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Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati OH 45268

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HEALTH EFFECTS ASSESSMENT FOR ETHYLBENZENE

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U.S. Environmental Protection Agency

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with ethylbenzene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria Document for Ethylbenzene. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 400/5-80-048. NTIS PB81-117590.

U.S. EPA. 1985. Drinking Water Criteria Document for Ethylbenzene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. Final draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Data concerning the toxicological effects of ethylbenzene are extremely limited. A major issue of concern is limited data which suggest teratogenic/fetotoxic effects of this compound. Inhalation exposures to ethylbenzene have resulted in fetotoxicity in rats and rabbits. A threshold exposure level was not established and therefore neither an AIS nor an AIC for inhalation exposure was estimated.

Adequate investigations are not available concerning teratogenic/fetotoxic effects of oral exposure. However, the data on xylene/ethylbenzene exposures suggest that if ethylbenzene is fetotoxic, relatively high doses should be required to produce these effects. The NOEL for fetotoxicity in this study was 2.06 g/kg, even with only 17% of this mixture being ethylbenzene. The ethylbenzene dose administered was still higher than reported NOELs for other endpoints. Therefore, the NOEL from the only available oral subchronic study was used to estimate an oral AIS of 68 mg/day. An additional uncertainty factor of 10 was applied to estimate an oral AIC (6.8 mg/day). This corresponds to the estimate suggested by U.S. EPA (1985). These estimates should be reviewed when more complete toxicological data, especially chronic studies and gestational exposures, are available.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
CNS	Central nervous system
CS	Composite score
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RD_{50}	Dose at which the average respiratory rate is depressed 50%
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister chromatid exchange
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of ethylbenzene (CAS No. 100-41-4) are given below.

Chemical class	monocyclic aromatic
Molecular weight	106.16 (Callahan et al., 1979)
Vapor pressure	7 mm Hg at 20°C (Callahan et al., 1979)
Water solubility	152 mg/ℓ at 20°C (Callahan et al., 1979)
Log octanol/water partition coefficient	3.15 (Callahan et al., 1979)
Soil mobility (predicted as retardation factor for soil depth of 140 cm and organic carbon content of 0.087%)	<4 (estimated)
Bioconcentration factor	4.7 in clam tissue, Tapes semidecussata (Nunes and Benville, 1979)
Half-life in	
Air	35 hours (NAS, 1980)
Water	1.5-7.5 days (estimated)

A soil mobility factor has been estimated from the soil partition coefficient value determined from the equation given by Schwarzenbach and Westall (1981) and a comparison of the retardation factor values given by Wilson et al. (1981).

A half-life of ethylbenzene in water has been estimated on the basis of the reaeration rate ratio of 0.465 and the oxygen reaeration rate of 0.19-0.96 day^{-1} (Mabey et al., 1981).

A half-life value for ethylbenzene in soil could not be located in the available literature. However, evaporation is expected to be the predominant loss mechanism from the soil surface. The half-life for soil evaporation should be longer than the evaporation from water. Based on the biodegradability study of Tabak et al. (1981), ethylbenzene may biodegrade in subsurface soil. Small amounts of ethylbenzene may also leach from soil into groundwater, particularly from sandy soils.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Although quantitative data regarding the absorption of ethylbenzene from the gastrointestinal tract were not located in the available literature, ingestion of ethylbenzene by rats has been reported to cause effects similar to those produced by inhalation of ethylbenzene by rats (Wolf et al., 1956).

2.2. INHALATION

By measuring the amount of ethylbenzene that had to be added to maintain a constant concentration in the chamber housing the experimental rats, Chin et al. (1980) determined that young rats (100 g) absorbed 44% of the ethylbenzene to which they were exposed. Unfortunately, the authors did not consider the percutaneous rate of absorption that occurred during their experiment. Without explaining the derivation of their absorption coefficient, Bardodej and Bardodejova (1970) determined that human volunteers (n=18) absorbed 64% of the total ethylbenzene to which they were exposed at dose levels ranging from 100-370 mg/m^3.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

In contrast to the target organs of acute ethylbenzene exposure, the CNS and the lungs (Smyth et al., 1962; Faustov, 1958, 1960), the main effects of subchronic or chronic exposure to ethylbenzene by the oral and respiratory routes appeared in the liver and kidneys (Wolf et al., 1956) (Table 3-1). In rats and guinea pigs, the increase in hepatic and renal weight caused by ethylbenzene was accompanied by cloudy swelling of hepatocytes and renal tubular epithelial cells (Wolf et al., 1956). Slight testicular degeneration caused by ethylbenzene exposure was described in rabbits and monkeys (Wolf et al., 1956).

Russian studies have reported leukocytosis, decreased numbers of lymphocytes, increased numbers of reticulocytes, and decreased albumins but increased globulins in serum as a result of exposure to 100 and 1000 mg/m³ of ethylbenzene for 4 hours daily during a 7-month period (Ivanov, 1962). Further details were not provided. In a subsequent paper, dystrophic changes in the liver and kidneys, muscle chronaxia and altered blood cholinesterase activity were reported at an exposure level of 1000 mg/m³ (Ivanov, 1964). Faustov and Kramsakov (1968) reported decreased antibody titers in rabbits chronically exposed to ethylbenzene at a level of 1500 mg/m³.

3.2. CHRONIC

Pertinent data regarding the chronic inhalation toxicity of ethylbenzene could not be located in the available literature.

TABLE 3-1

Subchronic Toxicity of Ethylbenzene*

Route	Vehicle	Exposure or Dose	Duration	Species	Number Tested	Effects
Oral	olive oil	control	5 days/week for	F/Wistar	10	None
		13.6 mg/kg/day	6 months or	rats	10	None
		136 mg/kg/day	130 days out of		10	None
		408 mg/kg/day	182 days total		10	Increased liver and kidney
		680 mg/kg/day			10	weight; cloudy swelling in hepatocytes and renal tubular epithelium
Inhalation	NA	control	7 hours/day;	M/F rats	10-25	None
		400 ppm	4-5 days/week,			Slight increase in liver and
		(1737 mg/m³)	103-138 days out			kidney weight
		600 ppm	of 144-214 days			Slight increase in liver and
		(2606 mg/m³)	total			kidney weight
		1250 ppm				Slight increase in liver and
		(5428 mg/m³)				kidney weight; cloudy swelling of hepatocytes and renal cells
		2200 ppm		M only		Slight increase in liver and
		(9500 mg/m³)				kidney weight; decreased growth
Inhalation	NA	control	7 hours/day;	guinea	5-10	None
		400 ppm	5 days/week for	pigs		None
		(1700 mg/m³)	186 days			
		600 ppm				Increased liver weight
		(2600 mg/m³)				
		1250 ppm	7 hours/day;	F only		Increased liver weight;
		(5400 mg/m³)	138/214 days			decreased growth
Inhalation	NA	400 ppm	7 hours/day;	rabbits	1-2	None
		(1700 mg/m³)	5 days/week for			
		600 ppm	186 days			Slight degeneration in
		(2600 mg/m³)				testicular germinal epithelium
		1250 ppm	7 hours/day for	F only		None
		(5400 mg/m³)	138/214 days			
Inhalation	NA	600 ppm	7 hours/day;	rhesus	1-2	Increased liver weight; slight
		(2600 mg/m³)	5 days/week for	monkeys	1 M	testicular degeneration
		400 ppm	186 days			None
		(1700 mg/m³)				

*Source: Wolf et al., 1956

NA = Not applicable

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Administration of ethylbenzene which constituted 17% of a xylene mixture in doses of 0.6, 1.2, 2.4, 3.0 or 3.6 mℓ/kg/day on days 6-15 of gestation was reported to be teratogenic in mice at doses of $\geq$3 mℓ/kg (Marks et al. 1982). However, the dose levels are higher than the level (291.43 mg/kg/day) which is judged to be the lowest subchronic LOAEL (Section 6.1.1.). In addition, the mixture of xylene with ethylbenzene precludes the use of the Marks et al. (1982) study in risk assessment, especially since xylene alone has been shown to be teratogenic.

3.3.2. Inhalation. Pregnant New Zealand rabbits were exposed to ethylbenzene vapor at a dose level of 435 or 4348 mg/m^3 for 6-7 hours/day on days 1-24 of gestation (Hardin et al., 1981). On day 30 the rabbits were killed; maternal organs were weighed and examined grossly and microscopically. Fetuses were weighed, sexed, measured for crown-rump length and examined for external, internal and skeletal abnormalities. There was a statistically significant reduction in the number of live kits/litter ($p<0.05$) at both exposure levels, although the number of dead and resorbed fetuses was not increased above matched controls. Neither maternal toxicity nor fetal malformations were evident.

Pregnant rats were exposed to ethylbenzene vapor at a dose level of 435 or 4348 mg/m^3 for 6-7 hours/day on days 1-19 of gestation (Hardin et al., 1981). On day 21 the rats were killed. At the higher dose level, maternal toxicity was indicated by increased liver, kidney and spleen weights. A statistically significant increase in extra ribs ($p<0.05$) occurred in the offspring of mothers exposed to both dose levels. The authors concluded that the results of their experiment in rats suggested (rather than indicated) a teratogenic potential for ethylbenzene.

3.4. TOXICANT INTERACTIONS

Ethylbenzene constitutes ≈20% of technical grade xylene (Andersson et al., 1981). When male Wistar rats were exposed to m-xylene and ethylbenzene (200 and 600 ppm, 6 hours/day for 5 days), the metabolism of m-xylene was preferred to the metabolism of ethylbenzene (Elovaara et al., 1982). Ethylbenzene potentiates the toxicity of acrylonitrile (Gut et al., 1981).

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenicity of ethylbenzene could not be located on the available literature.

4.2. BIOASSAYS

Ethylbenzene is on the list of chemicals which have been deferred for carcinogenicity testing (NTP, 1983).

4.3. OTHER RELEVANT DATA

Ethylbenzene, with or without activation by S-9, has been found not to be mutagenic to Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 (Florin et al., 1980; Nestmann et al., 1980) or to Saccharomyces cerevisiae strain D7 (Nestmann and Lee, 1983). At the highest dose tested, ethylbenzene had a marginal effect in inducing SCE after a 48-hour treatment of human whole-blood lymphocytes in vitro (Norppa and Vainio, 1983). Four common metabolites of ethylbenzene did not elicit a positive response in the Ames bacterial assay (Salmona et al., 1976).

4.4. WEIGHT OF THE EVIDENCE

An IARC classification of ethylbenzene was not located. Based on the criteria for weight of evidence proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), since there appear to be no data regarding the carcinogenicity of ethylbenzene in either humans or animals, the chemical is most appropriately designated a Group D-Not Classified compound.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1983) has recommended a TLV-TWA for ethylbenzene of 100 ppm and a TLV-STEL of 125 ppm. OSHA currently limits occupational exposure to ethylbenzene to a TWA concentration of 100 ppm (Code of Federal Regulations, 1981). The U.S. EPA (1980b) recommended a criterion level for drinking water of 1.4 mg/ℓ based on the TLV.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. In the only study available on oral exposure to ethylbenzene (Wolf et al., 1956), the two lowest dose levels (13.6 and 136 mg/kg/day) are NOELs and the other two dose levels (408 and 680 mg/kg/day) are LOAELs. The highest NOEL (136 mg/kg/day) was used to compute the AIS. Because the rats in this study (Wolf et al., 1956) were treated with ethylbenzene 5 days/week, the reported dose must be multiplied by 5 days/7 days to reflect continuous exposure (97.14 mg/kg/day). To derive an AIS (mg/day), the NOEL is multiplied by 70 kg and divided by an uncertainty factor of 100 to account for the use of animal data in deriving human criteria (interspecies extrapolation) and the range of sensitivity in the human population to any particular chemical. The oral AIS for ethylbenzene exposure obtained through this calculation is 68.0 mg/day for a 70 kg human.

6.1.2. Inhalation. In the Wolf et al. (1956) study of inhalation exposure to ethylbenzene, the lowest exposure level tested (400 ppm; 1737 mg/m^3) produced a slight increase in liver and kidney weight in rats. Other effects were produced at higher concentrations in the same tissues (i.e., slight increase in liver and kidney weights at 600 ppm, cloudy swelling of hepatocytes and renal cells at 1250 ppm) and in other species (increased liver weight in guinea pigs and monkeys, and slight testicular degeneration in rabbits and monkeys at 600 ppm). Therefore, 1250 ppm would be considered the LOAEL in the Wolf study. However, in the teratogenicity study of Hardin et al. (1981), fetotoxicity indicated by a significantly increased number of extra ribs in the offspring of mothers exposed to ethylbenzene on days 1-19 of gestation occurred at an exposure level of 435 mg/m^3 (100 ppm). A dose in mg/kg/day is estimated from exposure levels in

mg/m³ by multiplying by an estimated rat inhalation rate of 0.26 m³/day, dividing by the estimated body weight of a rat (0.35 kg) and converting intermittent exposure to an equivalent continuous exposure level. This yields a continuous exposure dose of 663.26 mg/kg/day in the Wolf et al. (1956) study and 87.52 mg/kg/day in the Hardin et al. (1981) study. The lower LOAEL from the fetotoxicity study precludes the use of the higher LOAEL from the subchronic toxicity study for human risk assessment. Because a NOEL for fetotoxicity has not been identified and there is no NOAEL or LOAEL from a subchronic toxicity study lower than the LOAEL for fetotoxicity, no criteria for subchronic inhalation exposure to ethylbenzene can be derived at this time.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Because no chronic toxicity studies of ethylbenzene were located in the available literature, the subchronic toxicity study of Wolf et al. (1956) was used to estimate chronic exposure criteria.

6.2.1. Oral. An additional uncertainty factor of 10 must be applied to obtain an AIC from an AIS. Using an uncertainty factor of 1000, a chronic oral ADI of 6.80 mg/human/day is calculated from the subchronic NOEL in rats of 97.14 mg/day identified from the Wolf et al. (1956) study.

6.2.2. Inhalation. Because there are no experimental data on chronic inhalation of ethylbenzene and the subchronic data are not adequate to use in human risk assessment, the TLV of 100 ppm (435 mg/m³), recommended by the ACGIH (1983) and OSHA (Code of Federal Regulations, 1981), is considered a NOEL for derivation of chronic ethylbenzene inhalation criteria. The exposure level of 435 mg/m³ is converted to 44.4 mg/kg/day by multiplying by the human breathing volume/8 hour workday (10 m³) and the fraction of the total week spent at work (5/7 days), and dividing by the estimated human

body weight (70 kg). However, the NOEL (44.4 mg/kg/day) derived from the TLV is too close to the LOAEL (87.52 mg/kg/day) for fetotoxicity to be of any use in human risk assessment. Therefore, no AIC for ethylbenzene inhalation exposure can be derived at this time.

An RQ has been calculated based on the increased liver and kidney weight of rats exposed to ethylbenzene by inhalation. These effects were noted at 400 ppm (1737 mg/m^3), 7 hours/day and 5 days/week for 144-214 days. The human MED is calculated by expanding to continuous exposure, assuming a human breathing rate of 20 m^3/day and an absorption factor of 0.5, and applying an uncertainty factor of 5 to extrapolate from subchronic to chronic data. The resulting human MED, 724 mg/day, corresponds to an RV_d of 1.2. The RV_e associated with the effect of increased liver and kidney weights is 4. A CS of 5, the product of RV_d and RV_e, is calculated.

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APPENDIX

Summary Table for Ethylbenzene

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	NA	NA	NA	ND	NA
AIC	NA	NA	NA	ND	NA
Maximum composite score	rats	400 ppm (1737 mg/m³) 7 hours/day, 5 days/week for 144-214 days (RV_d = 1.2)	increased liver and kidney weights (RV_e = 4)	5	Wolf et al., 1956
Oral					
AIS	rats	136 mg/kg/day, 5 days/week, TWA= 97.14 mg/kg/day	increased liver and kidney weights with cloudy swelling	68.0 mg/day	Wolf et al., 1956
AIC	rats	136 mg/kg/day, 5 days/week, TWA= 97.14 mg/kg/day	NA	6.80 mg/day	Wolf et al., 1956

ND = Not derived; NA = not available