ETHYLBENZENE

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

CRITERION DOCUMENT

ETHYLBENZENE

CRITERIA

Aquatic Life

For freshwater aquatic life, no criterion for ethylbenzene can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

For saltwater aquatic life, no criterion for ethylbenzene can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the protection of human health from the toxic properties of ethylbenzene ingested through water and contaminated aquatic organisms, the ambient water quality criterion is 1.1 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 1976 was approximately 6 to 7 billion pounds of which about 98 percent was used in the manufacture of styrenes (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 found, there exist many environmental sources for ethylbenzene, e.g., vaporization during solvent use, pyrolysis of gasoline and emitted vapors at filling stations.

Ehtylbenzene ($C_6H_5C_2H_5$, molecular weight 106.16) is a flammable, colorless liquid with a boiling point of 136.25° C and a freezing poınt 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). Vapor pressures range from 7 to 15.3 mm Hg at 20° C (Am. Hyg. Assoc., 1957) to 20 mm Hg at 38.6° C (Cier, 1970). Ethylbenzene is slightly soluble (less than 0.1 percent or 866 mgl) in water (Hann and Jensen, 1970), but ıt is freely soluble in organic solvents (Windholz, 1976).

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

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

Acute Toxicity

Pickering and Henderson (1966) conducted 96-hour tests with the goldfish, fathead minnow, guppy, and bluegill and the unadjusted LC50 values ranged from 32,000 to 97,100 µg/l (Table 1). The two bluegill LC50 values, 32,000 and 155,000 µg/l, do not agree well but no explanation is available. After adjustment for test procedures and species sensitivity, the Final Fish Acute Value based on these data is 10,000 µg/l.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] 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 the calculations for deriving various measures of toxicity as described in the Guidelines.

An acute test with Daphnia magna (U.S. EPA, 1978) resulted in an unadjusted 48-hour EC50 value of 75,000 µg/l (Table 2). The Final Invertebrate Acute Value is 3,000 µg/l and this also becomes the Final Acute Value since the comparable concentration for fish is higher.

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 3). This datum results in a Final Fish Chronic Value greater than 33 µg/l.

Plant Effects

No adverse effects on cell number or chlorophyll a production of Selenastrum capricornutum were observed at test concentrations as high as 438,000 µg/l (Table 4).

Residues

No measured steady-state bioconcentration factor (BCF) is available for ethylbenzene. A BCF can be estimated using the octanol-water partition coefficient of 1,400. This coefficient is used to derive an estimated BCF of 150 for aquatic organisms that contain about 8 percent lipids. If it is known that the diet of the wildlife of concern contains a significantly different lipid content, an appropriate adjustment in the estimated BCF should be made.

CRITERION FORMULATION

Freshwater Aquatic-Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 10,000 µg/l

Final Invertebrate Acute Value = 3,000 µg/l

Final Acute Value = 3,000 µg/l

Final Fish Chronic Value = greater than 33 µg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = greater than 440,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = greater than 33 µg/l

0.44 x Final Acute Value = 1,300 µg/l

No freshwater criterion can be derived for ethylbenzene using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 1. Freshwater fish acute values for ethylbenzene

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Goldfish, Carassius auratus	S	U	96	94,440	51,630	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S	U	96	48,510	26,520	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S	U	96	42,330	23,140	Pickering & Henderson, 1966
Guppy, Poecilia reticulatus	S	U	96	97,100	53,080	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S	U	96	32,000	17,490	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S	U	96	155,000	84,700	U.S. EPA, 1978

* S = static

** U = unmeasured

Geometric mean of adjusted values: 40,200 µg/l $\frac{40,200}{3\ 9}$ = 10,000 µg/l

Table 2. Freshwater invertebrate acute values for ethylbenzene (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Cladoceran, *Daphnia magna*	S	U	48	75,000	64,000

* S = static

** U = unmeasured

Geometric mean of adjusted values = 64,000 µg/l $\frac{64,000}{21}$ = 3,000 µg/l

Table 3. Freshwater fish chronic values for ethylbenzene (U.S. EPA, 1978)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
Fathead minnow, *Pimephales promelas*	E-L	>440	>220

* E-L = embryo-larva

Geometric mean of chronic values = >220 µg/l $\frac{>220}{6.7}$ =>33 µg/l

Lowest chronic value = >220 µg/l

Table 4. Freshwater plant effects for ethylbenzene (U.S. EPA, 1978)

Organism	Effect	Concentration (ug/l)
Alga, *Selenastrum capricornutum*	EC50 96-hr chlorophyll *a*	>438,000
Alga, *Selenastrum capricornutum*	EC50 96-hr cell numbers	>438,000

Lowest plant value = >438,000

SALTWATER ORGANISMS

Introduction

The sheepshead minnow, a mysid shrimp, Mysidopsis bahia, and an alga, Skeletonema costatum, have been acutely exposed to ethylbenzene and the lowest 50 percent effect concentration was 87,600 µg/l.

Acute Toxicity

The unadjusted 96-hour LC50 for the sheepshead minnow is 275,000 µg/l (Table 5) and after adjustment of this concentration for test methods and species sensitivity the Final Fish Acute Value of 41,000 µg/l is obtained.

As with fish, only one test has been conducted with a saltwater invertebrate species. The Final Invertebrate Acute Value derived from the 96-hour LC50 for the mysid shrimp (87,600 µg/l) is 1,500 µg/l (Table 2). Since this concentration is lower than the equivalent value for fish, it also becomes the Final Acute Value.

Chronic Toxicity

No chronic tests have been conducted with saltwater organisms and ethylbenzene.

Residues

No measured steady-state bioconcentration factor (BCF) is available for ethylbenzene. A BCF can be estimated using the octanol-water partition coefficient of 1,400.[--] This coefficient is used to derive an estimated BCF of 150 for aquatic organisms that contain about 8 percent lipids. If it is known that the diet of the wildlife of concern contains a significantly different lipid content, an appropriate adjustment in the estimated BCF should be made.

CRITERION FORMULATION

Saltwater Aquatic-Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 41,000 µg/l

Final Invertebrate Acute Value = 1,500 µg/l

Final Acute Value = 1,500 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = greater than 440,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = greater than 440,000 µg/l

0.44 x Final Acute Value = 660 µg/l

No saltwater criterion can be derived for ethylbenzene using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 5. Marine fish acute values for ethylbenzene (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Sheepshead minnow, Cyprinodon variegatus	S	U	96	275,000	150,343

* S = static

** U = unmeasured

Geometric mean of adjusted values: 150,343 µg/l $\frac{150,343}{3.7}$ = 41,000 µg/l

Table 6: Marine invertebrate acute values for ethylbenzene (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Mysid shrimp, *Mysidopsis bahia*	S	U	96	87,600	74,197

* S = static

** U = unmeasured

Geometric mean of adjusted values: 74,197 µg/l $\frac{74,197}{49}$ = 1,500 µg/l

Table 7. Marine plant effects for ethylbenzene (U.S. EPA, 1978)

Organism	Effect	Concentration (ug/l)
Alga, *Skeletonema costatum*	EC50 96-hr chlorophyll *a*	>438,000
Alga, *Skeletonema costatum*	EC50 96-hr cell numbers	>438,000

Lowest plant value = >438,000

ETHYLBENZENE

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Mammalian Toxicology and Human Health Effects

Summary

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 Values (TLV's). The EPA proposed to evaluate the carcinogenic potential of 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,

2) liver disease,

3) chronic respiratory disease,

4) skin disease.

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

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

3) Exacerbation of pulmonary pathology might occur following exposure to EB. Individuals with impaired pulmonary function might be at risk.

4) 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

Introduction

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 1976 was 7.2×10^9 lbs (Table 1). 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.

Ethylbenzene - Chemical Structure

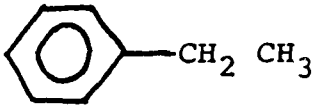

TABLE 1

Possible Environmental Sources of Ethylbenzene
*U.S. International Trade Commission 1976.

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

TABLE 2

Ethylbenzene / Physical Properties[a]

Molecular weight	106.17
Color	colorless
Boiling Point, 760 torr	136.2 C
Freezing Point	-95° C
Flashpoint	16° C
Density (gm/ml) @ 20° C	0.87
Vapor Pressure, torr	20 at 38.6° C
Water Solubility wt. %	0.02[bc]

[a]Taken from Cier (1970); Gerarde (1963).

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

[c]EB water solubility 161 ppm at 25° C in distilled water
111 ppm at 25° C in seawater

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 10^{-6}g/l. 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 Foods

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 water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble

compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

No measured steady-state bioconcentration factor (BCF) is available for ethylbenzene, but the equation "Log BCF = 0.76 Log P - 0.23" can be used (Veith, et al. Manuscript) to estimate the BCF for aquatic organisms that contain about eight percent lipids from the octanol-water partition coefficient (P). Based on an octanol-water partition coefficient of 1,400, the steady-state bioconcentration factor for ethylbenzene is estimated to be 145. An adjustment factor of

2.3/8.0 = 0.2875 can be used to adjust the estimated BCF from the 8.0 percent lipids on which the equation is based to the 2.3 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 aquatic organimsm consumed by Americans is calculated to be 145 x 0.2875 = 42.

Inhalation

EB probably represents about 10 percent of the total aromatic compounds detected in the air, and roughly one percent of the total carbon 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 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 3) 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 LD50 for EB (via skin application) in rabbits of 17.8 ml/kg.

TABLE 3

Skin Absorption of EB in Man
(Dutkiewicz and Tyras, 1968)

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

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 3).

EB is readily absorbed by inhalation (see Table 6). 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 presented in a modified form from the work of Kiese and Lenk (1974) (Table 4). This metabolic outline is consistent with reports on the metabolic fate 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 4 indicate that the major metabolites of EB are 1-phenylethanol, hippuric acid and phenaceturic acid.

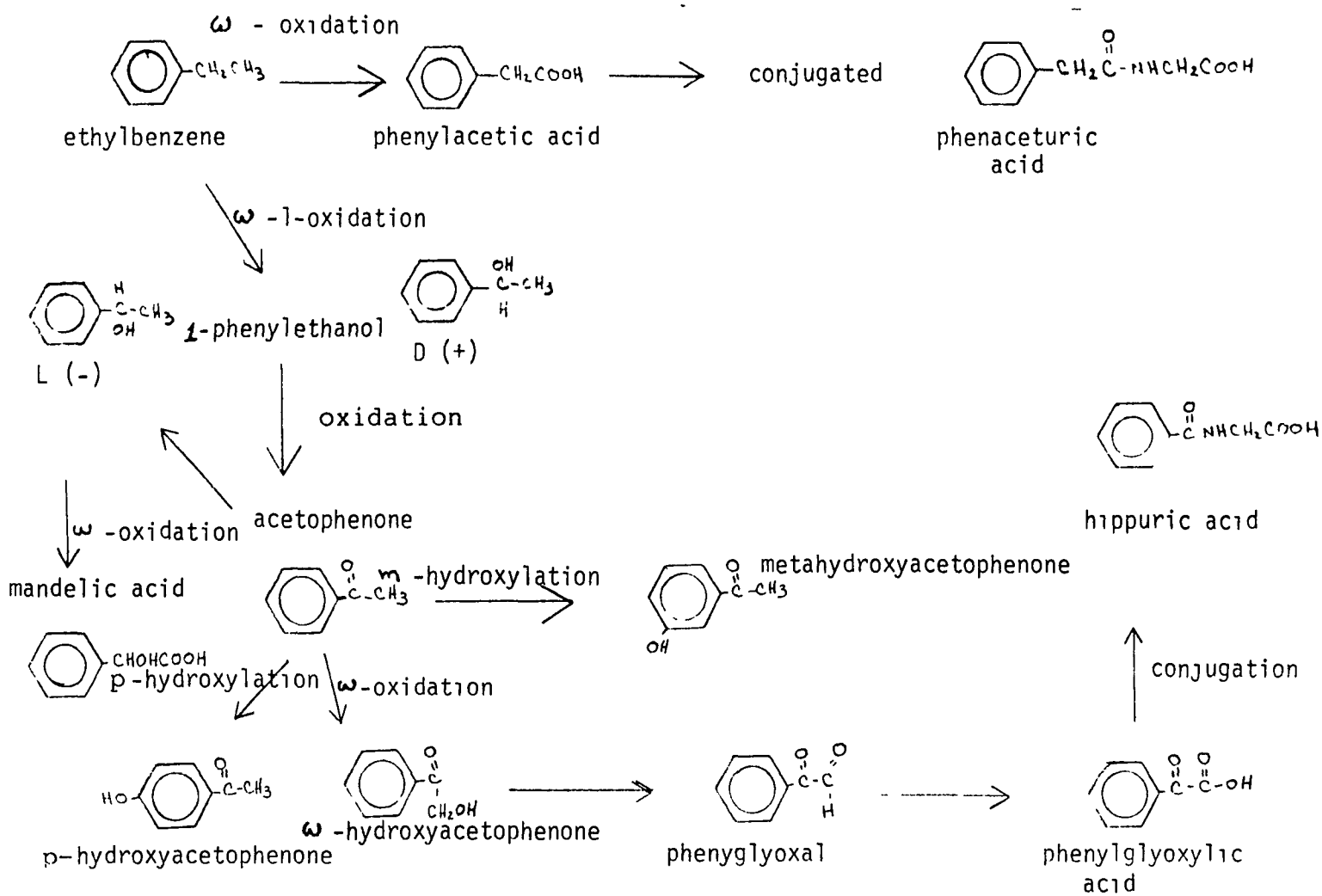

Figure 1: Metabolic Pathways of Ethylbenzene
(Based on Kiese and Lenk, 1974)

TABLE 4

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(-)]

*These data are abstracted from Figure 1 of the report by Kiese and Lenk (1974). Similar data were obtained by El Masry, et al. (1956).

The study reported in Table 5 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, w-hydroxyacetophenone, hippuric acid and mercapturic acid. Despite these shortcomings, this study contributes to our understanding of EB

TABLE 5

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 at 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%

*Based on Bardodej and Bardedjova (1970).

metabolism in man. A considerable amount of EB was absorbed in the respiratory tract; only traces of EB were expired at the end of the experiment (Table 5). The major metabolites found in the urine included mandelic and phenylglyoxylic acid, 64 percent and 25 percent respectively, and 1-phenyl-ethanol, 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, sleepiness, headache, and mild irritation of the eyes and respiratory tract.

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

Gerarde (1959) has reviewed the acute toxicity data in humans to EB via inhalation; these data are summarized in Table 6.

TABLE 6

Human Response to Ethylbenzene Vapors
(Gerarde, 1959)

Concentration mg/l	Concentration p.p.m.	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.

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 7). 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 five to ten 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.

TABLE 7

Acute Toxicity of EB

Route of Administration	Species	Sex	No. of Animals	LD50
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]

(a) Wolf, et al. (1956)

(b) Smyth, et al. (1962)

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 five 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 for approximately six months to ten white rats. They received a daily single dose 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 rats that received 2.5 ml olive-oil emulsified in gum arabic. The findings (Table 8) 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.

TABLE 8

Repeated Oral Dosing of EB
(Wolf, et al. 1956)

Dose (mg/kg/day)	No. of Feedings	Days of Exposure	Effects
13.6	130	182	No effects
136	130	182	No effects
408	130	182	Positive Findings[a]
680	130	182	

[a]Positive findings: (1) slight increase in liver and kidney weights; (2) histopathological changes in liver and kidney which include cloudy swelling of liver parenchymal cells and of the tubular epithelium in the kidney. No hematopoietic effects were observed.

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; chapped appearance and exfoliation of large patches of skin and skin blistering were also observed.

The effects of repeated exposures of EB via inhalation are summarized in Table 9. 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 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 include primarily changes (slight) 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

TABLE 9

Repeated Exposure by Vapor Inhalation to EB in Animals*

Species	Average Vapor Concentrations ppm	mg/l	Sex	7hr. Exposures No.	Duration Days	Effects
rat	2200	9.5	male	103	144	moderate growth depression, slight and moderate increase of liver and kidney weights (respectively) and slight histopathological changes in liver and kidney
	1250	5.4	both	138	214	questionable growth depression, slight and moderate increase in liver and kidney weights (respectively) and slight histopathological changes in liver and kidney
	600	2.6	both	130	186	slight change in liver and kidney weights
	400	1.7	both	130	186	slight change in liver and kidney weights
guinea pig	1250	5.4	male	138	214	moderate growth depression
	600	2.6	both	130	186	slight liver weight change
	400	1.7	both	130	186	no effect
rabbit	1250	5.4	male	138	214	not reported
	600	2.6	both	130	186	slight testicular histopathology
	400	1.7	both	130	186	no effect
rhesus monkey	600	2.6		130	186	slight testicular histopathology; slight change in liver weight
	400	1.7		130	186	no effect

*Modified from Wolf, et al. (1956)

"changes in blood cholinesterase activity, 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

No published information is available on the possible synergism and/or antagonism of EB with other substances.

Teratogenicity

No reports on the teratogenic activity of EB are available.

Mutagenicity

There are no available data on the mutagenicity of EB, though four common metabolites of EB (D and L mandelic, phenylglyoxylic, and hippuric acids) gave negative results in the Ames test using the five tester strains (Salmona, et al. 1976).

Carcinogenicity

There is no available information on the carcinogenicity of EB.

Possibility of Mutagenic and /or Carcinogenic Activity of EB

As mentioned above, there are no data on the mutagenic and/or carcinogenic potential of EB. However, speculation on such a possibility 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) (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 eight-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 found in most of the potable waters tested. No data were reported on the levels of EB in potable waters.

Food: Except for 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 electroencephalograms, and impaired psychological functions such as visuomotor accuracy and psychomotor performance.

A 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 Criterion

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 (Amer. Conf. Gov't. Ind. Hyg., 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 taken into the bloodstream and presumed to be noninjurious and which, hence, may be taken in water each day is:

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 human data are available, and there is very little information from experimental animals (Natl. Acad. Sci., 1977). Thus, 1555 mg/day divided by 1000= 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 18.7 grams of fish/shell-fish per day, a bioconcentration factor of 42 for fish and 50 percent absorption.

(x) (2 + 42 (0.0187)) 0.5 = 1.6 mg/day

Upper Intake Limit --	Oral Intake Term	Gastrointestinal Absorption Coefficient	Maximum Noninjurious Intake

Solving for x, the value derived is 1.1 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 avoidance of irritation, rather than chronic effects (Am. Conf. Ind. Hyg., 1977). Should chronic effects data become available, both TLV's and recommendations based on them will warrant reconsideration.

A second approach to calculating a maximum noninjurious level of EB in humans involves the use of the no observable adverse effect level in the six month toxicity study by Wolf, et al. 1956. Table 8 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 10^3 (Natl. Acad. Sci., 1977), this daily intake would be reduced to 9.5 mg/EB/day. Using the same equation as above, assuming 2 liters of water and 18.7g of fish ingested per day the equation becomes:

$$X\ (2 + 0.0187 \times 42) \cdot 0.5 = 9.5$$

$$1.39\ X = 9.5$$

$$X = 6.8\ mg/l$$

Therefore, using two different endpoints a criterion of 1.1 mg/l or 6.8 mg/l was calculated. The lower level will be selected for the protection of public health.

It should be stated at this point that several important assumptions were made in order to arrive at the Acceptable Daily Intake (ADI). These include the facts that 1) the TLV for EB was arrived at based on irritation; 2) no published data exist on the percentage of EB absorbed; 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) 10^3 safety factor was used since no chronic toxicity studies or reports on the teratogenicity, mutagenicity or carcinogenicity of EB are available; 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 1000, the criterion level for ethylbenzene corresponding to the calculated acceptable daily intake of 1.6 mg/day, is 1.1 mg/l. Drinking water contributes 72 percent of the assumed exposure while eating contaminated fish products accounts for 28 percent. The criterion level can alternatively be expressed as 2.0 mg/l if exposure is assumed to be from the consumption of fish and shellfish products alone.

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