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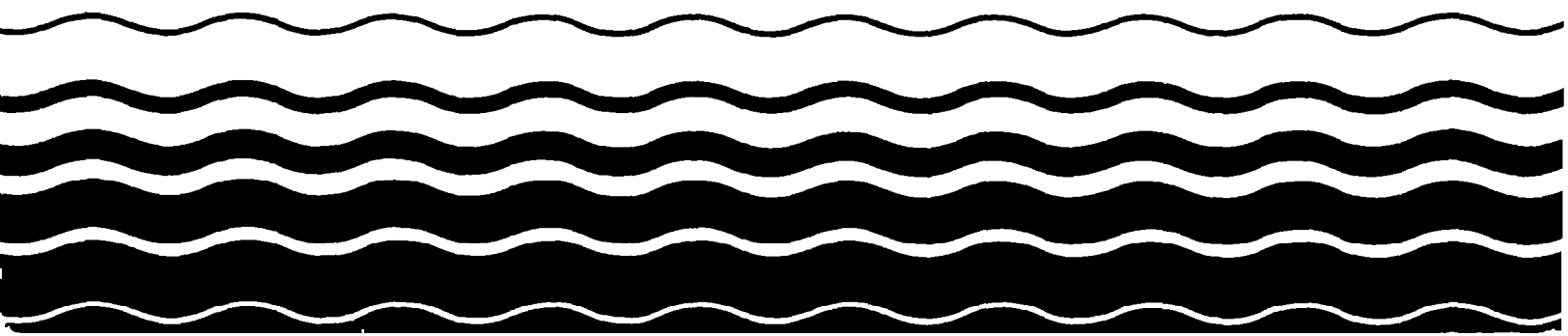
Ambient Water Quality Criteria for Ethylbenzene



AMBIENT WATER QUALITY CRITERIA FOR

ETHYLBENZENE

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
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ETHYLBENZENE

CRITERIA

Aquatic Life

The available data for ethylbenzene indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 32,000 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No definitive data are available concerning the chronic toxicity of ethylbenzene to sensitive freshwater aquatic life.

The available data for ethylbenzene indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 430 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of ethylbenzene to sensitive saltwater aquatic life.

Human Health

For the protection of human health from the toxic properties of ethylbenzene ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 1.4 mg/l.

For the protection of human health from the toxic properties of ethylbenzene ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 3.28 mg/l.

INTRODUCTION

Ethylbenzene (EB) is an alkyl-substituted aromatic compound which has a broad environmental distribution due to its widespread use in a plethora of commercial products and its presence in various petroleum combustion processes. The two primary commercial uses of EB are in the plastic and rubber industries where it is utilized as an initial substrate reactant in the production of styrene (Paul and Soder, 1977). The majority of these commercial sites of production are geographically clustered in Texas and Louisiana. The amount of EB produced in the United States in 1975 was approximately 6 to 7 billion pounds of which about 98 percent was used in the manufacture of styrenes (Table 1) (U.S. Int. Trade Comm., 1976).

Commercial production of EB currently utilizes a liquid phase Friedel-Crafts alkylation of benzene with ethylene. According to Paul and Soder (1977), at least 50 percent of the benzene used in the United States goes into the production of ethylbenzene. Significant quantities of EB are present in mixed xylenes. These are used as diluents in the paint industry, in agricultural sprays for insecticides, and in gasoline blends (which may contain as much as 20 percent EB). In light of the large quantities of EB produced and the diversity of products in which it is used, there exist many environmental sources for ethylbenzene, e.g., vaporization during solvent use, pyrolysis of gasoline, and emitted vapors at filling stations.

Ethylbenzene ($C_6H_5C_2H_5$, molecular weight 106.16) (Figure 1) is a flammable, colorless liquid with a boiling point of 136.25°C and a freezing point of -95.01°C (Windholz, 1976). Its density at 25°C (relative to water at the same temperature) is 0.866 (Windholz, 1976) and it has a specific gravity of 0.8669 (Cier, 1970). Its vapor pressure is 20 mm Hg at 38.6°C

TABLE 1

Possible Environmental Sources of Ethylbenzene*

Source	EB Production/annum
Commercial	6–7 billion pounds
Petroleum Cracking	0.57–0.96 billion pounds
(2–3%-of gasoline (volume) is EB)	
Residues in polystyrene	0.19 billion pounds
Motor vehicle exhaust (and other combustion and pyrolysis products)	0.28 billion pounds

*Source: U.S. International Trade Commission, 1976.

FIGURE 1

Ethylbenzene - Chemical Structure

TABLE 2

Ethylbenzene / Physical Properties*

Molecular weight	106.16
Color	colorless
Boiling Point, 760 torr	136.2°C
Freezing Point	-95°C
Flashpoint	16°C
Density (g/ml) @ 20°C	0.87
Vapor Pressure, torr	20 at 38.6°C
Water Solubility wt. %	0.02**+

* Taken from Cler (1970); Gerarde (1963).

** For all practical purposes, EB is 'insoluble' in water and due to its vapor pressure is probably present only in the atmosphere.

\+ EB water solubity 161 ppm at 25°C in distilled water
111 ppm at 25°C in seawater

(Cier, 1970). The log of the octanol/water partition coefficient for ethylbenzene is 3.15 (Tute, 1971). Ethylbenzene is slightly soluble (less than 0.1 percent or 866 mg/l) in water (Hann and Jensen, 1970), but it is freely soluble in organic solvents (Table 2) (Windholz, 1976).

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Aquatic Life Toxicology*

INTRODUCTION

The acute toxicity data base for ethylbenzene and freshwater organisms indicates that there is not a large difference in sensitivity among the four tested fish species and that Daphnia magna has similar sensitivity to ethylbenzene. Algal assays indicated that Selenastrum capricornutum was much more resistant.

There was a wide range of acute toxicity among saltwater species represented by three invertebrate and two fish species. This range was from 430 to 1,030,000 µg/l.

EFFECTS

Acute Toxicity

An acute test with Daphnia magna (U.S. EPA, 1978) resulted in a 48-hour EC_{50} value of 75,000 µg/l (Table 1).

Pickering and Henderson (1966) conducted 96-hour tests with the goldfish, fathead minnow, guppy, and bluegill and the LC_{50} values ranged from 32,000 to 97,100 µg/l (Table 1). Two different investigators' bluegill LC_{50} values, 32,000 and 155,000 µg/l, do not agree well but no explanation is available.

Only three tests have been conducted with saltwater invertebrate species, the 96-hour LC_{50} for the mysid shrimp was 87,600 µg/l, for the bay shrimp the LC_{50} was 3,700 µg/l, and for the Pacific oyster it was 1,030,000 µg/l (Table 1).

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

There is an extreme, and unexplainable difference (Table 1) between the 96-hour LC_{50} values for the striped bass (430 µg/l) and the sheepshead minnow (275,000 µg/l). This extreme variability in fish and invertebrate data suggests possible difficulties in testing ethylbenzene in saltwater.

Chronic Toxicity

The embryo and larval stages of the fathead minnow have been exposed to ethylbenzene (U.S. EPA, 1978) and no adverse effects were observed at the highest test concentration, 440 µg/l (Table 2).

Plant Effects

No adverse effects on cell number or chlorophyll *a* production of *Selenastrum capricornutum* or *Skeletonema costatum* were observed at test concentrations as high as 438,000 µg/l (Table 3).

Miscellaneous

Potera (1975) conducted a variety of 24-hour exposures with the grass shrimp using static procedures with measured concentrations (Table 4). Temperature (19 and 20°C), salinity (15 and 25 ppt), and life stage (larval and adult) were the variables considered. The total range of LC_{50} values is 10,200 to 17,300 µg/l which small difference indicates that these variables did not have a very great effect. The copepod, *Nitocra spinipes*, was exposed to ethylbenzene at salinities of 15 and 25 ppt and the 24-hour LC_{50} values were both 16,000 µg/l (Table 4).

Summary

Four freshwater fish species have been acutely tested with ethylbenzene understatic test conditions without measured concentrations. The 96-hour LC_{50} values ranged from 32,000 to 15,000 µg/l. The 48-hour EC_{50} value for *Daphnia magna* was 75,000 µg/l indicating comparable sensitivity with fishes. No effects on the embryo and larval stages of the fathead minnow

were observed at concentrations as high as 440 µg/l, a concentration about one-hundredth of the 96-hour LC_{50}. No effects were observed on an alga at concentrations as high as 438,000 µg/l.

The LC_{50} values for two saltwater fish and three invertebrate species varied widely with a range of 430 to 1,030,000 µg/l, no adverse effect on an alga was observed at concentrations as high as 438,000 µg/l. No chronic test with any saltwater species has been conducted. The effect of temperature, salinity, and life stage on the toxicity of ethylbenzene to the grass shrimp was studied and all LC_{50} values were within a range of 10,200 to 17,300 µg/l, which results indicate no significant effect of those variables on the 24-hour LC_{50} values.

CRITERIA

The available data for ethylbenzene indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 32,000 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No definitive data are available concerning the chronic toxicity of ethylbenzene to sensitive freshwater aquatic life.

The available data for ethylbenzene indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 430 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of ethylbenzene to sensitive saltwater aquatic life.

Table 1. Acute values for ethylbenzene

Species	Method*	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
		FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	S, U	75,000	75,000	U.S. EPA, 1978
Goldfish, *Carassius auratus*	S, U	94,440	94,440	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	48,510	-	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	42,330	45,300	Pickering & Henderson, 1966
Guppy, *Poecilia reticulata*	S, U	97,100	97,100	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S, U	32,000	-	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S, U	155,000	70,400	U.S. EPA, 1978
		SALTWATER SPECIES		
Pacific oyster, *Crassostrea gigas*	S, U	1,030,000	1,030,000	LeGore, 1974
Bay shrimp, *Crago franciscorum*	S, M	3,700	3,700	Benville & Korn, 1977
Mysid shrimp, *Mysidopsis bahia*	S, U	87,600	87,600	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	275,000	275,000	U.S. EPA, 1978
Striped bass, *Morone saxatilis*	S, M	430	430	Benville & Korn, 1977

* S = static, U = unmeasured, M = measured

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Chronic values for ethylbenzene (U.S. EPA, 1978)

Species	Method*	Limits (µg/l)	Chronic Value (µg/l)
FRESHWATER SPECIES			
Fathead minnow, *Pimephales promelas*	E-L	>440	-

* E-L = embryo-larval

No acute-chronic ratio is calculable.

Table 3. Plant values for ethylbenzene (U.S. EPA, 1978)

Species	Effect	Result (µg/l)
FRESHWATER SPECIES		
Alga, *Selenastrum capricornutum*	Chlorophyll *a* 96-hr EC50	>438,000
Alga, *Selenastrum capricornutum*	Cell numbers 96-hr EC50	>438,000
SALTWATER SPECIES		
Alga, *Skeletonema costatum*	Chlorophyll *a* 96-hr EC50	>438,000
Alga, *Skeletonema costatum*	Cell numbers 96-hr EC50	>438,000

Table 4. Other data for ethylbenzene (Potera, 1975)

Species	Duration	Effect	Result (µg/l)
	SALTWATER SPECIES		
Copepod, *Nitocra spinipes*	24 hrs	LC50	16,000
Copepod, *Nitocra spinipes*	24 hrs	LC50	16,000
Grass shrimp (adult), *Palaemonetes pugio*	24 hrs	LC50	14,500
Grass shrimp (adult), *Palaemonetes pugio*	24 hrs	LC50	14,400
Grass shrimp (adult), *Palaemonetes pugio*	24 hrs	LC50	17,300
Grass shrimp (adult), *Palaemonetes pugio*	24 hrs	LC50	17,300
Grass shrimp (larva), *Palaemonetes pugio*	24 hrs	LC50	10,200
Grass shrimp (larva), *Palaemonetes pugio*	24 hrs	LC50	10,200

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Mammalian Toxicology and Human Health Effects

INTRODUCTION

The paucity of information available on the biological effects of ethylbenzene (EB) in man and other mammalian species is rather surprising considering the degree of exposure to EB in our environment. EB is present in drinking waters and in the atmosphere. It has been shown to persist in man for days after exposure (Wolff, et al. 1977). It is present in the respiratory tract (Conkle, et al. 1975), umbilical cord and maternal blood (Dowty, et al. 1976), and subcutaneous fat (Wolff, et al. 1977) of exposed humans. There is little reason to suspect that the current sources of EB in our environment will be abated. The sources of EB include: (1) commercial, e.g., petroleum and petroleum by-products, (2) motor vehicle exhaust, and (3) cigarette smoke. These appear to be integral parts of our society. In man and in animals, EB is an irritant of mucous membranes. It is this response which forms the basis for the current Threshold Limit Value (TLV). The U.S. EPA recommended carcinogenicity testing for EB in 1976, but test results are not yet available. Similarly, no data exist for mutagenicity and teratogenicity of ethylbenzene. The potential adverse human health effects following exposure to EB were stated (40 FR 1910.1034) to be:

1) kidney disease,
   EB is not nephrotoxic. Concern is expressed because the kidney is the primary route of excretion of EB and its metabolites.

2) liver disease,
   EB is not hepatotoxic. Since EB is metabolized by the liver, concern is expressed for this tissue.

3) chronic respiratory disease,
Exacerbation of pulmonary pathology might occur following exposure to EB. Individuals with imparied pulmonary function might be at risk.

4) skin disease,
EB is a defatting agent and may cause dermatitis following prolonged exposure. Individuals with pre-existing skin problems may be more sensitive to EB.

EXPOSURE

Ethylbenzene has a broad environmental distribution due to its widespread use in a plethora of commercial products and its presence in various petroleum combustion processes. The two primary commercial uses of EB are in the plastic and rubber industries where it is utilized as an initial substrate reactant in the production of styrene (Paul and Soder, 1977). The amount of EB produced in the United States in 1975 was between 6-7 billion pounds. Almost all (97 percent) was captively consumed by the producers. The majority of these commercial sites are geographically clustered in Texas and Louisiana.

Commercial production of EB currently utilizes a liquid phase Friedel-Crafts alkylation of benzene with ethylene. According to Paul and Soder (1977), at least 50 percent of the benzene used in the United States goes into the production of ethylbenzene. Significant quantities of EB are present in mixed xylenes. These are used as diluents in the paint industry, in agricultural sprays for insecticides and in gasoline blends (which may contain as much as 20 percent EB). In light of the large quantities of EB produced and the diversity of products in which it is found, there exist many environmental sources for ethylbenzene, e.g., vaporization during

solvent use, pyrolysis of gasoline, and emitted vapors at filling stations.

Ingestion from Water

In a survey of water contaminants present in the drinking water of ten cities in the United States, ethylbenzene (EB) was detected but not quantified in six of ten samples (U.S. EPA, 1975). This report indicated that alkylated benzenes were present in U.S. drinking water at µg/l concentration. A broad distribution was estimated in a document prepared for the U.S. EPA by Shackelford and Keith (1976); EB was present in finished drinking water in the United States, the United Kingdom, and Switzerland. EB was also found in river water, chemical plant effluents, raw water, textile plant effluents, and well water at 15 ppb (Burnham, et al. 1972).

Ingestion From Food

The only report in the literature indicating the presence of ethylbenzene in food is that of Kinlin, et al. (1972), wherein they reported the presence of 227 organic compounds including EB in roasted filbert nuts (no quantitative data given).

Styrene food packaging techniques represent another possible source of EB contamination in food products. Though styrene has been detected in certain food products, the presence of EB in these products has not been reported.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus the per capita

ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

No measured steady-state bioconcentration factor (BCF) is available for ethylbenzene, but the equation "Log BCF = (0.85 Log P) - 0.70" can be used (Veith, et al. 1979) to estimate the BCF for aquatic organisms that contain about 7.6 percent lipids (Veith, 1980) from the octanol/water partition coefficient (P). Based on a measured Log P value of 3.15 (Hansch and Leo, 1979), the steady-state bioconcentration factor for ethylbenzene is estimated to be 95. An adjustment factor of 3.0/7.6 = 0.395 can be used to adjust the estimated BCF from the 7.6 percent lipids on which the equation is based to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for ethylbenzene and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 95 x 0.395 = 37.5.

Inhalation

EB probably represents about 10 percent of the total aromatic compounds detected in the air and roughly one percent of the total organic compounds detected. Altshuller and Bellar (1963) detected 0.01 ppm EB in the air around Los Angeles, California. Lonneman, et al. in 1968 detected EB in the air around Los Angeles at a level of 0.006 ppm. Neligan, et al. (1965) surveyed five different sites in California; EB levels averaged 0.01 ppm. These authors have suggested that commercial sources and motor vehicles are the major contributors to EB in the atmosphere.

EB is present in cigarette smoke. Conkle, et al. (1975) measured trace quantities of EB in the expired air of eight male subjects with a range of 23 to 47 years of age, median age 38. Using gas chromatography techniques they detected EB in five of eight subjects with the smokers in this group having the highest levels of EB (0.78 to 14 x 10^{-6}g/hr).

Dermal

No data are available on the dermal exposure of humans to ethylbenzene.

PHARMACOKINETICS

Absorption and Distribution

When administered subcutaneously to 40 rats (2.5 ml, 1:1 v/v), ethylbenzene was detected in the blood within 2 hours, and the levels of EB (10-15 ppm in blood) were maintained for at least 16 hours (Gerarde, 1959).

Although little quantitive data on the absorption of EB is available, absorption has been demonstrated via the skin and

respiratory tract in a number of toxicity studies. Two representative studies have reported that significant amounts of EB can be absorbed through the skin. Dutkiewicz and Tyras (1967, 1968) have shown (Table 1) that when human subjects are exposed to EB, there is a "significant increase in the amount of urinary mandelic acid excreted" (see Metabolism section). In addition, Smyth, et al. (1962) reported an LD_{50} for EB (via skin application) in rabbits of 17.8 ml/kg.

Dutkiewicz and Tyras (1968) also compared the skin absorption of several other organic solvents, and they concluded that by comparison significantly more EB was absorbed (Table 1).

EB is readily absorbed by inhalation (see Table 2). Symptomatology associated with acute intoxication of EB by this route includes coordination disorders, narcosis, convulsions, pulmonary irritation, and conjunctivitis (Ivanov, 1962) (see Effects section).

Ingestion of EB has been reported by a number of investigators to produce a variety of dose-related toxicities in several different species (see Effects section). The evidence presented above indicates that EB can be absorbed via several different routes of administration, producing systemic effects in various species of animals including man.

Metabolism and Excretion

The metabolism of EB is summarized in Figure 1. These data were taken from a series of different studies on rabbits as adapted from the work of Kiese and Lenk (1974) (Table 3). This proposed metabolic outline is consistent with reports on the metabolic fate

TABLE 1

Skin Absorption of EB in Man*

EB concentration	Rate of Absorption (mg/cm^2) hour	24-hour mandelic acid excretion (% of absorbed dose)
112-156 mg/l	0.11-0.21	4.6

*Source: Dutkiewicz and Tyras, 1968

TABLE 2

Human Response to Ethylbenzene Vapors*

Concentration mg/l	Concentration ppm	Exposure time	Response
21.75	5000	Few seconds	Intolerable irritation of nose, eyes and throat.
8.7	2000	Few seconds	Severe eye, nose and mucous membrane irritation. Lacrimation.
8.7	2000	6 minutes	Central nervous system effects. Dizziness.
4.35	1000	Few seconds	Eye irritation.
4.35	1000	Minutes	Eye irritation diminishes
0.87	200	Threshold limit.	
0.043	10	Few seconds	Odor detectable.

*Source: Gerarde, 1963

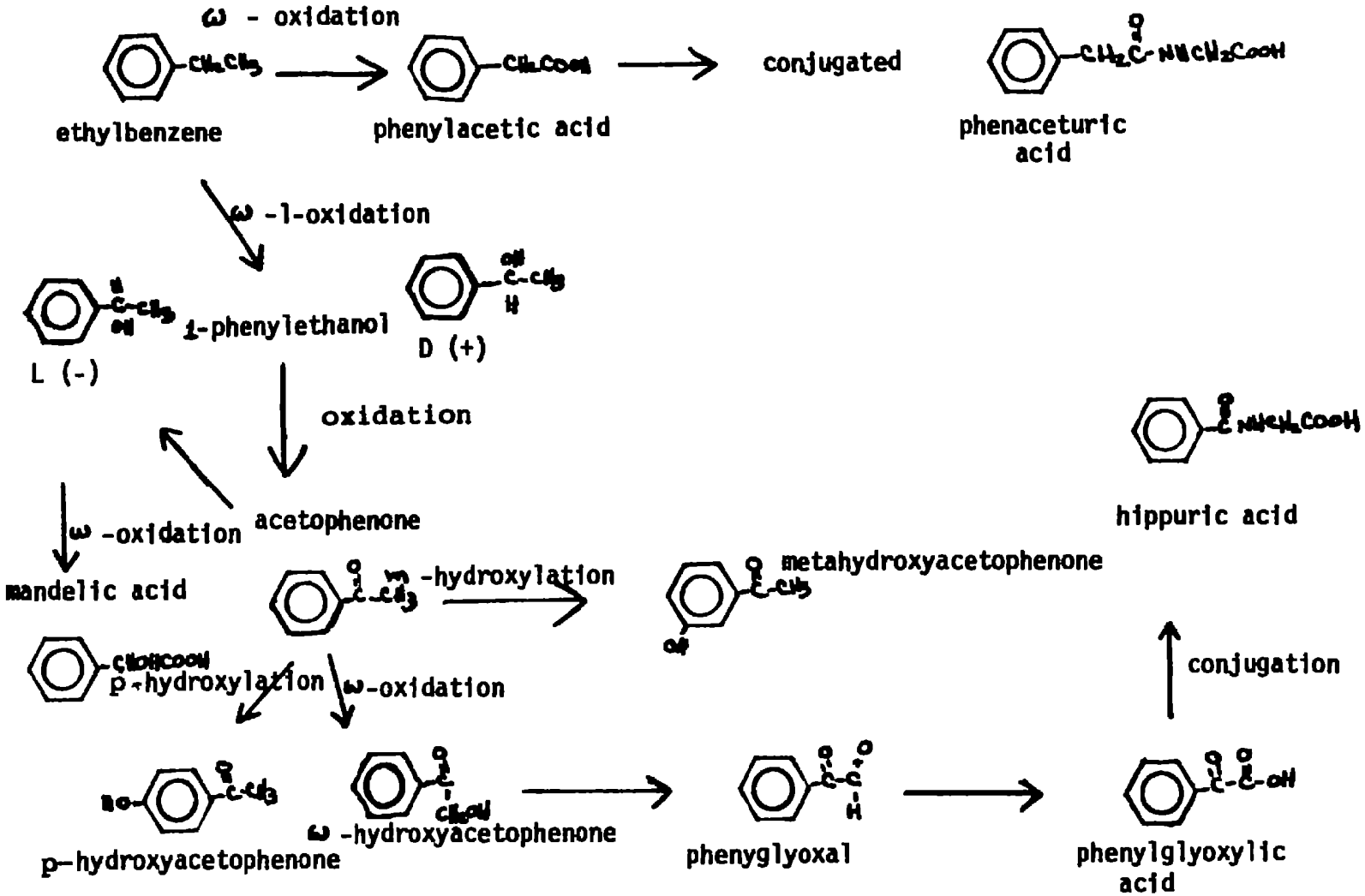

FIGURE 1

Metabolic Pathways of Ethylbenzene
Source: Kiese and Lenk, 1974

TABLE 3

EB Metabolites Found in Urine
of Rabbits given 1 gram i.p.*

	% of administered EB
phenaceturic acid	10-20
mandelic acid	1-2
p-hydroxyacetophenone	0.13
m-hydroxyacetophenone	0.03
o-hydroxyacetophenone	0.1
hippuric acid	22-41
1-phenylethanol	30% 75% D(+),25% L(-)

*Source: Kiese and Lenk, 1974

Similar data were obtained by El Masry, et al., 1956.

of EB in dogs (Nencki, 1878; Nencke and Giacosa, 1880; El Masry, et al. 1956), rat liver microsomes (McMahon and Sullivan, 1966; McMahon, et al. 1969), and in man (Bardodej and Bardedjeva, 1970; Logemann, et al. 1964). The data presented in Table 3 indicate that the major metabolites of EB are 1-phenylethanol, hippuric acid and phenaceturic acid.

The study reported in Table 4 is excerpted in a modified form from Bardodej and Bardedjova (1970). In this study of the metabolism of EB by human volunteers, there are several significant omissions which hamper a clear interpretation of the data. These include no indication of number, age, or sex of subjects or of their physical condition prior to EB exposure. The methodologies described in the text include spectrophotometry and paper chromatography. These were probably not sensitive enough to detect many of the metabolites. Indeed, the authors were unable to detect several common metabolites of ethylbenzene, including acetophenone, phenylethyleneglycol, ω-hydroxyacetophenone, hippuric acid, and mercapturic acid. Despite these shortcomings, this study contributes to our understanding of EB metabolism in man. A considerable amount of EB was absorbed in the respiratory tract; only traces of EB were expired by the end of the experiment (Table 4). The major metabolites found in the urine included mandelic and phenylglyoxylic acid, 64 percent and 25 percent respectively, and 1-phenylethanol, 5 percent. These authors (Bardodej and Bardedjova, 1970) also indicated that if the concentration of EB is increased above 85 ppm (level not specified), subjects reported fatigue,

TABLE 4

Metabolism of EB in Man*

EB concentrations in inspired air (ppm)	23,43,46,85
Duration	8 hours
% of vapor retained in respiratory tract (arithmetic average)	64
Excreted in expired air by the end of the experiment	traces (2-4%)
retained dose eliminated in the urine as mandelic acid	64%
as phenylglyoxlic acid	25%
as 1-phenylethanol	5%

*Source: Bardodej and Bardedjova, 1970

sleepiness, headache, and mild irritation of the eyes and respiratory tract.

EFFECTS

Acute, Subacute, and Chronic Toxicity

Gerarde (1963) has reviewed the acute toxicity data in humans to EB via inhalation; these data are summarized in Table 2.

The acute toxicity data on EB in both rat and rabbit via the oral or dermal route indicate the low toxicity of this compound (Table 5). In the study by Wolf, et al. (1956) young adult white rats were intubated via a rubber stomach tube with either undiluted EB or an olive oil or corn oil solution of EB emulsified with a 5 to 10 percent aqueous solution of gum arabic. The total volume administered never exceeded 7 ml. The EB used in these studies was 98 percent pure (ultraviolet and infrared spectroscopy), BP 136.2°C with a specific gravity (20°C) = 0.86.

These authors (Wolf, et al. 1956) also assessed the response of administration of EB on the eyes of rabbits. Two drops of EB were placed on the right eyeball. Observations were made at three minutes; one hour; and one, two, and seven days. A 5 percent flourescein dye solution (water) was used to assess external injury of the cornea (after three minutes). EB produced a slight conjunctival irritation but did not produce any injury to the cornea.

Wolf, et al. (1956) administered EB via the oral route to ten white rats for approximately six months. They received daily single doses of EB (98 percent pure) dissolved in olive oil, five days/week for six months. The total daily volume administered did not exceed 2 to 3 ml. Controls for this study included 20 white

TABLE 5

Acute Toxicity of Ethylbenzene*

Route of Administration	Species	Sex	No. of Animals	LD_{50}
oral	rat	both	57	3.5 gm/kg[a]
oral	rat	male	5	5.46 ml/kg[b]
skin	rabbit	male	4	17.8 ml kg[b]
inhalation	rat	female	6	4000 ppm x 4 hrs.[b]

*Sources:

[a]Wolf, et al. 1956

[b]Smyth, et al. 1962

rats that received 2.5 ml olive oil emulsified in gum arabic. The findings (Table 6) indicate that repeated oral administration of EB produced histopathological changes in both the kidney and the liver at 408 and 680 mg/kg/day. The authors reported that at these doses of EB no effects on the hematopoietic system were observed, as indicated by bone marrow counts of nucleated cells.

Wolf, et al. (1956) also evaluated the ability of EB to produce injury to the skin (rabbit). EB was tested undiluted, 10 to 20 applications to the ear and onto the shaved abdomen for two to four weeks. EB produced moderate "erythemal" edema, superficial necrosis, skin blistering, and chapped appearance and exfoliation of large patches of skin.

The effects of repeated exposures of EB via inhalation are summarized in Table 6. Matched groups of 10 to 25 rats, 5 to 10 guinea pigs, 1 to 2 rabbits, and 1 to 2 rhesus monkeys were used in these studies. Exposure in the chambers was for seven to eight hours daily, five days/week. These authors (Wolf, et al. 1956) concluded that a no effect concentration of EB is 200 ppm (rat, guinea pig, rabbit). Effects with EB were observed at doses equal to or greater than 400 ppm; these effects are primarily only slight changes in liver and kidney weights.

When acutely exposed to ethylbenzene vapors at concentrations of 1,000 to 10,000 ppm, guinea pigs developed leukocytosis (Yant, et al. 1930). Ivanov (1964) reported a study in which rabbits were subchronically exposed to EB via inhalation. The animals were exposed to approximately 230 ppm EB, four hours/day for seven months. This author reported "changes in blood cholinesterase activity,

TABLE 6

Repeated Exposure by Vapor Inhalation to EB in Animals*

Species	Average Vapor Concentrations ppm	mg/l	Sex	7hr. Exposures No.	Duration Days	Effects**
rat	2,200	9.5	male	103	144	G++; Lw+; Kw++; Lp+; Kp+
	1,250	5.4	both	138	214	G±; Lw+; Kw+; Lp+; Kp+
	600	2.6	both	130	186	Lw+; Kw+
	400	1.7	both	130	186	Lw+; Kw+
guinea pig	1,250	5.4	female	138	214	G+
	600	2.6	both	130	186	Lw+
	400	1.7	both	130	186	no effect
rabbit	1,250	5.4	female	138	214	
	600	2.6	both	130	186	Tp+
	400	1.7	both	130	186	no effect
rhesus monkey	600	2.6	both	130	186	Lw+; Tp+
	400	1.7	female	130	186	no effect

*Source: Wolf, et al. 1956

**G = growth depression
w = weight
p = histopathology
L = liver
K = kidney
T = testes

The intensity of response is noted as follows:
± = questionable
+ = slight
++ = moderate

decreased plasma albumin, increased plasma globulins, leukocytosis, reticulocytosis, cellular infiltration and lipid dystrophy in the liver, dystrophic changes in the kidney and muscle chronaxia."

Synergism and/or Antagonism

Pertinent data could not be located in the available literature regarding the possible synergism and/or antagonism of EB with other substances.

Teratogenicity

Pertinent data could not be located in the available literature regarding the terotogenic activity of EB.

Mutagenicity and Carcinogenicity

Pertinent data could not be located in the available literature regarding the mutagenicity of EB, although four common metabolites of EB (d-l-mandelic, phenylglyoxylic, and hippuric acids) gave negative results in the Ames test using the five tester strains (Salmona, et al. 1976).

Pertinent data could not be located in the available literature regarding the carcinogenicity of EB.

Speculation on mutagenic and carcinogenic activities may be appropriate. Gillete, et al. (1974) have reviewed certain considerations of drug toxicity including those related to possible carcinogens. EB or its known metabolites in man and in animals (Bardodej and Bardedjova, 1970; Kiese and Lenk, 1973, 1974; McMahon and Sullivan, 1966) do not fit into any of the presently known physical/chemical categories of mutagenic and/or carcinogenic agents. Although EB metabolites do not show any mutagenic activity, styrene, an EB manufacturing product, can undergo metabolism to

an epoxide intermediate (Salmona, et al. 1976), which is a possible carcinogen and which demonstrates a positive mutagenic response in the Ames test.

CRITERION FORMULATION

Existing Guidelines and Standards

The U.S. Occupational Standard for "permissable" exposure has been set at 100 ppm (435 mg/m^3) (American Conference of Governmental Industrial Hygienists (ACGIH), 1974, 1977; U.S. EPA, 1976; 40 FR 1910.1034). At this level of exposure eye irritation is minimal. The Soviet standards (TLV) for EB are approximately 8-fold less than current U.S. TLV standards (ACGIH, 1974).

Current Levels of Exposure

Air: Several investigators have reported that ethylbenzene is present in the ambient atmosphere at a level of approximately 0.01 ppm. (Altshuller and Bellar, 1963; Lonneman, et al. 1968; Neligan, et al. 1965).

Water: Shackelford and Keith (1976) reviewed the literature on EB contamination and concluded that it was detected in most of the potable waters tested. No data were reported on the levels of EB in potable waters.

Food: With the exception of the report by Kinlan, et al. (1972), EB has not been reported to be present in food.

Industrial: EB can be found in a number of volatile compounds with widespread industrial use (including gasoline and solvents).

Special Groups at Risk

Those individuals who are involved in the use of petroleum by-products, e.g., polymerization workers involved in styrene production, may be at risk. In a study of 494 styrene workers, Lilis, et al. (1978) reported various neurotoxic manifestations. These included prenarcotic symptoms, incoordination, dizziness, headache

and nausea (13 percent of worker group), and a decrease in a radial and peroneal nerve conduction velocity (19 percent of workers). In 50 percent of the workers, distal hypoasthesia involving the lower limbs was observed. It is difficult to assess occupational reports evaluating such a situation since these workers are exposed to a number of different precursors, by-products, and end products. In this particular study, toxic effects were reported, but there was a general lack of symptoms among workers who were exposed for many years, suggesting that the risk of severe neurologic deficiencies may be minimal. Recently, however, Harkonen, et al. (1978) reported on the relationship between styrene exposure and symptoms of central nervous system dysfunction in 98 occupationally exposed workers. Urinary mandelic acid concentration was used as an index of exposure intensity. Although no exposure-response relationship was observed between symptoms of ill health and urinary mandelic acid concentration, the exposed group expressed significantly more symptoms than the unexposed group. Symptoms included abnormal electro-encephalograms, and impaired psychological functions such as visuomotor accuracy and psychomotor performance.

A National Institute for Occupational Safety and Health (NIOSH) report by Rivera and Rostand (1975) on worker exposure to various lacquer constituents (including EB in a baseball bat manufacturing facility) concluded that no health hazard existed with the exception of mucous membrane irritation and the potential for contact dermatitis under the conditions at the plant. This occupational situation again illustrates the fact that these workers were exposed to more than one chemical in addition to EB.

Cigarettes contain 7 to 20 x 10^{-6}g of EB per cigarette (Johnstone, et al. 1962). Conkle, et al. 1975 have reported that moderate cigarette smokers expired up to 14 x 10^{-6} g/hr of EB (during an eight-hour measurement).

Groups of individuals who are exposed to EB to the greatest extent and could represent potential pools for the expression of EB toxicity include: (1) individuals in commercial situations where petroleum products or by-products are manufactured (e.g., rubber or plastics industry); (2) individuals residing in areas with high atmospheric smog generated by motor vehicle emissions.

Basis and Derivation of Criteria

The threshold limit value (TLV) of 435 mg/m^3 (100 ppm) EB represents what is believed to be a maximal concentration to which a worker may be exposed for eight hours per day, five days per week over his working lifetime without hazard to health or well-being (ACGIH, 1977). To the TLV, Stokinger and Woodward (1958) apply terms expressing respiratory volume during an eight hour period (assumed to be 10 m^3) and a respiratory absorption coefficient appropriate to the substance under consideration. In addition, the five-day-per-week occupational exposure is often converted to a seven-day-per-week equivalent in keeping with the more continuous pattern of exposure to drinking water.

According to the model, the amount of ethylbenzene that may be absorbed without effect can be calculated as follows:

435 mg/m^3	X 10 m^3	X 0.5*	X 5/7 week = 1555 mg/day
(TLV)	Respiratory Intake Term	Respiratory Absorption Coefficient	Proportion of week Exposed	Maximum Noninjurious Intake

A safety factor of 1000 is used since no long-term or acute ingestion human data are available, and there is very little information from experimental animals (National Academy of Sciences (NAS), 1977). Thus, 1555 mg/day divided by 1000 = an allowable daily intake (ADI) of 1.555 or 1.6 mg/day.

To calculate an acceptable amount of EB in ambient water, the methodology assumes a maximal daily intake of 2 liters of water per day, the consumption of 6.5 grams of fish/shellfish per day, a bioconcentration factor of 37.5 for fish and 50 percent absorption.

(x)	(2 + 37.5 (0.0065))	0.8*	=	1.6 mg/day
Upper Intake Limit	Oral Intake Term	Gastrointestinal Absorption Coefficient		Maximum Noninjurious Intake

Solving for x, the value derived is 0.89 mg/l. According to Stokinger and Woodward (1958),

> This derived value represents an approximate limiting concentration for a healthy adult population; it is only a first approximation in the development of a tentative water quality criterion....several adjustments in this value may be necessary...Other factors, such as taste, odor and color may outweigh health considerations because acceptable limits for these may be below the estimated health limit.

It should also be noted that the basis for the above recommended limit, the TLV for EB, is the prevention of irritation, rather than chronic effects (ACGIH, 1977). Should chronic effects data become available, both TLVs and recommendations based on them will warrant reconsideration.

*Given the chemical and physical properties of ethylbenzene, these absorption coefficients seem reasonable. They are recognized to be somewhat judgemental due to the limited data; however, their effect on the final criteria is minimal.

A second approach in calculating an allowable daily intake (ADI) level of EB in humans involves the use of the no-observable-adverse-effect level (NOAEL) in the six month toxicity study by Wolf, et al. (1956). Table 6 indicates that 136.0 mg/kg/day of EB produced no observable effects following oral administration in rats. A 70 kg man could then ingest 9,520 mg of EB/day. Using a safety factor of 1,000 (NAS, 1977), this daily intake would be reduced to 9.5 mg of EB/day. Using the same equation as above, assuming 2 liters of water and 6.5 g of fish ingested per day the equation becomes:

$$X\ (2 + 0.0065 \times 37.5) \cdot 0.5 = 9.5$$

$$1.12\ X = 9.5$$

$$X = 8.5\ mg/l$$

Therefore, using two different endpoints a criterion of 1.4 mg/l or 8.5 mg/l was calculated. Although both criteria are defensible, the criterion based on the TLV is recommended for two reasons. First, the animal toxicity study involved an exposure period of only six months. Secondly, the TLV represents a body of human experience with the chemical which is apparently protective. It should be noted that the criteria are not substantially different.

The assumptions used to derive the Acceptable Daily Intake (ADI) were based on the TLV for EB. Several of these assumptions can be supported further by published data: (1) Although the TLV of 435 mg/m^3 was based on irritation, Bardodej and Bardedjova (1970) reported a NOEL of 370 mg/m^3, with higher levels causing fatigue, sleepiness, and headache, in addition to eye and respiratory tract irritation; (2) although a 50 percent inhalation

absorption factor was used, Bordodej and Bardedjova (1970) reported that 64 percent of the EB vapor was retained (absorbed) in the respiratory tract; (3) the Wolf, et al. (1956) dosing study, upon which a no-effect dose level for EB-contaminated water is based, was carried out with ethylbenzene dissolved in olive oil. It has been demonstrated (Withey, 1976a,b) that the rate and extent of uptake from the G.I. tract of lipid soluble compounds is greatly reduced when solutions in vegetable oil rather than water are used; (4) a safety factor of 1,000 was used since no chronic toxicity studies or reports on the teratogenicity, mutagenicity or carcinogenicity of EB are available; and (5) extrapolating the dose effects from rat to man based on the no-effect data of Wolf, et al. (1956) assumes, in part, equal absorption, distribution and excretion of EB. Extensive animal data are necessary before a definitive value can be determined. It is to be stressed that this criterion is based on inadequate chronic effects data and should be re-evaluated upon completion of chronic oral toxicity studies.

In summary, based on a threshold limit value and an uncertainty factor of 1,000, the criterion level for ethylbenzene corresponding to the calculated acceptable daily intake of 1.6 mg/day is 1.4 mg/l. Drinking water contributes 89 percent of the assumed exposure, while eating contaminated fish products accounts for 11 percent. The criterion level can alternatively be expressed as 3.28 mg/l if exposure is assumed to be from the consumption of fish and shellfish products alone.

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