SRC TR 81-526

SECOND DRAFT

Information Profiles on Potential Occupational Hazards: Trimethylbenzenes

Center for Chemical Hazard Assessment
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16. Abstract (Limit: 200 words)

Information on potential occupational hazards from hemimellitene (526738), pseudocumene (95636), and mesitylene (108678) was reviewed. Topics discussed included chemical and physical properties, production, use, manufacturers and distributors, manufacturing processes, occupational exposures and biological effects. Studies indicated that these compounds enter the body primarily through inhalation but can also be absorbed through the skin. Central nervous system depression, irritation of mucous membranes, and respiratory irritation have been caused by exposure to these chemicals in experimental animals. Pneumonitis, edema, tissue necrosis and hemorrhage of the lungs have been brought about by the aspiration of liquid trimethylbenzenes. The use of an organic solvent containing 50 percent pseudocumene, 30 percent mesitylene, and traces of hemimellitene caused hypochromic anemia, hemopoietic disturbances, chronic asthmatic bronchitis, and central nervous system depression in humans. Rabbits receiving subcutaneous injections of mesitylene and pseudocumene experienced temporary leukopenia and thrombocytopenia plus a reduction in erythrocytes. Hemimellitene was used in the making of polyfunctional acids and miscellaneous chemical syntheses. The major use for this chemical was in automobile gasoline. Pseudocumene was used in the production of trimellitic-anhydride and pseudocumidene, a dye intermediate. It was also present in most automobile fuels. Mesitylene was used in paint thinners and solvents, in the production of trimesic-acid, and in stabilizers for plastics.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms

NIOSH-Publication, NIOSH-Contract, Contract-210-79-0030, Plastics-industry, Inhalants, Chemical-manufacturing-industry, Benzenes, Paint-manufacturing-industry, Dye-industry, Occupational-exposure, Toxic-effects

c. COSATI Field/Group

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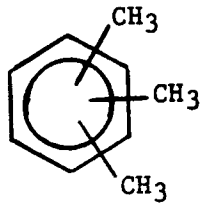
I. SCOPE OF DOCUMENT AND SUMMARY OF MAJOR FINDINGS

A. CLASS IDENTIFICATION

The trimethylbenzenes are identified chemically as a benzene ring that contains three methyl functional groups attached to any of the six possible ring positions; this is shown by the following general chemical structure:



Although trimethylbenzenes may contain heteroatoms such as chlorine, the trimethylbenzenes contained in these profiles do not contain any heteroatoms.

B. CHEMICALS TO BE ADDRESSED

Only three trimethylbenzenes are structurally possible, and all have been treated in individual profiles. They are as follows:

1,2,3-Trimethylbenzene (hemimellitene)
1,2,4-Trimethylbenzene (pseudocumene)
1,3,5-Trimethylbenzene (mesitylene)

C. SUMMARY OF BIOLOGICAL ACTIVITY

The three isomers of trimethylbenzene appear to be toxicologically and pharmacologically very similar. They are absorbed primarily by inhalation of vapors and, less readily, through the intact skin. Acute and chronic exposures of experimental animals to the chemicals result in central nervous system depression, irritation of mucous membranes, and respiratory irritation. Aspiration of liquid trimethylbenzenes can cause pneumonitis, edema, tissue necrosis, and hemorrhage of the lungs.

In humans, hypochromic anemia, hemopoietic disturbances, chronic asthmatic bronchitis, and central nervous system depression resulted from the chronic inhalation of an industrial solvent that contained 50% 1,2,4-trimethylbenzene,

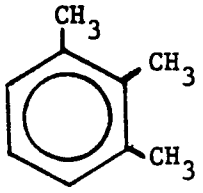
30% 1,3,5-trimethylbenzene, and traces of 1,2,3-trimethylbenzene. Temporary leukopenia and thrombocytopenia and a reduction in erythrocytes have been reported in rabbits following subcutaneous injection of the 1,3,5- and 1,2,4-trimethylbenzene isomers; however, the hemopoietic disturbances observed in humans following exposure to the solvent may have been due to small proportions of benzene, which was present as a contaminant.

II. INFORMATION PROFILES

A. 1,2,3-TRIMETHYLBENZENE

1. Chemical Name: 1,2,3-Trimethylbenzene

2. Chemical Structure:



3. Synonyms: Hemimellitene
Benzene, 1,2,3-trimethyl

4. Chemical Abstracts Service (CAS) Number: 526-73-8

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

DC3300000

6. Chemical and Physical Properties:

Description:	colorless liquid
Molecular Weight:	120.20
Boiling Point:	176°C
Melting Point:	-25.5°C
Vapor Pressure:	1 mm Hg (16.8°C); 10 mm Hg (55.9°C)
Solubility:	nearly insoluble in water miscible with alcohol, ether, acetone, benzene, CCl_4, petroleum ether
Specific Gravity:	0.8944 (20°C)
Stability:	combustible; flash point: 128°F (TCC)

7. Production

As of 1968, production of 1,2,3-trimethylbenzene as an end-use product had not achieved significant commercial status (Earhart, 1968).

Data from the U.S. EPA (1980) list Sun Petroleum (Corpus Christi, TX) as a manufacturer of 1,2,3-trimethylbenzene with a production range between 0.1 and 1.0 million pounds in 1977.

8. Use

1,2,3-Trimethylbenzene is used in the production of polyfunctional acids and miscellaneous syntheses (Sun Oil Co., n.d.). It can also be used as a chemical intermediate in the production of hemimellitic anhydride (Towle et al., 1968).

A major use of 1,2,3-trimethylbenzene is its use (or presence) in automobile gasoline; this application represents a potential source of exposure to the chemical. 1,2,3-Trimethylbenzene is a small-volume component that is present in most automobile fuels. Ioffe et al. (1978) identified 1,2,3-trimethylbenzene and many other hydrocarbons in analyses of air from six Soviet cities. The hydrocarbon composition in the air differed significantly from exhaust gas compositions, but was very close to the composition of motor fuel. The role of gasoline evaporation during transport and storage was suggested.

9. Manufacturers and Distributors

SRI International (1980) lists Aldrich Chemical (Milwaukee, WI) and Sun Petroleum (Sun Oil, Corpus Christi, TX) as manufacturers. USITC (1980) and the U.S. EPA (1980) list only Sun as a manufacturer.

1,2,3-Trimethylbenzene (hemimellitene) is distributed by, in addition to the manufacturers (1980-81 OPD Chemical Buyers Directory, 1980; Chem Sources--USA, 1980):

Alfa Prod.	Chemsampo Inc.
API Standard Reference Mat.- Carnegie-Mellon Univ.	Columbia Organic Chem.
Bio-Clinical Lab.	Fallek Chem.
Chemical Procurement Labs	ICN/K and K
	Tridom Chem.

10. Manufacturing Processes

Large amounts of 1,2,3-trimethylbenzene are present in the aromatics that exist in crude oils and in catalytic reformates; for example, 8.2% of the C_9 aromatics present in catalytic reformates is 1,2,3-trimethylbenzene

(Earhart, 1968). It is not economically feasible, however, to recover this 1,2,3-trimethylbenzene from the catalytic reformate (Earhart, 1960).

1,2,3-Trimethylbenzene can be manufactured by the catalytic isomerization of pseudocumene (1,2,4-trimethylbenzene) in either liquid or vapor phase. It can also be made by the catalytic methylation of xylenes with methyl chloride (Earhart, 1960).

11. Impurities or Additives

Commercial grade 1,2,3-trimethylbenzene contains 90.5% hemimellitene, 4.0% pseudocumene, and 5.5% other C_9-C_{10} aromatics (Lilley, 1972).

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 1,2,3-trimethylbenzene.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1,2,3-trimethylbenzene were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Gerarde (1960) stated that a single oral administration of 4472 mg/kg 1,2,3-trimethylbenzene in rats was lethal. Direct contact of the liquid with mucous membranes or skin causes vasodilation, erythema, and irritation (Gerarde, 1959). Chemical pneumonitis characterized by pulmonary edema, hemorrhage, and tissue necrosis results from direct contact of the liquid with pulmonary tissue (Gerarde, 1959).

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

1,2,3-Trimethylbenzene is absorbed by inhalation of the vapor, from the gastrointestinal tract, and, less readily, through intact skin (Gerarde, 1959). 1,2,3-Trimethylbenzene was metabolized in the liver and excreted in the urine as the conjugates of glycine, glucuronic acid, and sulfuric acid following an oral dose in rats (Mikulski and Wiglusz, 1975). Approximately 33% of this oral dose of 1,2,3-trimethylbenzene was excreted in the urine within 48 hours. 1,2,3-Trimethylbenzene was more slowly metabolized and excreted than either 1,3,5-trimethylbenzene or 1,2,4-trimethylbenzene; this characteristic may account for its relatively greater toxicity.

Mikulski et al. (1979) also reported that 1,2,3-trimethylbenzene orally administered to rats was metabolized to phenol, which was detectable in the blood approximately 6 hours later.

b. Human Studies

(1) Pharmacokinetics

Dowty and Laseter (1976) reported the presence of trimethylbenzene (isomers unspecified) in maternal and cord blood samples collected

at birth. It was noted that the transplacental passage and abnormal accumulation of such compounds may have resulted from the ingestion of medications, environmental exposure, or metabolic imbalance.

(2) Health Effects

Sax (1979) rates 1,2,3-trimethylbenzene as moderately toxic to man via the oral route; that is, it may cause reversible or irreversible changes to exposed tissues but no permanent injury or death.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 1,2,3-trimethylbenzene were found.

16. Exposure Standards

A Threshold Limit Value-Time Weighted Average (TLV-TWA) of 25 ppm 1,2,3-trimethylbenzene has been recommended as a ceiling limit by the ACGIH (1980); the Short Term Exposure Limit (STEL) has been set at 35 ppm.

17. Sources of Additional Relevant Information

A study has been proposed to investigate the mutagenic activity of 1,2,3-trimethylbenzene as a primary pollutant (Pitts, 1980).

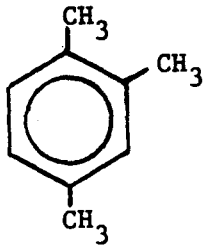
18. Other Pertinent Data

No other information that would aid in the assessment of 1,2,3-trimethylbenzene as an occupational hazard was found in the literature searched.

B. 1,2,4-TRIMETHYLBENZENE

1. Chemical Name: 1,2,4-Trimethylbenzene

2. Chemical Structure:



3. Synonyms: Pseudocumene
1,2,5-Trimethylbenzene
psi-Cumene
Pseudocumol
asym-Trimethylbenzene
asymmetrical Trimethylbenzene

4. Chemical Abstracts Service (CAS) Number: 95-63-6

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

DC3325000

6. Chemical and Physical Properties:

Description:	liquid
Molecular Weight:	120.20
Boiling Point:	169.5°C
Melting Point:	-60.5°C
Vapor Pressure:	1 mm Hg (13.6°C); 10 mm Hg (50.7°C)
Solubility:	0.0057 g/100 ml water (20°C) miscible with alcohol, ether, acetone, benzene, CCl_4, petroleum ether
Specific Gravity:	0.889^{4}_{4}
Stability:	combustible; flash point: 120°F

7. Production:

Data available from the U.S. EPA (1980) regarding producers of 1,2,4-trimethylbenzene and production volumes are presented in Table 1.

Table 1. Próducers of 1,2,4-Trimethylbenzene and Production Ranges (U.S. EPA, 1980)

Producer and Location	Type of Production	1977 Production Range
Coastal States Petrochemical Corpus Christi, TX	Manufacturer	50 - 100 million lb
Koppers Co. Follansbee, WV	Manufacturer	0.1 - 1.0 million lb
Sun Petroleum Corpus Christi, TX	Manufacturer	10 - 50 million lb

8. Use

1,2,4-Trimethylbenzene is used commercially as a raw material in the production of trimellitic anhydride (Towle et al., 1968). This is a primary commercial use. Trimellitic anhydride is made by Amoco (Joliet, IL), which has a plant capacity of 50 million pounds per year (Connolly, 1976).

1,2,4-Trimethylbenzene is used in the production of pseudocumidene, a dye intermediate (Lawler, 1977). It is also used as a dye carrier solvent by the dyeing industry (Sun Oil, 1976) and as an intermediate in making pharmaceuticals (Hawley, 1977). It can be used in a variety of organic syntheses, such as in the derivation of dimethylbenzoic acid, as alkyd resin modifiers (Earhart, 1960), and as a component in high octane fuel (Sittig, 1967).

1,2,4-Trimethylbenzene is a small-volume component that is present in most automobile fuels. Ioffe et al. (1978) identified 1,2,4-trimethylbenzene and many other hydrocarbons in analyses of air from six Soviet cities. The hydrocarbon composition in the air differed significantly from exhaust gas compositions, but was very close to the composition of motor fuel. The role of gasoline evaporation during transport and storage was suggested.

9. Manufacturers and Distributors

SRI International (1980) lists Sun Oil Co. (Corpus Christi, TX) and Phillips Petroleum (Borger, TX) as manufacturers. USITC (1980) lists only Sun as a manufacturer; the U.S. EPA (1980) lists Sun, Koppers Co., and Coastal States Petrochemical as manufacturers. The capacity of the Sun Oil facility to make 1,2,4-trimethylbenzene is estimated to be 50 million pounds per year (Connolly, 1976).

In addition to the manufacturers, the following are distributors of 1,2,4-trimethylbenzene (1980-81 OPD Chemical Buyers Directory, 1979; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	Eastman Kodak
Alfa Prod.	EM Lab.
API Stand. Mat.-	Fallek Chem.
Carnegie-Mellon Univ.	Fisher Sci.
J.T. Baker Chem.	Henley and Co.
Bio-Clinical Lab.	ICN/K and K
Chemical Procurement Lab.	Lachat Chem.
Chemsampo Inc.	MCB Reagents
Chem Services	Pfaltz and Bauer
Crowley Chem.	Tridom Chem.
Eastern Chem.	

10. Manufacturing Processes

Large amounts of 1,2,4-trimethylbenzene are present in the aromatics that exist in crude oils and in catalytic reformates; for example, 41.3% of the C_9 aromatics present in catalytic reformates is 1,2,4-trimethylbenzene. 1,2,4-Trimethylbenzene can be separated from this C_9 reformate by distillation (Earhart, 1968). The operation requires a distillation column of more than 100 plates to obtain material of approximately 95% purity (Earhart, 1960).

A number of synthesis methods are available to produce 1,2,4-trimethylbenzene. For example, the catalytic methylation of xylene with methyl chloride will produce 1,2,4-trimethylbenzene (Earhart, 1960). 1,2,4-Trimethylbenzene can also be manufactured from methylcyclohexane and isobutylene according to the following equation (Sittig, 1967):

$$C_6H_{11}CH_3 + C_4H_8 \longrightarrow C_6H_3(CH_3)_3 + C_2H_6 + 2H_2$$

Figure 1 outlines the basic operations in this manufacturing scheme.

11. Impurities or Additives

Commercial grade 1,2,4-trimethylbenzene contains 100% pseudocumene (Lilley, 1972).

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 1,2,4-trimethylbenzene.

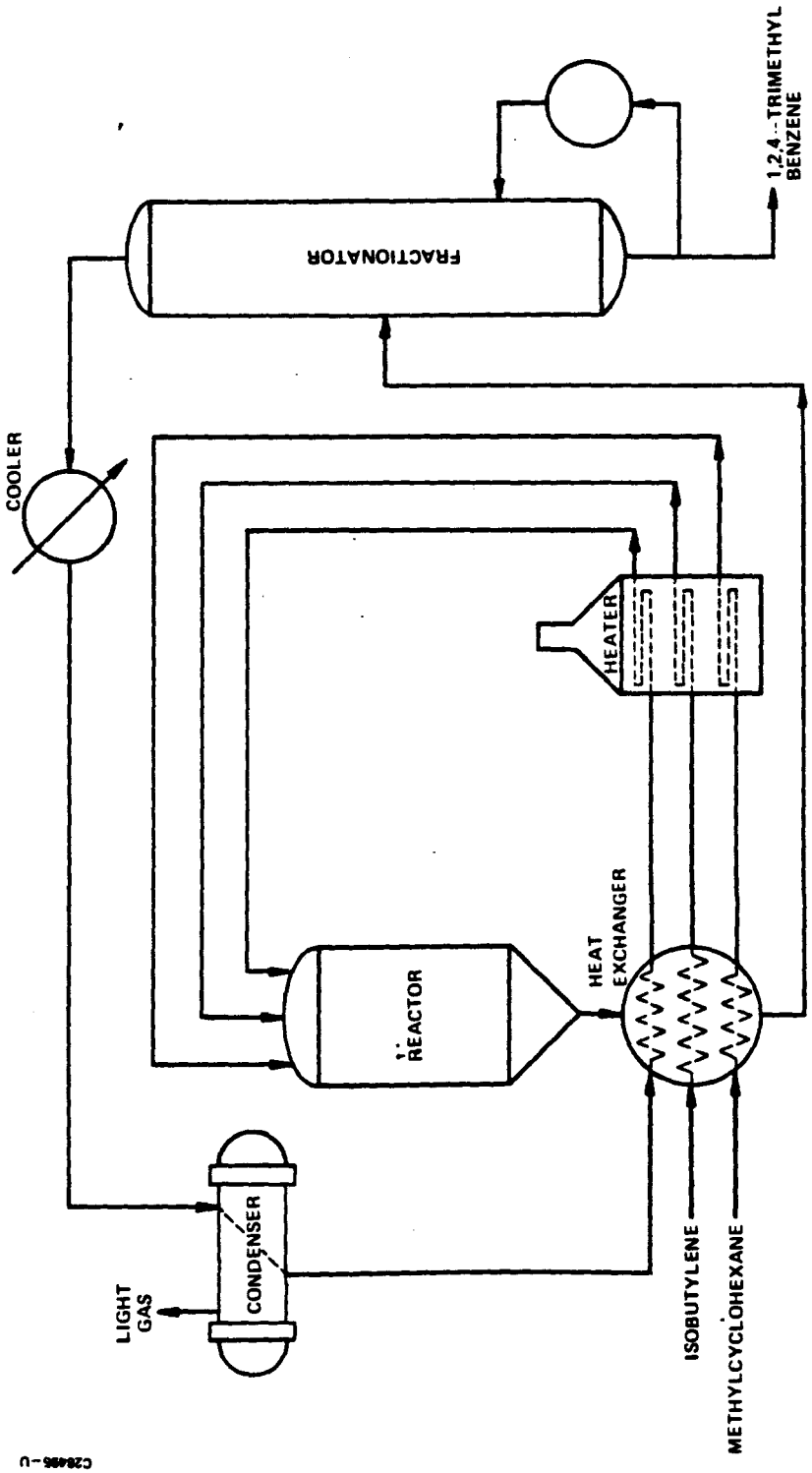


Figure 1. Manufacture of 1,2,4-Trimethylbenzene from Methylcyclohexane and Isobutylene (Sittig, 1967; based upon Blue and Holm, 1956)

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1,2,4-trimethylbenzene were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute effects of 1,2,4-trimethylbenzene are summarized in Table 2. 1,2,4-Trimethylbenzene is a central nervous system depressant and respiratory irritant (Browning, 1965). Aspiration of the liquid causes pulmonary edema, hemorrhage, and chemical pneumonitis (Gerarde, 1960). Repeated dermal contact with 1,2,4-trimethylbenzene causes scaling and fissuring of the skin (Gerarde, 1960). Sax (1979) states that 1,2,4-trimethylbenzene will also cause anemia.

(2) Subchronic Exposures

Cameron et al. (1938) found that rats and mice tolerated atmospheric concentrations of 2000 ppm 1,2,4-trimethylbenzene for 14 daily exposures of 8 hours' duration with no adverse signs of intoxication.

Gage (1970) reported nose and eye irritation, respiratory difficulty, lethargy, tremors, and diminished weight gain following exposure of rats for 6 hours to 2000 ppm 1,2,4-trimethylbenzene vapor for 12 days. An exposure to 6 hours of 1000 ppm 1,2,4-trimethylbenzene vapor for 15 days resulted in initial slight eye and nose irritation. In both instances, autopsy and blood tests proved normal.

Woronow (1929) observed local inflammation, infiltration, and necrosis of subcutaneous tissue in rabbits following daily subcutaneous injections of 2000 to 3000 mg 1,2,4-trimethylbenzene for 21 days. Hematological examination revealed a slight leukocytosis and a moderate reduction in erythrocytes.

Table 2. Acute Effects of 1,2,4-Trimethylbenzene

Route[a]	Species	Dose (mg/kg)	Response	Reference
oral	rats	4447	LDLo, generalized vasodilation, hyperemia of the GI tract, and pulmonary hemorrhage; caused death in 3 out of 10 animals, complete recovery of survivors	Gerarde, 1960
i.p.	rats	1334-1779	LDLo, death within 24 h[b]	Cameron et al., 1938
i.p.	rats	1750	LDLo	The Merck Index, 1976
i.p.	guinea pigs	1788	LDLo	Von Oettingen, 1940
s.c.	rats	10,673	No deaths	Cameron et al., 1938
inhalation	mice	1800-2000 ppm/12 h	No deaths	Cameron et al., 1938
inhalation	rats	1800-2000 ppm/48 h	No deaths; no ill effects	Cameron et al., 1938
inhalation	rats	8100 ppm/2 h	Loss of reflexes and narcosis	Lazarew, 1929

[a] i.p. = intraperitoneal; s.c. = subcutaneous.

[b] h = hour.

Battig conducted an investigation of the paint thinner "Fleet-X-DV-99," which contains 50% 1,2,4-trimethylbenzene, 30% 1,3,5-trimethylbenzene, and trace amounts of 1,2,3-trimethylbenzene (Battig et al., 1956a, 1956b, 1958). Fifty percent mortality resulted when rats were exposed to an atmospheric concentration of 1700 ppm of the solvent, 8 hours/day, 5 days/week, for 4 months. Growth retardation, diuresis, and central nervous system depression were evident during the first 3 weeks. Lymphopenia and neutrophilia developed after this initial exposure. Fatty changes in the liver and hyperemia of the lungs accompanied by thickening of the alveolar walls were observed upon post-mortem examination.

Rossi and Grandjean (1957) reported no fatalities or adverse toxicological effects when rats were exposed to 1700 ppm of an isomeric mixture of trimethylbenzene (30% 1,3,5-trimethylbenzene; 50% 1,2,4-trimethylbenzene) for 10 to 21 days. Diminished weight gain, lymphopenia, neutrophilia, and marked depression of the central nervous system were observed when rats were exposed for 4 months at the same concentration.

According to Dyshinevich (1979), in an abstract of a report from the USSR, the central nervous system and the liver of rats were affected (unspecified) by a 4-month constant exposure to 4.1 ppm 1,2,4-trimethylbenzene over poly(vinyl chloride) linoleum.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

Cameron et al. (1938) reported that several female rats gave birth to healthy offspring during a 14-day exposure to 1800-2000 ppm 1,2,4-trimethylbenzene for 8 hours/day. Normal growth was observed after these young rats were separated from their mothers.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

1,2,4-Trimethylbenzene is absorbed from the gastrointestinal tract, by inhalation of the vapors, and, less readily, through intact skin (Gerarde, 1960; Browning, 1965). It is distributed by the blood to the tissues in proportion to their fat content, as is benzene (Gerarde, 1959).

Biotransformation most likely takes place in the liver, where 3,4-dimethylbenzoic acid, 2,4-dimethylbenzoic acid, 2,5-dimethylbenzoic acid, 2,5-dimethylhippuric acid, 2,4-dimethylhippuric acid, 3,4-dimethylhippuric acid, and possibly 2,4,5-trimethylphenol are formed (Williams, 1959; Mikulski and Wiglusz, 1975; Bakke and Scheline, 1970). The phenolic compounds are subsequently converted to conjugates of glucuronic acid, sulfuric acid, and glycine and are eliminated in the urine (Bakke and Scheline, 1970; Gerarde, 1960; Mikulski and Wiglusz, 1975; Rossi and Grandjean, 1957).

Liver microsomal enzyme turnover was not detected following oral administration of 1,2,4-trimethylbenzene to rats (Gershbein, 1975) or intraperitoneal injection in mice (Fabacker and Hodgson, 1977).

b. Human Studies

(1) Pharmacokinetics

Absorption of 1,2,4-trimethylbenzene occurs from the gastrointestinal tract, by inhalation of the vapor, and, less readily, through intact skin (Gerarde, 1960; Browning, 1965).

Dowty and Laseter (1976) reported the presence of trimethylbenzene (isomers unspecified) in maternal and cord blood samples collected at birth. It was noted that the transplacental passage and abnormal accumulation of such compounds may have resulted from the ingestion of medications, environmental exposure, or metabolic imbalance.

(2) Health Effects

Workers exposed to the paint thinner "Fleet-X-DV-99" (30% 1,3,5-trimethylbenzene, 50% 1,2,4-trimethylbenzene, and trace amounts of 1,2,3-trimethylbenzene) in atmospheric concentrations of 10-60 ppm reported headache, anxiety, fatigue, drowsiness, asthmatic bronchitis, frequent bleeding from the gums and nose, hypochromic anemia, delayed coagulation time, and a tendency to develop hematomas (Battig et al., 1956a, 1958). Gerarde (1960) later observed that the hemopoietic disturbances could possibly have been the result of benzene, which was present as a contaminant in the solvent.

Sax (1979) rates 1,2,4-trimethylbenzene as moderately toxic to man via oral and intraperitoneal routes; that is, it may cause reversible or irreversible changes to exposed tissues, but no permanent injury or death.

(3) Target Organ Toxicity

Exposure of workers to "Fleet-X-DV-99" caused central nervous system depression, respiratory irritation, and hemopoietic disturbances (Battig et al., 1956a, 1958). Liquid 1,2,4-trimethylbenzene is a primary skin irritant, but systemic intoxication due to skin absorption is unlikely (ACGIH, 1977a).

(4) Epidemiology

Battig et al. (1956a) attributed the complaints of 27 workers exposed to the paint thinner "Fleet-X-DV-99" to its trimethyl benzene

constituency. Atmospheric concentrations of 10-60 ppm trimethylbenzene caused blood coagulation disturbances in 40% of the cases reviewed (a decrease in thrombocytes and erythrocytes) and asthmatic bronchitis in 70% of the severely exposed group; these effects were accompanied by headache, fatigue, and drowsiness in 70% of the workers exposed to higher concentrations.

15. Ongoing Studies

No current toxicological or environmental studies of 1,2,4-trimethylbenzene were found.

16. Exposure Standards

A Threshold Limit Value-Time Weighted Average (TLV-TWA) of 25 ppm 1,2,4-trimethylbenzene has been recommended as a ceiling limit by the ACGIH (1980); the Short Term Exposure Limit (STEL) has been set at 35 ppm.

17. Sources of Additional Relevant Information

1,2,4-Trimethylbenzene has been identified as an atmospheric pollutant, originating from coke-oven emissions and coal conversion processes. Several studies have been proposed to investigate the mutagenic (Pitts, 1980; Hart et al., 1980; Legato, 1980) and carcinogenic, teratogenic, and reproductive effects (Hart et al., 1980) of 1,2,4-trimethylbenzene as an air pollutant.

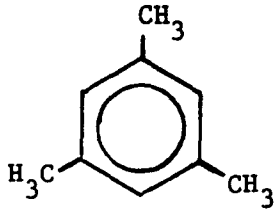
18. Other Pertinent Data

No other information that would aid in the assessment of 1,2,4-trimethylbenzene as an occupational hazard was found in the literature searched.

C. 1,3,5-TRIMETHYLBENZENE

1. Chemical Name: 1,3,5-Trimethylbenzene

2. Chemical Structure:



3. Synonyms: Mesitylene
Fleet-X
TMB
sym-Trimethylbenzene
Trimethylbenzol

4. Chemical Abstracts Service (CAS) Number: 108-67-8

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

OX6825000

6. Chemical and Physical Properties:

Description:	liquid, peculiar odor
Molecular Weight:	120.20
Boiling Point:	164.7°C
Melting Point:	-52.7°C
Vapor Pressure:	1 mm Hg (9.6°C) 10 mm Hg (47.4°C) 1.86 mm Hg (20°C)
Solubility:	0.002 g/100 g water miscible with alcohol, ether, benzene, acetone, CCl_4, and petroleum ether
Specific Gravity:	0.8637
Stability:	combustible; Flash point: 116°F (TCC)

7. Production

As of 1968, production of 1,3,5-trimethylbenzene as an end-use product has not achieved significant commercial status (Earhart, 1968).

Data available from the U.S. EPA (1980) regarding producers of 1,3,5-trimethylbenzene and production volumes are presented in Table 3.

8. Use

1,3,5-Trimethylbenzene is used industrially as a constituent of paint thinners and solvents, which usually contain other trimethylbenzene isomers (Browning, 1965). The solvent Fleet-X-DV-99 contains 30% 1,3,5-trimethylbenzene and 50% 1,2,4-trimethylbenzene.

1,3,5-Trimethylbenzene is used in the production of trimesic acid, a crosslinking agent for resins and polyols and a plasticizer intermediate (Towle et al., 1968; Earhart, 1960).

Other intermediate uses of 1,3,5-trimethylbenzene include anthraquinone vat dyes and ultraviolet oxidation stablizers for plastics (Hawley, 1977). Mesitylene chromium tricarbonyl and mesitylene tungsten tricarbonyl may also be made from 1,3,5-trimethylbenzene.

1,3,5-Trimethylbenzene is a small-volume component that occurs in most automobile fuels. Ioffe et al. (1978) identified 1,3,5-trimethylbenzene and many other hydrocarbons in analyses of air from six Soviet cities. The hydrocarbon composition in the air differed significantly from exhaust gas compositions, but was very close to the composition of motor fuel. The role of gasoline evaporation during transport and storage was suggested.

9. Manufacturers and Distributors

SRI International (1980) and USITC (1979) list Sun Oil Co. (Corpus Christi, TX) as the only manufacturer. The U.S. EPA (1980) also lists Koppers Co. (Follansbee, WV).

Additional distributors of 1,3,5-trimethylbenzene include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Table 3. Producers of 1,3,5-Trimethylbenzene and Production ranges (U.S. EPA, 1980)

Producer and Location	Type of Producer	1977 Production Range
Koppers Co. Follansbee, WV	Manufacturer	0.1-1.0 million lb
Sun Petroleum Corpus Christi, TX	Manufacturer	0.1-1.0 million lb
Mitsui and Co. (USA) Houston, TX	Importer	0.1-1.0 million lb
Henley and Co. New York City, NY	Importer	confidential

Aldrich Chem.	Eastman Kodak
Alfa Prod.	EM Lab.
Anachemia Chem.	Fallek Chem.
Anic USA	Fisher Sci.
API Stand. Mat.-	Gallard-Schlesinger Chem.
Carnegie-Mellon Univ.	ICN/K and K
Atomergic Chemetals	Lachat Chem.
J.T. Baker Chem.	Mallinckrodt
Bio-Clinical Lab.	MCB Reagents
Chemical Procurement Lab.	Mitsubishi Gas Chem.
Chemsampo Inc.	Orlex Chem.
Chem Services	Pfaltz and Bauer
Columbia Organics	Riches-Nelson Inc.
Crompton and Knowles	SSF Dottikon
Eastern Chem.	Tridom Chem.

10. Manufacturing Processes

Large amounts of 1,3,5-trimethylbenzene are present in the aromatics that exist in crude oils and in catalytic reformates; for example, 7.6% of the C_9 aromatics present in catalytic reformate is 1,3,5-trimethylbenzene (Earhart, 1968). It is not economically feasible, however, to recover this 1,3,5-trimethylbenzene from the catalytic reformate (Earhart, 1960). 1,2,3-Trimethylbenzene can be produced by fractionating coal tar (Browning, 1965).

1,3,5-Trimethylbenzene can be manufactured by the catalytic isomerization of pseudocumene (1,2,4-trimethylbenzene) in either liquid or gas phase. It can also be made by the catalytic methylation of xylenes with methyl chloride (Earhart, 1960).

11. Impurities or Additives

Commercial grade 1,3,5-trimethylbenzene contains 98.50% mesitylene (Sun Oil Co., n.d.).

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 1,3,5-trimethylbenzene.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1,3,5-trimethylbenzene were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute effects of 1,3,5-trimethylbenzene are summarized in Table 4. Acute administration of 1,3,5-trimethylbenzene caused central nervous system depression and respiratory irritation in experimental animals (Cameron et al., 1938; Wiglusz et al., 1975b; Gerarde, 1960).

Hultgren (1926) found no change in the peripheral blood leukocyte count following subcutaneous injections for 3 to 5 days of 104 mg in rabbits. Injections of 173 mg 1,3,5-trimethylbenzene, however, caused transient leukopenia and 2159 mg/kg resulted in temporary leukopenia and thrombocytopenia.

Rats exposed to a concentration of 560 ppm 1,3,5-trimethylbenzene continuously for a 24-hour period showed no evidence of intoxication (Cameron et al., 1938).

Following exposures to 610 ppm 1,3,5-trimethylbenzene vapor for 6 hours, serum alkaline phosphatase levels were increased in rats; however, no change was observed in the levels of glutamic pyruvic transaminase, glutamate dehydrogenase, or ornithine carbamyl transferase (Wiglusz et al., 1975a).

(2) Subchronic Exposures

Central nervous system depression was also evident with subchronic exposures of experimental animals to 1,3,5-trimethylbenzene.

Battig conducted a series of investigations on the paint thinner "Fleet-X-DV-99," which contains 30% 1,3,5-trimethylbenzene, 50% 1,2,4-trimethylbenzene, and trace amounts of 1,2,3-trimethylbenzene (Battig et al., 1956a, 1956b, 1958). Fifty percent mortality resulted when rats were exposed to an atmospheric concentration of 1700 ppm solvent 8 hours/day,

Table 4. Acute Effects of 1,3,5-Trimethylbenzene

Route[a]	Species	Dose (mg/kg)	Response	Reference
oral	rats	4319	Caused death in 1 of 10 animals	Gerarde, 1960
i.p.	rats	1296-1727 mg	LDLo, death within 24 h[b]	Cameron et al., 1938
i.p.	guinea pigs	1303	LDLo	Von Oettingen, 1940
i.p.	guinea pigs	976 mg[c]	LDLo	Gerarde, 1960
s.c.	rats	10,364	No deaths	Cameron et al., 1938
s.c.	rats	6910-8637	Caused leukocytosis	Hultgren, 1926
inhalation	rats	2240 ppm/24 h	LDLo, central nervous system depression, narcotic effect; 4 out of 16 rats died of respiratory failure; autopsy revealed lung congestion	Cameron et al., 1938
inhalation	mice	5000-7000 ppm/2 h	Sedation	Lazarew, 1929
inhalation	mice	7000-9000 ppm/2 h	Loss of reflexes; central nervous system depression	Lazarew, 1929
inhalation	rats	305, 610, or 1221 ppm/6 h	No changes in hemoglobin levels or erythrocyte and leukocyte counts; dose response increase in percentage of segmented neutrophilic granulocytes	Wiglusz et al., 1975b

[a] i.p. = intraperitoneal; s.c. = subcutaneous.

[b] h = hour

[c] total dose.

5 days/week, for 4 months. Growth retardation, diuresis, and central nervous system depression were evident during the first 3 weeks. Lymphopenia and neutrophilia developed after this initial exposure. Fatty changes in the liver and hyperemia of the lungs accompanied by thickening of the alveolar walls were observed upon post-mortem examination.

Rossi and Grandjean (1957) reported no fatalities or adverse toxicological effects when rats were exposed to 1700 ppm of an isomeric mixture (30% 1,3,5-trimethylbenzene; 50% 1,2,4-trimethylbenzene) of trimethylbenzene for 10-21 days. Diminished weight gain, lymphopenia, neutrophilia, and marked central nervous system depression were observed when rats were exposed for 4 months at the same concentration.

Cameron et al. (1938) found that rats and mice tolerated 560 ppm 1,3,5-trimethylbenzene vapor for 14 daily exposures of 8 hours' duration with no adverse signs of intoxication.

Long-term exposure of rats to 610 ppm 1,3,5-trimethylbenzene (6 hours/day, 6 days/week, for 5 weeks) did not affect the hemoglobin concentration or erythrocyte and leukocyte counts (Wiglusz et al., 1975b). After 14 days' exposure, however, a slight increase in the percentage of segmented neutrophilic granulocytes was observed.

According to Dyshinevich (1979), in an abstract of a report from the USSR, the central nervous system and the liver of rats were affected (unspecified) by a 4-month constant exposure to 4.1 ppm 1,3,5-trimethylbenzene over poly(vinyl chloride) linoleum.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

1,3,5-Trimethylbenzene is readily absorbed by inhalation of the vapor; the liquid is absorbed from the gastrointestinal tract and through intact skin (Gerarde, 1960). It is distributed by the blood to the tissues in proportion to their fat content, as is benzene (Gerarde, 1959).

1,3,5-Trimethylbenzene is oxidized in the liver to 3,5-dimethylbenzoic acid (mesitylenic acid) and 3,5-dimethylhippuric acid in various animal species (Mikulski and Wiglusz, 1975; Gerarde, 1960; Williams, 1959; Browning, 1965; Laham and Matutina, 1973). Curci (1894) claimed that 2,4,6-trimethylphenol and 3,5-dimethyl-4-hydroxybenzoic acid were also formed.

The phenolic compounds are subsequently conjugated with glucuronic acid, sulfuric acid, and glycine and are eliminated in the urine (Bakke and Scheline, 1970; Rossi and Grandjean, 1957; Mikulski and Wiglusz, 1975; Mikulski et al., 1979; Gerarde, 1960). The lungs excrete only a small amount as unchanged 1,3,5-trimethylbenzene, depending on the blood concentration (Browning, 1965).

Oral administration of a diet supplement containing 30 mmol/kg 1,3,5-trimethylbenzene for 10 days had no effect on liver regeneration in partially hepatectomized rats (Gershbein, 1975).

b. Human Effects

(1) Pharmacokinetics

Absorption of 1,3,5-trimethylbenzene occurs most readily by inhalation of the vapor, but it is also absorbed from the gastrointestinal tract and intact skin (Gerarde, 1960).

Laham and Matutina (1973) reported that 3,5-dimethylbenzoic acid (mesitylenic acid) is a metabolite of 1,3,5-trimethylbenzene that is present in human urine after exposure to 1,3,5-trimethylbenzene.

Dowty and Laseter (1976) reported the presence of trimethylbenzne (isomers unspecified) in maternal and cord blood samples collected at birth. It was noted that the transplacental passage and abnormal accumulation of such compounds may have resulted from the ingestion of medications, environmental exposure, or metabolic imbalance.

(2) Health Effects

Workers exposed to the paint thinner "Fleet-X-DV-99" (30% 1,3,5-trimethylbenzene, 50% 1,2,4-trimethylbenzene, and trace amounts of 1,2,3-trimethylbenzene) in atmospheric concentrations of 10-60 ppm reported headache, anxiety, fatigue, drowsiness, asthmatic bronchitis, frequent bleeding from the gums and nose, delayed coagulation time, hypochromic anemia, and a tendency to develop hematomas (Battig et al., 1956a, 1958). Gerarde (1960) later observed that the hemopoietic disturbance could possibly have been the result of benzene, which was present as a contaminant in the solvent.

Sax (1979) rates 1,3,5-trimethylbenzene as moderately toxic to man via intraperitoneal and oral routes; that is, it may cause reversible or irreversible changes to exposed tissues, but no permanent injury or death.

(3) Target Organ Toxicity

Exposure of workers to "Fleet-X-DV-99" caused central nervous system depression, respiratory irritation, and hemopoietic disturbances (Battig et al., 1956a, 1958).

Liquid 1,3,5-trimethylbenzene is a primary skin irritant, but systemic intoxication due to skin absorption is unlikely (ACGIH, 1979). It may, however, cause erythema, drying, and defatting of the skin. The aspiration of liquid 1,3,5-trimethylbenzene into the lungs will cause chemical neumonitis, and, because of its low surface tension, a small aspirated volume will cover a large area of tissue (Gerarde, 1960). Chronic 1,3,5-trimethylbenzene intoxication causes irritation of the eyes, nose, and mucous lmembranes (Gerarde, 1960).

(4) Epidemiology

Battig et al. (1956a) attributed the complaints of 27 workers exposed to the paint thinner "Fleet-X-DV-99" to its trimethylbenzene constituency. Atmospheric concentrations of 10-60 ppm trimethylbenzene caused blood coagulation disturbances in 40% of the cases reviewed (a decrease in thrombocytes and erythrocytes) and asthmatic bronchitis in 70% of the severely exposed group; these effects were accompanied by headache, fatigue, and drowsiness in 70% of the workers exposed to higher concentrations.

15. Ongoing Studies

No current toxicological or environmental studies of 1,3,5-trimethylbenzene were found.

16. Exposure Standards

A Threshold Limit Value-Time Weighted Average (TLV-TWA) of 25 ppm 1,3,5-trimethylbenzene has been recommended as a ceiling limit by the ACGIH (1980); the Short Term Exposure Limit (STEL) has been set at 35 ppm.

17. Sources of Additional Relevant Information

1,3,5-Trimethylbenzene has been identified as an atmospheric pollutant originating from coke-oven emissions. Two studies have been proposed to investigate the mutagenic potential of 1,3,5-trimethylbenzene as an air pollutant (Legató, 1980; Pitts, 1980).

18. Other Pertinent Data

No other information that would aid in the assessment of 1,3,5-trimethylbenzene as an occupational hazard was found in the literature searched.

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