO DATA []

Test Results: In the 750 ppm group (both sexes), mouse liver weights were elevated, and there were increased proliferation of centrilobular and midzonal hepatocytes, as evidenced by the increased in BrdU uptake, and increased incidence of mitotic figures. Males were more affected than females. Lesser effects were observed in the 75 ppm-exposed group. Increased liver weights also correlated with minimal induction of CYP1A and/or CYP2B. Histopathological changes consisting of increased mitotic figures in centrilobular and midzonal areas accompanied these changes. In mouse lungs, there appeared to be a dose-dependent loss of CYP1A and CYP2B in both males and females. There were changes in cell population dynamics, as suggested by an observed 3-fold increase in cell proliferation in the bronchiolar epithelium and, possibly, in apoptosis of bronchiolar and alveolar epithelia of the 750 ppm-exposed animals.

Reference: Stott, WT, Johnson, KA, Day, SJ, and McGuirk, RJ, Ethylbenzene: Mechanism of Tumorigenicity in Fischer 344 Rats and B6C3F1 Mice. Dow Chemical Company, Laboratory Project Study ID #981138 (1999).

5.4 M Test Species: B6C3F1 mouse, male and female

Test Substance: Ethylbenzene (purity: 99.7%)

Test Method: Other; 5 animals per sex per group

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day, 5 days/week

Duration of Exposure: 4 weeks

Post Exposure Observation Period: none

Doses: 0, 99, 382, 782 ppm (0, 429, 1656 or 3390 mg/m³)

GLP: YES
NO
NO DATA

Test Results: No effect on survival, body weight gain, hematology, gross or microscopic pathology. Mice that received 782ppm ethylbenzene did not show consistent liver weight increases; weights relative to body weight were not statistically significantly different in females (about 15%, $p < 0.05$) and relative to brain weights (about 15%, $p < 0.01$). The authors interpreted the liver changes as adaptive metabolic response, due to the absence of liver histopathology or abnormal clinical chemistry. The NOAEL is considered to be 382ppm (1656 mg/m³).

Reference: Cragg, ST, Clarke, EA, Daly, IW, Miller, RR, Terrill, JB, and Ouellette, RE, Subchronic inhalation toxicity of ethylbenzene in mice, rats and rabbits. Fund. Appl. Tox. 13:399-408 (1989)

5.4 N Test Species: B6C3F1 mouse, male and female

Test Substance: Ethylbenzene (purity: 99.9%)

Test Method: Other; 48 animals per sex per group

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day, 5 days/week

Duration of Exposure: 4 weeks

Post Exposure Observation Period: none

Doses: 0 or 750 ppm (0 or 3251mg/m³)

GLP: YES [x]
NO []
NO DATA []

Test Results: Seven females exposed to 750 ppm ethylbenzene died within the first five days. There were no treatment-related differences in body weight in either the male or female animals. Liver weights, both absolute and relative to body weight, were increased for both male and female mice exposed to 750 ppm ethylbenzene relative to control. In both sexes, this change was associated with a minimal degree of hypertrophy in the centrilobular and mid-zonal liver cells, and increased occurrence of mitotic figures. Increased BrdU staining (S-Phase DNA synthesis) of liver cells was seen in males (354%) and females (56%) in the centrilobular regions. CYP2B activity, was elevated 81% and 130% in the ethylbenzene-exposed animals, respectively. Lung weights were not affected following exposure of mice to ethylbenzene. Nevertheless, S-phase DNA synthesis rates in bronchiolar epithelium were increased 82% and 115% in males and females, respectively. Activities of CYP2E1 and UDP-glucuronosyl transferase were increased in males while the activities of most MFOs were decreased in females. No histopathologic effects were found in the lungs of the treated mice. Increased BrdU staining of the terminal bronchioles was seen in both males (82%) and females (115%), relative to controls. In males, but not females, there was a slight decrease in alveolar staining.

Reference: Stott, WT, Day, SJ, McGuirk, RJ, Johnson, KA, and Bahnemann, R, Ethylbenzene: 4-Week Vapor Inhalation Toxicity Study in Fischer 344 Rats and B6C3F1 Mice. Dow Chemical Company, Laboratory Project Study ID #991224 (2001).

5.4 O Test Species: B6C3F1 mouse, male and female

Test Substance: Ethylbenzene (purity: > 99%)

Test Method: Meets the requirements of OECD Guideline 413: Subchronic Inhalation Toxicity: 90-Day Study with the following exceptions: food consumption not measured, ophthalmic examinations not conducted, and adrenals not weighed.

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day, 5 days/week

Duration of Exposure: 13 weeks

Post Exposure Observation Period: none

Doses: 0, 100, 250, 500, 750, 1000 ppm (0, 434, 1084, 2168, 3251, or 4335mg/m³)

GLP: YES [x]
NO []
NO DATA []

Test Results: There were no deaths, clinical signs, effects on body weight, or gross pathology at termination. There were dose-related higher absolute and relative liver weights

in males and females exposed at 750 or 1000 ppm, and a higher relative kidney weight in females at 1000 ppm. There were no treatment-related histopathologic findings in any organs. No differences from control were found in evaluation of sperm or vaginal cytology. The data were interpreted to indicate only minimal effects upon exposure of mice to up to 1000 ppm for 13 weeks.

Reference: NTP. Toxicity studies of ethylbenzene (CAS No. 100-41-4) in F344/N rats and B6C3F1 mice (inhalation studies). NTP Tox. 10. NIH Publication No., 92-3129. PB93-149722. National Toxicology Program, U.S. Dept. of Health and Human Services. Research Triangle Park, NC (1992)

5.4 P Test Species: B6C3F1 mouse male and female

Test Substance: Ethylbenzene (purity: >99%)

Test Method: National Toxicology Program carcinogenicity test

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day 5 days/week

Duration of Exposure: 104 weeks

Post Exposure Observation Period: none

Doses: 0, 75, 250, 750 ppm (0,325, 1084, or 3251mg/m³)

GLP: YES []
NO []
NO DATA []

Test Results: In the lung at 750 ppm, male rats exhibited increased alveolar epithelial metaplasia (12% vs. 0% in control), but there was no increase in alveolar hyperplasia. In females, no significant increase in the incidence of either hyperplasia or metaplasia was observed. No effects were observed in either male or female mice at 250 or 75 ppm.

In the liver, females (but not males) exposed to 750 ppm had an increased incidence of eosinophilic foci (44% vs. 10% in controls), a lesion which is judged to be a precursor of hepatocellular adenomas. The incidence of eosinophilic foci in either males or females exposed to 250 or 75 ppm were not significantly different from the control incidences. There were, however, increased incidences of syncytial alteration, hypertrophy and necrosis in the liver of males exposed to 750 ppm ethylbenzene. There were increased follicular cell hyperplasia in the thyroid gland in both the 750 ppm males and females; and hyperplasia in the pituitary gland in the 250 and 750 ppm females. The NOAELs for male and female mice are considered to be 250ppm (1084mg/m³) and 75ppm (325mg/m³), respectively.

The lung and liver sections of mice from the National Toxicology Program (NTP) two-year bioassay were re-evaluated by Brown (2000). This re-evaluation revealed an increased incidence of male and female mice of the 750 ppm exposure group with decreased eosinophilia of the terminal bronchiolar epithelium. Also, a dose-related increased incidence in multifocal hyperplasia of the bronchiolar epithelium with extension to the

peribronchiolar alveolar epithelium was observed in all male treated groups and mid- and high-exposure females. The author noted that the necrotic hepatocytes in the high-dose males were usually that of a coagulation-type necrosis of single or small groups of cells, usually the enlarged, hypertrophied centrilobular hepatocytes. The morphology of this necrosis was histomorphologically different from "apoptosis." Also, the syncytial cells were not the predominant cell type with necrosis.

Reference: NTP. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ethylbenzene (CAS No. 100-41-4) in F344 Rats and B6C3F1 Mice (Inhalation Studies). NTP TR 466. NIH Publication 96-3956. US Department of Health and Human Services. Research Triangle Park, NC (1999)

Brown, WR, Toxicology and Carcinogenesis Study of Ethylbenzene in B6C3F1 Mice (CAS 100-41-4) NTP Report Number 466. Histopathology of Liver and Lung. Report prepared for the American Chemistry Council Ethylbenzene Panel (2000).

5.4 Q Test Species: New Zealand white rabbit male and female

Test Substance: Ethylbenzene (purity: 99.7%)

Test Method: Meets the requirements of OECD Guideline 413: Subchronic Inhalation Toxicity: 90-Day Study with the following exceptions: food consumption not measured, ophthalmic examinations not conducted, and adrenals not weighed.

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day, 5 days/week

Duration of Exposure: 4 weeks

Post Exposure Observation Period: none

Doses: 0, 382, 782, 1610 ppm (0, 1656, 3390, 6979mg/m³)

GLP: YES
NO
NO DATA

Test Results: Non-significant decrease in body weight gain. No organ weight effects, hematology, clinical chemistry, or gross or microscopic pathology changes. The NOAEL is 1610 ppm (6979mg/m³).

Reference: Cragg, ST, Clarke, EA, Daly, IW, Miller, RR, Terrill, JB, and Ouellette, RE, Subchronic inhalation toxicity of ethylbenzene in mice, rats and rabbits. Fund. Appl. Toxicol 13:399-408 (1989)

5.4 R Test Species: rabbit male and female

Test Substance: Ethylbenzene

Test Method: Other. Groups were comprised of only 1-2 rabbits.

Route of Exposure: inhalation

Frequency of Exposure: 7 hours/day, 5 days/week

Duration of Exposure: 130 to 138 days (see below)

Post Exposure Observation Period: see below

Doses: 0, 400, 600, 1250 ppm (0, 1734, 2601, 5419 mg/m³)
400 ppm for 130 exposures, then observed until day 186
600 ppm for 130 exposures, then observed until day 186
1250 ppm for 138 exposures (females), then observed until day 214

GLP: YES []
NO [x]
NO DATA []

Test Results: Report of degeneration of germinal epithelium of testes in rabbits assigned to the 600 ppm group is considered of questionable toxicological significance due to small group size of 1 or 2 rabbits, and the expected wide variability in morphological appearance of germinal epithelium of testes. The NOAEL is 400 ppm (1734mg/m³).

Reference: Wolf, MA, Rowe, VK, McCollister, DD, Hollingsworth, RL, and Oyen, F.,
Toxicological studies of certain alkylated benzenes and benzene. Amer. Med. Assoc. Arch.
Ind. Health 14: 387-398 (1956)

5.4 S Test Species: guinea pig, male and female

Test Substance: Ethylbenzene

Test Method: Other; 5-10 animals per dose

Route of Exposure: inhalation

Frequency of Exposure: 7-8 hours/day, 5 days/week

Duration of Exposure: 130 to 138 days (see below)

Post Exposure Observation Period: see below

Doses: 0, 400, 600, 1250 ppm (0, 1734, 2601, 5419 mg/m³)
400 ppm for 130 exposures, then observed until day 186
600 ppm for 130 exposures, then observed until day 186
1250 ppm for 138 exposures (females), then observed until day 214

GLP: YES []
NO [x]
NO DATA []

Test Results: There was depression in body weight gain at 1250 ppm and increase in liver weights at 600 ppm. In the absence of histopathology, the liver weight changes were not considered adverse and the NOAEL is 400 ppm (1734mg/m³)

Reference: Wolf, MA, Rowe, VK, McCollister, DD, Hollingsworth, RL, and Oyen, F., Toxicological studies of certain alkylated benzenes and benzene. Amer. Med. Assoc. Arch. Ind. Health 14: 387-398 (1956)

5.4 T Test Species: guinea pigs

Test Substance: Ethylbenzene (purity: 99%)

Test Method: Other; auditory function was tested by measuring compound action potentials (CAP). In addition, outer hair cell (OHC) loss was quantified by histological examinations.

Route of Exposure: inhalation

Frequency of Exposure: 8 hours on day 1; 6 hours/day for the next four days

Duration of Exposure: 5 days

Post Exposure Observation Period:

Doses: 0 or 2500 ppm (0 or 10,838 mg/m³)

GLP: YES []
NO []
NO DATA [x]

Test Results: There was no shift in auditory threshold or any outer cell loss.

Reference: Cappaert, NLM, The Damaging Effects of Noise and Ethyl Benzene on Hearing. Thesis from University of Utrecht, Netherlands (2000).

5.4 U Test Species: Rhesus monkey male and female

Test Substance: Ethylbenzene

Test Method: Other. Groups were comprised of 1-2 monkeys.

Route of Exposure: inhalation

Frequency of Exposure: 7 hours/day, 5 days/week

Duration of Exposure: 130 exposures

Post Exposure Observation Period: 56 days

Doses: 0, 400, 600 ppm (0, 1734, 2601mg/m³)

GLP: YES []

NO
NO DATA

Test Results: Increase in liver weights and degeneration of germinal epithelium in the testes were reported at 600 ppm. Report of degeneration of the germinal epithelium is considered of questionable toxicological significance due to small group size of only 1 or 2 monkeys, and the expected wide range of variability in morphological appearance of germinal epithelium of testes of monkeys. The NOAEL is 400 ppm (1734mg/m³).

Reference: Wolf, MA, Rowe, VK, McCollister, DD, Hollingsworth, RL, and Oyen, F., Toxicological studies of certain alkylated benzenes and benzene. Amer. Med. Assoc. Arch. Ind. Health 14: 387-398 (1956)

5.5 Genetic Toxicity *in Vitro*

5.5.1 A Bacterial test

Test type: Ames

Test system: *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538

Concentration: 0.2 - 2,000 ug/plate; vehicle: DMSO

Metabolic Activation: with and without

GLP: YES
NO
NO DATA

Test Results: negative

Reference: Dean, BJ, Brooks, TM, Hodson-Walker, G, and Hutson, DH, Genetic toxicology testing of 41 industrial chemicals. Mutat. Res. 153: 57-77 (1985)

5.5.1 B Bacterial test

Test type: Ames

Test system: *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537

Concentration: 0.03, 0.3, 3, 30 ug/plate

Metabolic Activation: with and without

GLP: YES
NO
NO DATA

Test Results: negative; 30 umol/plate was toxic

Reference: Florin, I, Rutberg, L, Curvall, M, and Enzell, CR, Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology 18: 219-232 (1980)

5.5.1 C Bacterial test

Test type: Ames

Test system: *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538

Concentration up to 0.4 mg/plate

Metabolic Activation: with and without

GLP: YES []
NO []
NO DATA [x]

Test Results: negative. Lethality was observed at the highest level tested, 0.4 mg/plate.

Reference: Nestmann, ER, Lee, EG-H, Matula, TI, Douglas, GR, and Mueller, JC, Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat. Res. 79: 203-212 (1980)

5.5.1 D Bacterial test

Test type: Ames

Test system: *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537

Concentration 10 - 1000 ug/plate; vehicle was DMSO; S9 was from rats and hamster liver.

Metabolic Activation: with and without

GLP: YES []
NO []
NO DATA [x]

Test Results: negative

Reference: Zeiger, E, Anderson, B, Haworth, S, Lawlor, T, and Mortelmans, K, Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ. Mol. Mutagen. 19 Supp. 21: 2-141 (1992)

5.5.1 E Bacterial test

Test type: Bacterial gene mutation assay

Test system: *Escherichia coli* WP2, WP2uvrA

Concentration:

Metabolic Activation: with and without

GLP: YES []
NO []
NO DATA [x]

Test Results: negative

Reference: Dean, BJ, Brooks, TM, Hodson-Walker, G, and Hutson, DH, Genetic toxicology testing of 41 industrial chemicals. *Mutat. Res.* 153: 57-77 (1985)

5.5.1 F Bacterial test

Test type: Gene mutation

Test system: *Saccharomyces cerevisiae* D7, XV 185-14 C

Concentration:

Metabolic Activation: with and without

GLP: YES []
NO []
NO DATA [x]

Test Results: negative

Reference: Nestmann, ER, and Lee, EG-H, Mutagenicity of constituents of pulp and paper mill effluent in growing cells of *Saccharomyces cerevisiae*. *Mutat. Res.* 119: 273-280 (1983)

5.5.1 G Bacterial test

Test type: Mitotic recombination (Biological endpoint: gene conversion.)

Test system: *Saccharomyces cerevisiae* JD1

Concentration:

Metabolic Activation: with and without

GLP: YES []
NO []
NO DATA [x]

Test Results: negative

Reference: Dean, BJ, Brooks, TM, Hodson-Walker, G, and Hutson, DH, Genetic toxicology testing of 41 industrial chemicals. *Mutat. Res.* 153: 57-77 (1985)

5.5.1 H *In vitro* mammalian test

Test type: Mouse lymphoma assay

Test system: Mouse L5178Y/TK lymphoma cells

Concentration: 10-160 ug/l

Metabolic Activation: without

GLP: YES []
NO []
NO DATA [x]

Test Results: Positive at 80 ug/ml, relative total growth less than 35% of control; totally lethal at 160 ug/ml

Reference: McGregor, DB, Brown, A, Cattanaach, P, Edwards, I, McBride, D, Riach, C, and Caspary, WJ, Responses of the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. Environ. Mol. Mutagen. 12: 85-154 (1988)

5.5.1 I *In vitro* mammalian test

Test type: Mouse lymphoma assay

Test system: Mouse L5178Y/TK lymphoma cells

Concentration: 8.6 – 100.0 ug/l without S9
68.8 – 900 ug/l with S9

Metabolic Activation: with and without

GLP: YES [x]
NO []
NO DATA []

Test Results: Positive

Three trials were performed with and without activation. In the first trial without activation, the results indicate a definitive positive at 34 and 69 µl/mg. In the same trial with activation there was a limited positive response at 825 µl/mg in which the relative growth (RTG: an indicator of cytotoxicity) of one culture was above the 20% level, which indicates a “definitive positive”, and one result was below. However, both results from this dose level were above 10% RTG indicating a “limited positive” response. In addition, positive responses were obtained in both large and small colonies, and thus both gene and chromosome mutations contribute to the response. In the second and third trials both with and without activation, the results were determined to be an inconclusive negative, due either to insufficiently high dose levels or to an inadequate positive control response.

Reference: Wollny, H.-E. Cell mutation assay at the thymidine kinase locus (TK+/-) in mouse lymphoma L5178Y cells (soft agar method) with ethylbenzene. RCC-CCR Project No. 635300. RCC-Cytotest Cell Research GmbH, Germany (2000).

5.5.2 A Cytogenetic assay

Test type: Chromosome aberrations

Test system: rat liver (RL4) epithelial-type cells

Concentration 0.5, 0.25, 0.125 of the concentration which caused 50% growth inhibition

Metabolic Activation: with and without

Duration of Exposure: 24 hr

GLP: YES []
NO []
NO DATA [x]

Test Results: negative

Reference: Dean, BJ, Brooks, TM, Hodson-Walker, G, and Hutson, DH, Genetic toxicology testing of 41 industrial chemicals. *Mutat. Res.* 153: 57-77 (1985)

5.5.2 B Cytogenetic assay

Test type: Chromosome aberrations

Test system: Chinese hamster ovary (CHO) cells

Concentration: 75, 100 and 125 µg/ml

Metabolic Activation: with and without

GLP: YES []
NO []
NO DATA [x]

Test Results: negative

Reference: NTP. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ethylbenzene (CAS No. 100-41-4) in F344 Rats and B6C3F1 Mice (Inhalation Studies). NTP TR 466. NIH Publication 96-3956. US Department of Health and Human Services. Research Triangle Park, NC (1999)

5.5.2 B Cytogenetic assay

Test type: Micronucleus

Test system: Syrian hamster embryo (SHE) cells

Test method: OECD Guideline No. 476

Test substance: ethylbenzene

Concentration: 25 to 200 µg/ml

Duration of Exposure: 24 hours

GLP: YES []
NO []
NO DATA [x]

Test Results: positive

Reference: Gibson, D.P., Brauning, R., Shaffi, H.S., Kerckaert, G.A., LeBoeuf, R.A., Isfort, R.J., and Aardema, M.J, Induction of micronuclei in Syrian hamster embryo cells: comparison to results in the SHE cell transformation assay for national toxicology program test chemicals Mutat. Res. 392: 61-90 (1997).

Hazleton, Development of an in vitro micronucleus assay using Syrian hamster embryo (SHE) cells (with ethylbenzene, nitromethane, & tetrahydrofuran), with cover letter dated 3/13/96. EPA/OTS; Doc #86960000309 (1996).

5.5.2 C Cytogenetic assay

Test type: Sister chromatid exchange assay

Test system: Chinese Hamster Ovary Cells; S9: rat

Concentration: 75.5-151 µg/ml without S9; 75-175 µg/ml with S9; vehicle: DMSO

Metabolic Activation: with and without metabolic activation

GLP: YES []
NO []
NO DATA [x]

Test Results: negative

Reference: NTP. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ethylbenzene (CAS No. 100-41-4) in F 344/N Rats and B6C3F₁ Mice (Inhalation Studies). NTP TR466. NIH Publication 96-3956. US Department of Health and Human Services, Research Triangle Park, NC (1999)

5.5.2 D Cytogenetic assay

Test type: Sister chromatid exchange assay

Test system: Human whole-blood lymphocyte culture

Concentration:

Metabolic Activation: none

GLP: YES []
NO []
NO DATA [x]

Test Results: Marginally positive at highest, toxic dose (10 mM). However, this study cannot be considered reliable since the study protocol has not been validated.

Reference: Norppa, H and Vainio, H, Induction of sister-chromatid exchanges by styrene analogues in cultured human lymphocytes. *Mutat. Res.* 116: 378-387 (1983)

5.5.2 E Cell transformation assay

Test type: *In vitro* cell transformation assay

Test system: Syrian hamster embryo (SHE) cells

Concentration: up to 500 µg/ml

GLP: YES []
NO []
NO DATA [x]

Test Results: negative following 24 hr incubation.
positive at 150 to 200 µg/ml following 7 day incubation; negative at 100 and 125.

Comments: Authors suggest this is indication of promotion-like mechanism.

Reference: Kerckaert, GA, Brauninger, R, Leboef, RA, and Isfort, RA., Use of the Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays, *Env. Health Perspectives* 104 Suppl. 5: 1075-1084 (1996)

Hazleton Washington Inc., Clonal transformation assay using Syrian hamster embryo (SHE) cells, with cover letter dated 07/27/95. EPA/OTS; Doc #86950000286 (1995a).

Hazleton Washington Inc., 7 Day clonal Syrian hamster embryo (SHE) cell transformation assay testing the *in vitro* transformation potential of ethylbenzene, with cover letter dated 07/27/95. EPA/OTS; Doc #86950000287 (1995b).

5.6 Genetic Toxicity *in Vivo*

5.6 A Test type: Micronucleus assay

Test Species: B6C3F1 mouse male and female

Test Substance: Ethylbenzene

Test Method: Other. Smears were prepared from peripheral blood samples at termination of the 13-week study. At least 2000 polychromatic erythrocytes and 10,000 normochromatic nuclei from each animal were scored for micronuclei.

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day

Duration of Exposure: 13 weeks

Post Exposure Observation Period: none

Doses: 0, 500, 750, 1000 ppm (0, 2168, 3251, 4335 mg/m³)

GLP: YES []
NO []
NO DATA [x]

Test Results: The study was negative.

Reference: NTP. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ethylbenzene (CAS No. 100-41-4) in F 344/N Rats and B6C3F1 Mice (Inhalation Studies). NTP TR466. NIH Publication 96-3956. US Department of Health and Human Services, Research Triangle Park, NC (1999).

5.6 B Test type: Micronucleus assay

Test Species: NMRI mouse

Test Substance: Ethylbenzene

Test Method: 5 animals per group. Method from Schmid (1977) in Kilbey et al. (eds), Handbook for mutagenicity test procedures. Elsevier, New York. pp. 235-242.

Route of Exposure: intraperitoneal

Frequency of Exposure: 2 doses 24 hours apart

Duration of Exposure: 2 days

Post Exposure Observation Period: none

Doses: 0.37, 0.50, 0.62, 0.75 ml/kg = 318, 430, 533, 645 mg/kg

GLP: YES []
NO []
NO DATA [x]

Test Results: The study was negative.

Reference: Mohtashampur, E, Norpoth, K, Woelke, U, and Huber, P, Effects of ethylbenzene, toluene, and xylene on the induction of micronuclei in bone marrow polychromatic ethyrcytes of mice. Arch. Toxicol. 58: 106-109 (1985)

5.6 C Test type: Unscheduled DNA synthesis

Test Species: mouse

Test Substance: Ethylbenzene (purity: 99.7%)

Test Method: OECD Guideline No. 486

Route of Exposure: inhalation

Frequency of Exposure: single 6 hour exposure

Duration of Exposure: 6 hours

Post Exposure Observation Period: none

Doses: males 500 and 1000 ppm (2168 and 4335 mg/m³); females 375 and 750 ppm (1626 and 3251mg/m³)

GLP: YES [x]
NO []
NO DATA []

Test Results: Ethylbenzene did not induce DNA repair as measured by unscheduled DNA synthesis (UDS) in liver cells following a single 6-hour inhalation exposure of ethylbenzene vapor. The exposure levels for each sex were based on a preliminary study which determined these exposure levels to be the maximum tolerated dose (MTD) based on observed patterns of clinical signs and lethalties.

Reference: Clay, P. Ethylbenzene: *In Vivo* Mouse Liver Unscheduled DNA Synthesis assay. Central Toxicology Laboratory Report CTL/SM0998/REG/REPT, (2001).

5.6 D Test type: Drosophila SLRL test

Test Species: *Drosophila melanogaster*

Test Substance: Ethylbenzene

Test Method: No information is given on methods.

Route of Exposure:

Frequency of Exposure:

Duration of Exposure:

Post Exposure Observation Period:

Doses:

GLP: YES []
NO []
NO DATA [x]

Test Results: The study was negative. However, this study is considered unreliable since the study details are poorly reported.

Reference: Donner, M, Mäki-Paakkanen, J, Norppa H, Sorsa, M, and Vainio, H, Genetic toxicology of xylenes. *Mutat. Res.* 74: 171-172 (1980)

5.7 Carcinogenicity

5.7 A Test Species: Human

Test Substance: Ethylbenzene

Test Method: Epidemiology of workers in ethylbenzene production in Czechoslovakia

Route of Exposure: inhalation, dermal

Frequency of Exposure: workplace exposure

Duration of Exposure: Workers employed an average of 12.2 years, monitoring for 20 years

Post Exposure Observation Period:

Doses: Mandelic acid urine concentration in these workers never exceeded 3.25 mmol/l

GLP: YES []
NO []
NO DATA [x]

Test Results: Medical records of 200 males involved in the production of ethylbenzene in Czechoslovakia did not indicate any increased incidence of cancer.

Reference: Bardoděj, Z and Círek, A, Long-term study on workers occupationally exposure to ethylbenzene. *J. Hyg. Epidemiol. Microbiol. Immunol.* 32:1-5.

5.7 B Test Species: Fischer 344 rat male and female

Test Substance: Ethylbenzene (purity: > 99%)

Test Method: National Toxicology Program carcinogenicity test

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day 5 days/week

Duration of Exposure: 104 weeks

Post Exposure Observation Period: none

Doses: 0, 75, 250, 750 ppm (0, 325, 1084, 3251 mg/m³)

GLP: YES
NO
NO DATA

Test Results: In males exposed to 750 ppm, there was an increased incidence of renal tubule adenomas (40% vs. 6% in control group) and combined renal tubule adenoma/carcinomas (42% vs. 6% in control group) based on combined original kidney sections and additional step-sectioning of the kidneys. The incidence of renal tubule carcinomas (6% vs. 0% in controls) was not significantly elevated. Based on combined single and step section evaluation, the incidence of renal tubule adenomas was 6%, 10%, 14%, and 40% in males exposed to 0, 75, 250 and 750 ppm, respectively. In females, no renal tubule carcinomas were found. However, at 750 ppm, there was an increased incidence of renal tubule adenomas (16% vs. 0% in controls). In males exposed to 750 ppm, there was a slight, but significant, increase in the incidence of testicular interstitial cell adenoma (88% vs. 72% in controls; historical control range 54 to 83%). Although this neoplasm occurs in high frequency in F344 male rats, the authors concluded that exposure to ethylbenzene appeared to enhance the formation of this tumor.

The kidney slides from this study, as well as the NTP 13-week study (see 5.4B above) were re-examined. Kidney slides were evaluated for hyaline droplet accumulation, sustained cytotoxicity/cell regeneration, interaction with chronic progressive nephropathy (CPN), and tumors. Ethylbenzene caused an exacerbation of age-related spontaneous renal disease, CPN, in the 750 ppm animals, markedly so in the male rats, and modestly so in the females. In addition, there was a high incidence of high-dose rats that had end-stage CPN, a terminal condition where the kidneys are so morphologically altered that renal failure (as well as secondary hyperthyroidism) occurs. Although there some evidence of a dose-related increase in hyaline droplet formation in the 13-week NTP study, it was not considered to be of the magnitude indicative of an α 2u-globulin associated mechanism of renal carcinogenesis. Other pathological effects associated with α 2u-globulin were absent in the male rat kidneys from the 2-yr NTP study. The author concluded that the re-evaluation of this study provided persuasive evidence that the apparent increase in renal tumors was strongly associated with CPN, a spontaneous age-related disease of rodents with no identical counterpart in humans.

Reference: NTP. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ethylbenzene (CAS No. 100-41-4) in F344 Rats and B6C3F1 Mice (Inhalation Studies). NTP TR 466. NIH Publication 96-3956. US Department of Health and Human Services. Research Triangle Park, NC (1999)

Hard, GC, Expert Report on Renal Histopathologic Changes in Rat Inhalation Studies with Ethyl Benzene. Report prepared for the American Chemistry Council Ethylbenzene Panel (2000).

5.7 C Test Species: B6C3F1 mouse male and female

Test Substance: Ethylbenzene (purity: > 99%)

Test Method: National Toxicology Program carcinogenicity test

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day 5 days/week

Duration of Exposure: 104 weeks

Post Exposure Observation Period: none

Doses: 0, 75, 250, 750 ppm (0, 325, 1084, 3251mg/m³)

GLP: YES
NO
NO DATA

Test Results: In male mice exposed to 750 ppm, there was an increased incidence of alveolar/bronchiolar adenomas (32% vs 10% in controls; historical control range 6 to 36%) and of combined alveolar/bronchiolar adenoma/carcinomas (38% vs. 14% in controls; historical control range 10 to 42%). Incidences of lung tumors at 75 and 250 ppm were not significantly different from the control incidence and were within the historical control range. In females, there was no significant increase in the incidence of lung tumors. There was a significantly increased incidence of hepatocellular adenomas in females exposed to 750 ppm (32% vs. 12% in controls; historical control range 0 to 40%) and combined hepatocellular adenoma/carcinomas (50% vs. 26% for controls; historical control range 3 to 54%). The incidence of tumors in females exposed to 75 and 250 ppm were not significantly different from the control incidences. In males there was no increase in liver tumors at any exposure concentration.

Reference: NTP. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ethylbenzene (CAS No. 100-41-4) in F344 Rats and B6C3F1 Mice (Inhalation Studies). NTP TR 466. NIH Publication 96-3956. US Department of Health and Human Services. Research Triangle Park, NC (1999)

5.7 D Test Species: Sprague-Dawley rat male and female

Test Substance: Ethylbenzene

Test Method: Other. Study of very limited use due to incomplete reporting of methods and results.

Route of Exposure: gavage

Frequency of Exposure: 4-5 doses/week

Duration of Exposure: 104 weeks

Post Exposure Observation Period: observed until spontaneous death, up to 141 weeks

Doses: 500 and 800 mg/kg

GLP: YES []
NO []
NO DATA [x]

Test Results: Increased total malignant tumors were reported at 500 and 800 mg/kg without a dose-response, and increased head cancers at 800 mg/kg in male and female rats.

Reference: Maltoni, C, Conti, B, Cotti, G, Belpoggi, F, Experimental studies on benzene carcinogenicity at the Bologna Institute of Oncology: current results and ongoing research. *Am. J. Ind. Med.* 7: 415-446 (1985)

Maltoni, C, Ciliberti, A, Pinto, C, Soffritti, M, Bellpoggi, F, Meranini, L. Results of long-term experimental carcinogenicity studies of the effects of gasoline, correlated fuels, and major gasoline aromatics in rats. *Ann. NY Acad. Sci* 837:15-52 (1997).

5.8 Toxicity to Reproduction

5.8 A Test type: reproductive parameters evaluated in a modified developmental/teratology study with a 3 week pre-exposure period.

Test Species: Wistar rat male/female

Test Substance: Ethylbenzene

Test Method: Other

Route of Exposure: inhalation

Frequency of Exposure: 7 hours/day, 5 days/week, then 7 hours/day through gestation

Duration of Exposure: 3 weeks before breeding and days 1-19 of gestation

Post Exposure Observation Period: none

Doses: 0, 100, or 1000 ppm (0, 434, 4335 mg/m³)

GLP: YES []
NO []

NO DATA [x]

Test Results: In the dams exposed to 1000 ppm throughout the experiment, there were increases in liver, kidney and spleen weights compared to the air only group or the ethylbenzene pre-mating-air only post-mating group. A higher percentage of ethylbenzene exposed females mated (were sperm positive) than the controls (67, 78 and 74% for 0, 100 and 1000 ppm, respectively) and a slightly smaller percentage of ethylbenzene-exposed females that mated were pregnant at gestation day 21 (89, 77 and 77%, for 0, 100 and 1000 ppm, respectively). When expressed on the basis of total females per group, 56, 60, and 57% of the females exposed to 0, 100, or 1000 ppm were pregnant at gestation day 21. Thus exposure of female rats to ethylbenzene at 100 or 1000 ppm for three weeks did not decrease fertility.

Reference: Hardin, B. D., Bond, G. P., Sikov, M. R., Andrew, F. D., Beliles, R. P., and Niemeier, R. W. (1981) Testing of selected workplace chemicals for teratogenic potential. *Scand. J Work Environ. Health* 7 (Suppl. 4): 66-75.

Andrew, F. D., Buschbom, R. L., Cannon, W. C., Miller, R. A., Montgomery, L. F., Phelp, D. W., Sikov, M. R. (1981) Teratologic Assessment of Ethylbenzene and 2-Ethoxyethanol. Battelle Pacific Northwest Laboratories, Richland, WA. Prepared for the National Institute for Occupational Safety and Health. NIOSH Contract #210-79-0037.

5.8 B Test type: reproductive parameters evaluated in 13-week study

Test Species: Fischer 344 rat male/female

Test Substance: Ethylbenzene (purity: > 99%)

Test Method: Meets the requirements of the OECD Guideline 413: Subchronic Inhalation Toxicity: 90-Day Study except for the following: food consumption was not measured, ophthalmic examinations were not conducted, and adrenals were not weighed.. Vaginal cytology was evaluated daily for the 12 days prior to sacrifice. Sperm motility, sperm count, spermatid count, testis weights, and epididymal weight were evaluated at termination of the study. Ovaries, uterus, seminal vesicles, prostate, testis, and epididymis were evaluated for microscopic pathology at the termination of the study.

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day, 5 days/week

Duration of Exposure: 13 weeks

Post Exposure Observation Period: none

Doses: 0, 100, 250, 500, 750, 1000 ppm (0, 434, 1084, 2168, 3251, 4335 mg/m³)

GLP: YES [x]

NO []

NO DATA []

Test Results: There was no treatment-related effects on sperm, testicular morphology, length of estrous cycle, spermatid counts, sperm motility, caudal or epididymal weights, or reproductive organs examined histopathologically. The parental NOAEL is 1000 ppm (4335mg/m³).

Reference: NTP. Toxicity studies of ethylbenzene (CAS. No. 100-41-4) in F344/N rats and B6C3F1 mice (inhalation studies). NTP Tox 10. NIH Publication No. 92-3129. PB93-149722. National Toxicology Program, U.S. Dept. of Health and Human Services. Research Triangle Park, NC (1992)

5.8 C Test type: reproductive parameters evaluated in 4-week study

Test Species: Fischer 344 rat male/female

Test Substance: Ethylbenzene (purity: 99.7%)

Test Method: Other

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day, 5 days/week

Duration of Exposure: 4 weeks

Post Exposure Observation Period: none

Doses: 0, 99, 382, 782 ppm (0, 429, 1656, 3390 mg/m³)

GLP: YES
NO
NO DATA

Test Results: No adverse histopathological effects in the ovaries, uterus, testes, or epididymides at 782 ppm. The parental NOAEL is 782 ppm (3390mg/m³).

Reference: Cragg, ST, Clarke, EA, Daly, IW, Miller, RR, Terrill, JB, and Ouellette, RE, Subchronic inhalation toxicity of ethylbenzene in mice, rats and rabbits. Fund. Appl. Tox. 13:399- 408 (1989)

5.8 D Test type: reproductive parameters evaluated in 13-week study

Test Species: B6C3F1 mouse male/female

Test Substance: Ethylbenzene (purity: > 99%)

Test Method: Meets the requirements of the OECD Guideline 413: Subchronic Inhalation Toxicity: 90-Day Study except for the following: food consumption was not measured, ophthalmic examinations were not conducted, and adrenals were not weighed.. Vaginal cytology was evaluated daily for the 12 days prior to sacrifice. Sperm motility, sperm count, spermatid count, testis weights, and epididymal weight were evaluated at termination of the

study. Ovaries, uterus, seminal vesicles, prostate, testis, and epididymis were evaluated for microscopic pathology at the termination of the study.

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day, 5 days/week

Duration of Exposure: 13 weeks

Post Exposure Observation Period: none

Doses: 0, 100, 250, 500, 750, 1000 ppm (0, 434, 1084, 2168, 3251, 4335mg/m³)

GLP: YES
NO
NO DATA

Test Results: There was no treatment-related effects on sperm, testicular morphology, length of estrous cycle, spermatid counts, sperm motility, caudal or epididymal weights, or reproductive organs examined histopathologically. The parental NOAEL is 1000 ppm (4335mg/m³).

Reference: NTP. Toxicity studies of ethylbenzene (CAS. No. 100-41-4) in F344/N rats and B6C3F1 mice (inhalation studies). NTP Tox 10. NIH Publication No.92-3129. PB93-149722. National Toxicology Program, U.S. Dept. of Health and Human Services. Research Triangle Park, NC (1992)

5.8 E Test type: reproductive parameters evaluated in a 4-week study

Test Species: B6C3F1 mouse male/female

Test Substance: Ethylbenzene (purity: 99.7%)

Test Method: Other

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day, 5 days/week

Duration of Exposure: 4 weeks

Post Exposure Observation Period: none

Doses: 0, 99, 382, 782 ppm (0, 429, 1656, 3390 mg/m³)

GLP: YES
NO
NO DATA

Test Results: No adverse histopathological effects in the ovaries, uterus, testes, or epididymides at 782 ppm. The parental NOAEL is 782 ppm (3990mg/m³).

Reference: Cragg, ST, Clarke, EA, Daly, IW, Miller, RR, Terrill, JB, and Ouellette, RE, Subchronic inhalation toxicity of ethylbenzene in mice, rats and rabbits. Fund. Appl. Tox. 13:399-408 (1989)

5.8 F Test type: reproductive parameters evaluated in a 4-week study

Test Species: New Zealand white rabbit male/female

Test Substance: Ethylbenzene (purity: 99.7%)

Test Method: Other

Route of Exposure: inhalation

Frequency of Exposure: 6 hours/day, 5 days/week

Duration of Exposure: 4 weeks

Post Exposure Observation Period: none

Doses: 0, 99, 382, 782 ppm (0, 429, 1656, 3390 mg/m³)

GLP: YES
NO
NO DATA

Test Results: No adverse histopathological effects in the ovaries, uterus, testes, or epididymides at 782 ppm. The parental NOAEL is 782 ppm (3390mg/m³).

Reference: Cragg, ST, Clarke, EA, Daly, IW, Miller, RR, Terrill, JB, and Ouellette, RE, Subchronic inhalation toxicity of ethylbenzene in mice, rats and rabbits. Fund. Appl. Tox. 13:399-408 (1989)

5.9 Developmental Toxicity/Teratogenicity

5.9 A Test Species: Wistar rat female

Test Substance: Ethylbenzene

Test Method: Other; This study meets the requirements for OECD Guideline No. 414. 29-33 rats per group. Parameters evaluated included body weight and body weight gain, food consumption, clinical observations, maternal gross pathology, organ weights (liver, kidney, spleen), histopathology (liver, kidney, lungs with trachea, ovaries, uterus), fetal body weight, fetal external, visceral, and skeletal examinations, fertility and reproductive status.

Route of Exposure: inhalation

Frequency of Exposure: 7 hours/day, 5 days per week, then 7 hours/day during gestation

Exposure Period: 3 weeks before breeding and days 1-19 of gestation

Duration of Test: euthanized on day 21 of gestation

Doses: 0, 100, 1000 ppm (0, 434, 4335mg/m³)

Exposure during 3 weeks before breeding Exposure during gestation days 1-19

Control	0 ppm	0 ppm
Group A	0 ppm	100 ppm
Group B	0 ppm	1000 ppm
Group C	100 ppm	0 ppm
Group D	100 ppm	100 ppm
Group E	1000 ppm	0 ppm
Group F	1000 ppm	1000 ppm

GLP: YES []

NO []

NO DATA [x]

Test Results: NOAEL Maternal Toxicity = 100 ppm

NOAEL Developmental Toxicity = 100 ppm

Maternal Toxicity: increased organ weights: liver(~ 22%), kidney (~ 10%), and spleen(~ 10%). There was no accompanying histopathological changes.

Developmental Toxicity: No effects on embryo- or fetal-toxicity or malformations were seen. However, there was a significant increase in the number of litters with pups with supernumerary ribs (14% increase in incidence) at 1000 ppm.. Thus skeletal variation, but not malformations, were seen at a maternally toxic dose.

Reference: Hardin, BD, Bond, GP, Sikov, MR, Andrew, FD, Beliles, RP, and Niemeier, RW, Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health 7 (Suppl 4): 66-75 (1981)

Andrew, FD, Buschbom, RL, Cannon, WC, Miller, RA, Montgomery, LF, Phelp, DW, and Sikov, MR, Teratologic assessment of ethylbenzene and 2-ethoxyethanol. Battelle Pacific Northwest Laboratories for the National Institute for Occupational Safety and Health, Cincinnati, OH. PB83-208074 (1981), 108p.

5.9 B Test Species: CFY rat female

Test Substance: Ethylbenzene

Test Method: Other

Route of Exposure: inhalation

Frequency of Exposure: (a) 6 hours/day at 600 mg/m³
(b) 24 hours/day at 600, 1200, 2400 mg/m³

Exposure Period: days 7-15 of gestation

Duration of Test: euthanized on day 21 of gestation

Doses: 600, 1200, 2400 mg/m³ = ~138, ~277, ~554 ppm

GLP: YES []
NO [x]
NO DATA []

Test Results: NOEL Maternal Toxicity = ? mg/m³
NOEL Teratogenicity = 2400 mg/m³ (based on 6 hr/day group)

Maternal Toxicity: It was described as “moderate” and dose-dependent without further characterization.

Developmental Toxicity: In all exposure concentrations in the 24-hr group, increased percentage of dead or resorbed fetuses and fetuses with retarded skeletal development was reported. It was also reported at in the high-dose group only, increased percentage of fetuses with weight retardation and all malformations (anomalies of the “uropoetic apparatus” and undefined skeletal malformations). No effects were reported from exposure to 600 mg/m³ ethylbenzene for 6 hr/day during days 6-15 of gestation.

Reference: Ungvary, G and Tatrai, E, On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats and rabbits. Arch. Toxicol. (Suppl.) 8: 425-430 (1985).

5.9 C Test Species: New Zealand white rabbit female

Test Substance: Ethylbenzene

Test Method: This study meets the requirements of OECD Guideline 414 for Teratogenicity, except for 2 exposure levels are tested rather than 3, and 22-24 rabbits per group. Parameters evaluated included body weight, body weight gain, food consumption, clinical observations, maternal gross pathology, organ weights (liver, kidney, spleen), histopathology (liver, kidney, lungs with trachea, uterus, ovaries), fetal body weight, fetal external, visceral and skeletal examinations, fertility and reproductive status.

Route of Exposure: inhalation

Frequency of Exposure: 7 hours/day during gestation

Exposure Period: days 1-24 of gestation

Duration of Test: sacrificed on day 30 of gestation

Doses: 0, 100, 1000 ppm (0, 434, 4335 mg/m³)

GLP: YES []
NO []
NO DATA [x]

Test Results: NOAEL Maternal Toxicity = 1000 ppm (4335 mg/m³)
NOAEL Developmental Toxicity = 1000 ppm (4335 mg/m³)

Maternal Toxicity: Increased liver weights at 1000 ppm without accompanying histopathological changes.

Developmental Toxicity: At both exposure levels, there were fewer live fetuses per litter than in the controls; however, this does not appear to be evidence of embryo- or fetal-toxicity because there was no increased dead or resorbed fetuses per litter.

Reference: Hardin, BD, Bond, GP, Sikov, MR, Andrew, FD, Beliles, RP, and Niemeier, RW, Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health 7 (Suppl 4): 66-75 (1981)

Andrew, FD, Buschbom, RL, Cannon, WC, Miller, RA, Montgomery, LF, Phelps, DW, and Sikov, MR, Teratologic assessment of ethylbenzene and 2-ethoxyethanol. Battelle Pacific Northwest Laboratories for the National Institute for Occupational Safety and Health, Cincinnati, OH. PB83-208074 (1981)

5.9 D Test Species: CFLP mouse female

Test Substance: Ethylbenzene

Test Method: Other

Route of Exposure: inhalation

Frequency of Exposure: 3 or 4 hours/day

Exposure Period: days 6-15 of gestation

Duration of Test: euthanized on day 18 of gestation

Doses: 0, 500 mg/m³ (0, 115 ppm)

GLP: YES []
NO [x]
NO DATA []

Test Results: NOEL Maternal Toxicity = Insufficient study data preclude determination
NOEL Teratogenicity = Insufficient study data preclude determination

Maternal Toxicity: Maternal toxicity was not described.

Developmental Toxicity: There were no effects on resorption, fetal weight or skeletal retardation; however, they reported an increase in percent (10% vs. 4% in controls) of pups any malformation, specifically anomalies of the "uropoetic apparatus." The description of the data is insufficient to determine the NOEL.

Reference: Ungvary, G and Tatrai, E, On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats and rabbits. Arch. Toxicol. (Suppl.) 8: 425-430 (1985.)

5.9 E Test Species: New Zealand white rabbit female

Test Substance: Ethylbenzene

Test Method: Other

Route of Exposure: inhalation

Frequency of Exposure: 24 hours/day

Exposure Period: days 7-20 of gestation

Duration of Test: sacrificed on day 30 of gestation

Doses: 0, 500, 1000 mg/m³ (0, 115, 231 ppm)

GLP: YES []
NO []
NO DATA [x]

Test Results: NOEL Maternal Toxicity = 500 mg/m³ (115 ppm)
NOEL Teratogenicity = 500 mg/m³ (115 ppm)

Maternal Toxicity: Decreased weight gain in females exposed to 1000 mg/m³, and 3 of 8 exposed does lost their fetuses through abortion.

Developmental Toxicity: Mean fetal body weight was lower in the high-dose group compared to controls. No other developmental effects were reported.

Reference: Ungvary, G and Tatrai, E, On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats and rabbits. Arch. Toxicol. (Suppl.) 8: 425-430 (1985.)

5.10 Other Relevant Information

5.10 A Estimated Exposure for the General Population

Comment: The daily ethylbenzene exposure for the general population was estimated to be approximately 130 ug/person or approximately 1.8 ug/kg/day, corresponding to an annual intake of approximately 46 mg/person. The majority (up to 99%) of ethylbenzene exposure was due to inhalation.

Reference: Tang, W, Hemm, I, Eisenbrand, G. Estimation of human exposure to styrene and ethylbenzene. Toxicology 144:39-50. (2000)

5.10 B Absorption by Dermal Exposure

Comment: Dermal absorption of ethylbenzene vapors in humans appears to be minimal (Gromiec and Piotrowski, 1984). Liquid ethylbenzene is readily absorbed through the skin if volatilization is impeded. Absorption rates of 22 to 33 mg/cm²/hr for ethylbenzene in solution have been reported (Dutkiewicz and Tyras, 1967), although evaporative losses may have been a source of error. In hairless mice exposed using a device to capture ethylbenzene lost by evaporation, the absorption rate was 2.22 mg/cm²/hr (Susten et al., 1990).

Reference: Gromiec, JP and Piotrowski, JK, Urinary mandelic acid as an exposure test for ethylbenzene. *Int. Arch. Occup. Environ. Health* 55: 61-72 (1984)

Reference: Dutkiewicz, T and Tyras, H, A study of the skin absorption of ethylbenzene in man. *Br. J. Ind. Med.* 24: 330-332 (1967)

Reference: Susten, AS, Niemeier, RW and Simon, SD, In vivo percutaneous absorption studies of volatile organic solvents in hairless mice. II. Toluene, ethylbenzene and aniline. *J. Appl. Tox.* 10: 217-225 (1990)

5.10 C Absorption by Inhalation and Oral Exposure

Comment: In studies of human volunteers, 49 to 64% of the inhaled ethylbenzene was absorbed by the respiratory tract. (Bardodej and Bardodejova, 1970; Gromiec and Piotrowski, 1984). When volunteers were exposed for two hours to 435 or 870 mg/m³ of "industrial xylene" (containing 40% ethylbenzene and 60% xylenes), about 65% was taken up by the lungs. If the workload was increased during exposure, the retention dropped to 50% (Åstrand et al, 1978). In rats, about 44 % of the inhaled ethylbenzene was retained (Chin et al., 1980).

At 24 hours, about 80% of the administered radioactivity was recovered in the urine of female rats following oral administration of 30 mg/kg [¹⁴C]ethylbenzene.

Reference: Gromiec, JP and Piotrowski, JK, Urinary mandelic acid as an exposure test for ethylbenzene. *Int. Arch. Occup. Environ. Health* 55: 61-72 (1984)

Reference: Bardodej, Z and Bardodejova, E, Biotransformation of ethylbenzene, styrene and alpha-methylstyrene in man. *Am. Ind. Hyg. Assoc. J.* 32: 1-5 (1970)

Reference: Åstrand, I., Engström, J. and Övrum, P. (1978) Exposure to xylene and ethylbenzene. I. Uptake, distribution and elimination in man. *Scand. J. Work Environ. Health* 4: 185-194.

Reference: Chin, BH, McKelvey, JA, Tyler, TR, Calisti, LJ, Kozbelt, SJ, and Sullivan, LJ Absorption, distribution, and excretion of ethylbenzene, ethylcyclohexane and methylbenzene isomers in rats. *Bull. Environ. Contam. Toxicol.* 24: 477-483 (1980)

Reference: Climie, IJG., Hutson, DH, and Stoydin, G. (1983) The metabolism of ethylbenzene hydroperoxide in the rat. *Xenobiotica* 13: 611-618.

5.10 D Distribution

Comment: Absorbed ethylbenzene is rapidly distributed in the body. Rats exposed by inhalation to 1000 mg/m³ (230 ppm) ¹⁴C-ring-labeled ethylbenzene for 6 hours and held in closed metabolism cages for 72 hours, showed very low levels of ethylbenzene in representative tissues. Total tissue radioactivity was less than 0.2% of the inhaled dose. Liver contained 0.014% of the absorbed dose, while fat contained 0.007%. Lung had 0.006% and the gastrointestinal tract had 0.008%. All other tissues contained less than 0.003% (Chin et al., 1980). The percentages of absorbed dose following dermal application were 15.5% in carcass, 4.5% in skin at application site, 14.3% in expired breath, and 65.5% in excreta (Susten et al, 1990). In humans exposed to a mixture of “industrial xylenes” (40% ethylbenzene and 60% xylenes), the amount of ethylbenzene taken up by the body was correlated with the amount of the body fat. Ethylbenzene appeared at levels ranging from 4 to 9 ng/kg of adipose tissue (Engström and Bjurström, 1978).

Reference: Chin, BH, McKelvey, JA, Tyler, TR, Calisti, LJ, Kozbelt, SJ, and Sullivan, LJ Absorption, distribution, and excretion of ethylbenzene, ethylcyclohexane and methylbenzene isomers in rats. *Bull. Environ. Contam. Toxicol.* 24: 477-483 (1980)

Reference: Susten, AS, Niemeier, RW and Simon, SD, In vivo percutaneous absorption studies of volatile organic solvents in hairless mice. II. Toluene, ethylbenzene and aniline. *J. Appl. Tox.* 10: 217-225 (1990)

Reference: Engström, J and Bjurström, R, Exposure to xylene and ethylbenzene. II. Concentration in subcutaneous adipose tissue. *Scan. J. Work Environ. Health* 4: 195-203 (1978)

5.10 E Excretion

Comment: The principal route of excretion from both oral and inhalation exposure is through urine. In rats, about 83% of the radioactivity of ethylbenzene inhaled during six hours of exposure at 1000 mg/m³ (~230 ppm) was excreted in the urine during the next 72 hours. About 8% was exhaled, 0.7% was excreted in the feces, 0.03% in exhaled CO₂, 8.2% in expired gases, 0.2% remained in the tissues, and 8.3% could not be accounted for (Chin et al., 1980). In human volunteers, about 4% of the inhaled ethylbenzene was exhaled unchanged during the next 19 hours (Åstrand et al., 1978). Elimination from fat was slow; there was little change in the fat concentration of ethylbenzene between the 4-hours post-exposure period and the 22-hour post-exposure period (Engström and Bjurström, 1978).

Reference: Chin, BH, McKelvey, JA, Tyler, TR, Calisti, LJ, Kozbelt, SJ, and Sullivan, LJ Absorption, distribution, and excretion of ethylbenzene, ethylcyclohexane and methylbenzene isomers in rats. *Bull. Environ. Contam. Toxicol.* 24: 477-483 (1980)

Reference: Åstrand, I., Engström, J. and Övrum, P. (1978) Exposure to xylene and ethylbenzene. I. Uptake, distribution and elimination in man. *Scand. J. Work Environ. Health* 4: 185-194.

Reference: Engström, J and Bjurström, R, Exposure to xylene and ethylbenzene. II. Concentration in subcutaneous adipose tissue. *Scan. J. Work Environ. Health* 4: 195-203 (1978)

5.10 F Metabolism

Comment: Two very different metabolic pathways for ethylbenzene have been cited in the literature through the alpha- or omega-oxidation of the side chain by cytochrome P-450 isozymes to 1- and 2-phenylethanol, respectively. The initial step of omega-oxidation of ethylbenzene to 2-phenylethanol leads to phenylacetic acid, which is conjugated with glycine to phenacetic acid (Kiese and Lenk, 1974).

Reference: Kiese, M, and Lenk, W, Hydroxyacetophenones: urinary metabolites of ethylbenzene and acetophenone in the rabbit. *Xenobiotica* 4: 337-343 (1974).

5.10 G Metabolism

Comment: The major pathway, however, is the alpha-oxidation of ethylbenzene to 1-phenylethanol, which has been shown to be under stereochemical control. 1-Phenylethanol excreted in the urine of rats dosed with ethylbenzene produced about 90% R(+)- and 10% S(-) 1-phenylethanol (McMahon and Sullivan, 1966). Phenobarbital pretreatment substantially diminished the stereospecificity of the microsomal hydroxylation of ethylbenzene (McMahon and Sullivan, 1966). The subsequent intermediates are acetophenone, ω -hydroxyacetophenone, phenylglyoxal, phenylglyoxylic acid, and finally hippuric acid (ref).

Reference: McMahon, RE, and Sullivan, HR, Microsomal hydroxylation of ethylbenzene Stereospecificity and the effect of phenobarbital induction. *Life Sci.* 5: 921-926 (1966)

5.10 H Metabolism

Comment: The pattern of the urinary metabolite excretion seems to vary with different mammalian species. In humans, ethylbenzene is mainly excreted in the urine as mandelic acid and phenylglyoxylic acids (Bardodej and Bardodejova, 1970; Åstrand et al., 1978; Engström et al., 1984; Gromiec and Piotrowski, 1984). The elimination of mandelic acid has been found to be biphasic, with half-lives of 3.1 and 24.5 hours (Gromiec and Piotrowski, 1984). In rats and rabbits, hippuric acid and phenacetic acid are the main metabolites of ethylbenzene (Kiese and Lenk, 1974; Engström, 1984). Phenacetic acid is formed from the glycine conjugation of phenylacetic acid, the ω -oxidation product of hippuric acid.

Reference: Bardodej, Z and Bardodejova, E, Biotransformation of ethylbenzene, styrene and alpha-methylstyrene in man. *Am. Ind. Hyg. Assoc. J.* 32: 1-5 (1970)

Reference: Åstrand, I, Engström, J, and Övrum, P, Exposure to xylene and ethylbenzene. I. Uptake, distribution and elimination in man. *Scand. J. Work Environ. Health* 4: 185-194 (1978).

Reference: Gromiec, JP and Piotrowski, JK, Urinary mandelic acid as an exposure test for ethylbenzene. *Int. Arch. Occup. Environ. Health* 55: 61-72 (1984)

Reference: Engström, K, Riihimäki, V, and Laine, A, Urinary disposition of ethylbenzene and m-xylene in man following separate and combined exposure. *Int. Arch. Occup. Environ. Health* 54: 355-364 (1984)

Reference: Kiese, M, and Lenk, W, Hydroxyacetophenones: urinary metabolites of ethylbenzene and acetophenone in the rabbit. *Xenobiotica* 4: 337-343 (1974).

Reference: Engström, KM, Metabolism of inhaled ethylbenzene in rats. *Scand. J. Work Environ. Health* 10: 83-87 (1984).

5.10 I Metabolism

Comment: Direct ring oxidation of ethylbenzene occurs to a limited extent. In humans, the combined share of 4-ethylphenol, m- and p-hydroxyacetophenones accounted for approximately 4% of the total amount of metabolites excreted (Engström et al., 1984). In rats the share of these compounds was even less (Engström, 1984). Angerer and Lehnert (1979) reported that between 1.0 and 1.4% of ethylbenzene (exposure at 34-41 ppm) was metabolized in humans to 2-ethylethanol. In vitro experiments have demonstrated that both 2- and 4-ethylphenol can readily be formed from ethylbenzene, if the reaction is fortified with rat liver microsomes (Kaubisch et al., 1972).

Reference: Engström, K, Riihimäki, V, and Laine, A, Urinary disposition of ethylbenzene and m-xylene in man following separate and combined exposure. *Int. Arch. Occup. Environ. Health* 54: 355-364 (1984)

Reference: Engström, KM, Metabolism of inhaled ethylbenzene in rats. *Scand. J. Work Environ. Health* 10: 83-87 (1984).

Reference: Angerer, J, and Lehnert, G, Occupational chronic exposure to organic solvents: VIII. Phenolic compounds: Metabolites of alkylbenzenes in man: Simultaneous exposure to ethylbenzene and xylenes. *Int. Arch. Occup. Environ. Health* 43: 145-150 (1979).

Reference: Kaubisch, D, Daly, J, and Jerina, D, Arene oxides as intermediates in the oxidative metabolism of aromatic compounds. Isomerization of methyl-substituted arene oxides. *Biochemistry* 11: 3080-3088 (1972).

5.10 J Metabolism

Comment: In vivo conversion of ethylbenzene to mandelic acid is stereoselective, and the R-enantiomer is mainly excreted in the urine (Sullivan et al, 1976; Drummond et al., 1989). Rats only excrete the R-enantiomer of mandelic acid in the urine when dosed with ethylbenzene (McMahon and Sullivan, 1968; Drummond et al., 1989). When two human volunteers were exposed by inhalation to 430 mg/m³ (100 ppm) ethylbenzene for four hours, only the mandelic acid was excreted as the R-enantiomer (Drummond et al, 1989). In urine taken from workers at the end of a workshift in a plant that made aromatic solvents containing ethylbenzene (ethylbenzene exposures were 1.5 to 33 ppm; the workers were not exposed to styrene), the ratio of R- to S-mandelic acid was 19:1 and was independent of airborne ethylbenzene concentration (Korn et al., 1992).

Reference: Sullivan, HR, Miller, WM, and McMahon, RE, Reaction pathways of in vivo stereoselective conversion of ethylbenzene to (-)-mandelic acid. *Xenobiotica* 6: 49-54 (1976).

Reference: McMahon, RE, and Sullivan, HR, The nature of the in vivo conversion of L(-) methylphenylcarbinol to D(-) mandelic acid in the rat. *Pharmacologist* 10: 203-208 (1968).

Reference: Drummond, L, Caldwell, J, and Wilson, HK, The metabolism of ethylbenzene and styrene to mandelic acid: stereochemical considerations. *Xenobiotica* 19: 199-207 (1989).

Reference: Korn, M., Gforerer, W., Herz, R., Wodarz, I., and Wodarz, R. (1992) Stereometabolism of ethylbenzene in man: Gas chromatographic determination of urinary excreted mandelic acid enantiomers and phenylglyoxylic acid and their relation to the height of occupational exposure. *Int. Arch. Occup. Environ. Health* 64: 75-78.

5.10 K Metabolism

Comment: In rats exposed up to 600 ppm ethylbenzene, 6 hrs/day, 5 days/week for up to 16 weeks, a significant dose-related decrease of phenylglyoxylic acid and hippuric acid plus benzoic acid was found in the urine. A corresponding increase of 1-phenylethanol and ω -hydroxyacetophenone excretion was noted. The total amount of metabolites in the urine, collected during 24 hours after onset of exposure remained constant at each exposure level throughout the study (Engström et al., 1985).

Reference: Engström, K, Elovaara, E, and Aito, A, Metabolism of ethylbenzene in the rat during long-term intermittent inhalation exposure. *Xenobiotica* 15: 281-286 (1985).

5.10 L Metabolism

Comment: The metabolic interaction of m-xylene and ethylbenzene was studied in rats were exposed for five days. m-Xylene metabolites were excreted faster than ethylbenzene metabolites in a manner pronounced with repetitive exposure and increased with dose. The metabolite pattern showed no difference between mixed and pure equimolar exposures, whereas the pattern of ethylbenzene metabolites was variable. 1-Phenylethanol was the major metabolite after pure ethylbenzene exposure, whereas after mixed exposure, it was hippuric acid. This change was considered due to changes in the excretion of hippuric acid and phenaceturic acid (both are also produced endogenously), and not due to alterations in the excretion of 1-phenylethanol, mandelic acid, or phenylglyoxylic acid (Elovaara et al, 1984).

Reference: Elovaara, E, Engström, K, and Vainio, H, (1984) Metabolism and disposition of simultaneously inhaled m-xylene and ethylbenzene in the rat. *Toxicol. Appl. Pharmacol.* 75: 466-478.

5.10 M Metabolism

Comment: Cytochrome P-450 induction by ethylbenzene and other alkylbenzenes result in changes in the metabolism of other chemicals. Intraperitoneal injection of 1060 mg/kg ethylbenzene for 3 days to male Holtzman rats increased the overall metabolism of toluene and shifted the oxidation from almost exclusively on the side chain to more ring hydroxylation (Sequeira et al., 1992).

Reference: Sequeira, DJ, Eyer, CS, Cawley, GF., Nick, TG, and Backes, WL, Ethylbenzene mediated induction of cytochrome P450 isozymes in male and female rats. *Biochem. Pharmacol.* 44: 1171-1182 (1992).

5.10 N Metabolism

Comment: Exposure of rats to very high doses of ethylbenzene either induce or inhibits a number of cytochrome P450 isozymes over different time courses. (Backes. et al., 1990; Bergeron et al., 1999; Gut, et al., 1993; Koop and Laetham, 1992; Sequeira et al., 1992, 1994; Yuan et al., 1995, 1997).

Reference: Backes, WL, Sequeira, DJ., Cawley, GF, and Eyer, CS, Relationship between hydrocarbon structure and induction of P450: Effects on protein levels and enzyme activities. *Xenobiotica* 23: 1353-1366 (1993).

Reference: Bergeron, RM, Desai, K, Serron, SC, Cawley, GF, Eyer, CS, Backes, WL, Changes in the expression of cytochrome P450s 2B1, 2B2, 2E1, and 2C11 in response to daily aromatic hydrocarbon treatment. *Toxicol. Appl. Pharmacol.* 157: 1-8 (1999).

Reference: Gut, I, Terelius, Y, Frantik, E, Linhart, I, Soucek, P, Filipcova, B, and Kluckova, H, Exposure to various benzene derivatives differently induces cytochromes P450 2B1 and P450 2E1 in rat liver. *Arch. Toxicol.* 67: 237-243 (1993).

Reference: Koop, DR, and Laetham, CL, Inhibition of rabbit microsomal cytochrome P-450 2E1-dependent p-nitrophenol hydroxylation by substituted benzene derivatives. *Drug Metab. Dispos.* 20: 775-777 (1992).

Reference: Sequeira, DJ, Eyer, CS, Cawley, GF., Nick, TG, and Backes, WL, Ethylbenzene-mediated induction of cytochrome P450 isozymes in male and female rats. *Biochem. Pharmacol.* 44: 1171-1182 (1992).

Reference: Sequeira, DJ, Cawley, GF, Eyer, CS, and Backes, WL, Temporal changes in P-450 2E1 expression with continued ethylbenzene exposure. *Biochim. Biophys. Acta* 1207: 179-186 (1994).

Reference: Yuan, W, White, TB, White, JW, Strobel, HW, and Backes, WL, Relationship between hydrocarbon structure and induction of P450: Effect on RNA levels. *Xenobiotica* 25: 9-16 (1995).

Reference: Yuan, W, Sequeira, DJ, Cawley, GF, Eyer, CS, and Backes, WL, Time course for the modulation of hepatic cytochrome P450 after administration of ethylbenzene and its correlation with toluene metabolism. *Arch. Biochem. Biophys.* 339: 55-63 (1997).

6.1 International Transport Classification

UN Number
Class
Packaging Group
Hazard identity no.
Proper shipping name
CEFIC-Tremcard No.
ADR and RID class
Symbol
Proper shipping name

IATA/ICAO (air)
Class
Packing Group
Symbol
Proper Shipping name

IMO/IMDG (sea)
Class
Page
EMS-No
MFAG-no
Packing Group
Symbol

EEC labeling
Classification
Class - F - flammable
R-Phrases - 10, 11-20
S-Phrases - 16024/25-29

6.2 Occupational Exposure Limit Values

Type of Limit: 8 hr TWA PEL (Permissible Exposure Limit)

Value: 100 ppm

Type of Limit: STEL (Short Term Exposure Limit)

Value: 125 ppm

Agency: Occupational Health and Safety Administration (OSHA)

ACC Ethylbenzene Panel. Worker exposures in U.S. ethylbenzene production (2000).

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Andrew, FD, Buschbom, RL, Cannon, WC, Miller, RA, Montgomery, LF, Phelp, DW, and Sikov, MR, Teratologic assessment of ethylbenzene and 2-ethoxyethanol. Battelle Pacific Northwest Laboratories. Prepared for the National Institute for Occupational Safety and Health, Cincinnati, OH. NIOSH Contract #210-79-0037

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