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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. 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. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. 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, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD 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. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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HEALTH EFFECTS ASSESSMENT FOR TRIMETHYLBENZENES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with trimethylbenzenes. All estimates of acceptable intake and carcinogenic potency presented in this document should be considered as preliminary reflecting limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. 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 intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens 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 or risk associated with exposure 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, RfD_S (formerly AIS) or subchronic reference dose, 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 RFD_S 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. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. 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 (1980) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) 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 identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, 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.

Very few data were located regarding the toxicity of the trimethylbenzenes to either animals or humans. ACGIH (1980, 1985) recommended a TLV of 25 ppm (~125 mg/m^3) based on inadequate animal and human data. However, lack of a pertinent toxicity data base in support of the TLV precludes the use of the TLV to derive an RfD_O or RfD_I. Data were not sufficient for computation of a CS.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CS	Composite score
K_{oc}	Soil sorption coefficient
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
SGOT	Serum glutamic oxaloacetic transaminase
STEL	Short-term-exposure level
TLV	Threshold limit value
WBC	White blood cells

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties of 1,2,3-trimethylbenzene, 1,2,4-trimethylbenzene and 1,3,5-trimethylbenzene are listed in Table 1-1.

In the atmosphere the trimethylbenzene compounds are expected to exist primarily in the vapor phase. The atmospheric half-lives listed in Table 1-1 were calculated using measured HO radical reaction rate constants of 26.4×10^{-12} cm^3/molecule/sec for 1,2,3-trimethylbenzene at 24°C, 33.5×10^{-12} cm^3/molecule-sec for 1,2,4-trimethylbenzene at 23.8°C, and 47.2×10^{-12} cm^3/molecule-sec for 1,3,5-trimethylbenzene at 24°C (Atkinson, 1985) and assuming an ambient HO radical concentration of 10^6 molecules/cm^3.

In water, volatilization and biodegradation may be important fate processes for the trimethylbenzenes (Wakeham et al., 1983). With respect to volatilization, approximate residence times for 1,3,5-trimethylbenzene in water from Narragansett Bay, RI, were estimated to be 220 hours (Wakeham et al., 1983). Zoeteman et al. (1980) estimated the half-life of 1,3,5-trimethylbenzene in Rhine River surface water (Netherlands) to be ~1 day. Based on recommended values for Henry's Law constant of 3.19×10^{-3}, 5.18×10^{-3} and 5.92×10^{-3} atm-m^3/mol at 25°C for 1,2,3-, 1,2,4,- and 1,3,5-trimethylbenzene, respectively, volatilization half-lives from a body of water 1 m deep flowing 1 m/sec with a wind speed of 3 m/sec were calculated to be 3.6 hours for 1,2,3-trimethylbenzene and 3.4 hours for 1,2,4- and 1,3,5-trimethylbenzene (Lyman et al., 1982; U.S. EPA, 1986b). Estimated BCF and K_{oc} values that suggest that bioaccumulation in aquatic organisms would be insignifi ant and that moderate adsorption to suspended solids and sediments may occur. The half-lives of the trimethylbenzenes in

TABLE 1-1

Selected Chemical and Physical Properties of Trimethylbenzene Isomers

Property	1,2,3-Tri-methylbenzene	1,2,4-Tri-methylbenzene	1,3,5-Tri-methylbenzene	Reference
CAS number:	526-73-8	95-63-6	108-67-8	
Chemical class:	alkylbenzene	alkylbenzene	alkylbenzene	
Molecular weight:	120.19	120.19	120.19	
Vapor pressure at 25°C:	1.5 mm Hg	2.03 mm Hg	2.5 mm Hg	Mackay and Shiu, 1981; U.S. EPA, 1986b
Water solubility at 25°C:	75 mg/ℓ	52-57 mg/ℓ	48-97 mg/ℓ	Mackay and Shiu, 1981; U.S. EPA, 1986b
Log octanol/water partition coefficient:	3.66	3.78	3.42-3.84	Hansch and Leo, 1985; U.S. EPA, 1986b
Bioconcentration factor:	356 (estimated)	439 (estimated)	234 (estimated)	Lyman et al., 1982
Soil adsorption coefficient:	406 (estimated)	472 (estimated)	353 (estimated)	Lyman et al., 1982
Half-lives:				
air	~7 hours	~6 hours	~4 hours	Atkinson, 1985
water	<1 day to <1 week	<1 day to <1 week	<1 day to <1 week	Lyman et al., 1982; Wakeham et al., 1983; Zoeteman et al., 1980
soil	NA	NA	NA	

NA = Not available

soil could not be located in the available literature. Based on aquatic data, both vaporization and biodegradation are expected to play significant roles in determining the half-lives of these compounds in soil; because of their estimated K_{oc} values, they are expected to be moderately mobile in soil (see Table 1-1).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Gerarde (1959) reported that alkylbenzenes are "absorbed into the blood from the various portals of entry." In addition, the rate of absorption and peak concentrations of aklylbenzenes in the blood appear to be porportional to their solubility in water (Gerarde, 1959).

In a discussion of the comparative metabolism of 1,3,5-, 1,2,4- and 1,2,3-trimethylbenzene, Mikulski and Wiglusz (1975) reported that 93.7, 62.6, and 56.6% of a single oral 1.2 g/kg dose of 1,3,5-, 1,2,4- and 1,2,3-trimethylbenzene, respectively, was excreted as metabolites in the urine of male Wistar rats over a period of 3 days. These figures may not be accurate estimates of absorption, since pulmonary, fecal, and biliary excretion were not monitored. In general, alkylbenzenes are excreted unchanged from the lung or as biotransformation products in the urine (Gerarde, 1959). The data suggest, however, that absorption is substantial following oral administration.

2.2. INHALATION

Except for the general information reported by Gerarde (1959), quantitative data regarding the absorption of inhaled trimethylbenzenes could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Oral subchronic studies regarding trimethylbenzenes could not be located in the available literature.

3.1.2. Inhalation. The only subchronic inhalation studies regarding trimethylbenzenes are abstracts from the foreign literature.

Bernshtein (1972) reported that phagocytic activity of leukocytes was inhibited in rats after inhalation of a mixture of trimethylbenzenes (1 mg/ℓ, 1000 mg/m³) 4 hours/day, 6 days/week for 6 months. This study was summarized in Sandmeyer (1981); further details were not provided.

Wiglusz et al. (1975a,b,) reported "slight" alteration in differential WBC count and elevated SGOT in male rats that had been exposed to 1,3,5-trimethylbenzene (3 mg/ℓ, 3000 mg/m³) 6 hours/day, 6 days/week for 5 weeks. No other details were reported.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding chronic oral exposure to trimethylbenzenes could not be located in the available literature.

3.2.2. Inhalation. Battig et al. (1957) reported symptoms of nervousness, tension, anxiety and asthmatic bronchitis in a "significant number" of 27 people who worked for several years with "Fleet-x-DV-99," a solvent containing 30% 1,3,5-trimethylbenzene and 50% 1,2,4-trimethylbenzene. Tendencies toward hyperchromic anemia and blood coagulation were also observed among these individuals. Concentration ranges for hydrocarbon vapor ranged from 10-60 ppm. Gerarde (1960) speculated that a small proportion of benzene in the hydrocarbon vapor was probably responsible for the hematologic effects.

Pertinent data regarding the toxicity to animals of chronically inhaled trimethylbenzenes could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the teratogenicity or reproductive effects associated with either inhaled or ingested trimethylbenzenes could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Benzene and its methyl derivatives are metabolized to derivatives of phenol and hippurate. Oral administration of benzene along with either 1,2,3- or 1,3,5-trimethylbenzene resulted in a higher concentration of phenol in the blood than when benzene was administered alone. Hippuric acid levels in the blood were also elevated when benzene was administered together with 1,2,3-trimethylbenzene, but were decreased when benzene was administered with 1,3,5-trimethylbenzene (Mikulski et al., 1979).

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenicity of trimethylbenzenes to humans from oral or inhalation exposure could not be located in the available literature. Thus, trimethylbenzenes are best classified in EPA Group D, not classified (U.S. EPA, 1986).

4.2. BIOASSAYS

Pertinent data regarding oral or inhalation cancer experiments in animals could not be located in the available literature. Trimethylbenzenes have not been recommended for testing (NTP, 1986).

4.3. OTHER RELEVANT DATA

Other relevant data regarding the carcinogenicity or mutagenicity of trimethylbenzenes could not be located in the available literature.

4.4. WEIGHT OF EVIDENCE

IARC has not evaluated the weight of evidence for carcinogenicity to humans of the trimethylbenzenes; because data are inadequate, an IARC classification of Group 3 is most appropriate. According to the EPA guidelines for evaluating the weight of evidence (U.S. EPA, 1986), an EPA classification of Group D (not classified) best reflects the lack of carcinogenicity test data.

5. REGULATORY STANDARDS AND CRITERIA

ACGIH (1980, 1985) recommended a TLV of 25 ppm (125 mg/m^3) with a STEL of 35 ppm (170 mg/m^3) for occupational exposure to trimethylbenzenes. These recommendations were based on the study of Battig et al. (1957) (see Section 3.2.2.). In this study, the workers were exposed to a solvent containing a mixture of aromatic hydrocarbons (50% pseudocumene, 30% mesitylene and other hydrocarbons such as 1,2,3-trimethylbenzene and 1-methyl-4-ethylbenzene). Since a pure chemical was not used in the study, a LOAEL cannot be obtained. Therefore, a lifetime health advisory cannot be derived for lack of data from adequate studies.

The Office of Toxic Substances (OTS) is also recommending testing for this chemical under TSCA Section 4 Test Rules at the present time.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). There are no data from which to derive an RfD_{SO} for trimethylbenzenes.

6.1.2. Inhalation (RfD_{SI}). The subchronic inhalation data consist only of three abstracts from the foreign literature (Bernshtein, 1972; Wiglusz et al., 1975a,b). Each abstract reported only a single level of exposure at which effects were seen. Information regarding the use of controls or other levels of exposure was not provided. These studies are not adequate for quantitative risk assessment.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_O). There are no data from which to derive an RfD_O or CS for trimethylbenzenes.

6.2.2. Inhalation (RfD_I). There are no adequate subchronic or chronic inhalation data that define dose-specific adverse effects; therefore, an RfD_I or a CS for trimethylbenzene cannot be derived.

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