United States
Environmental Protection
Agency

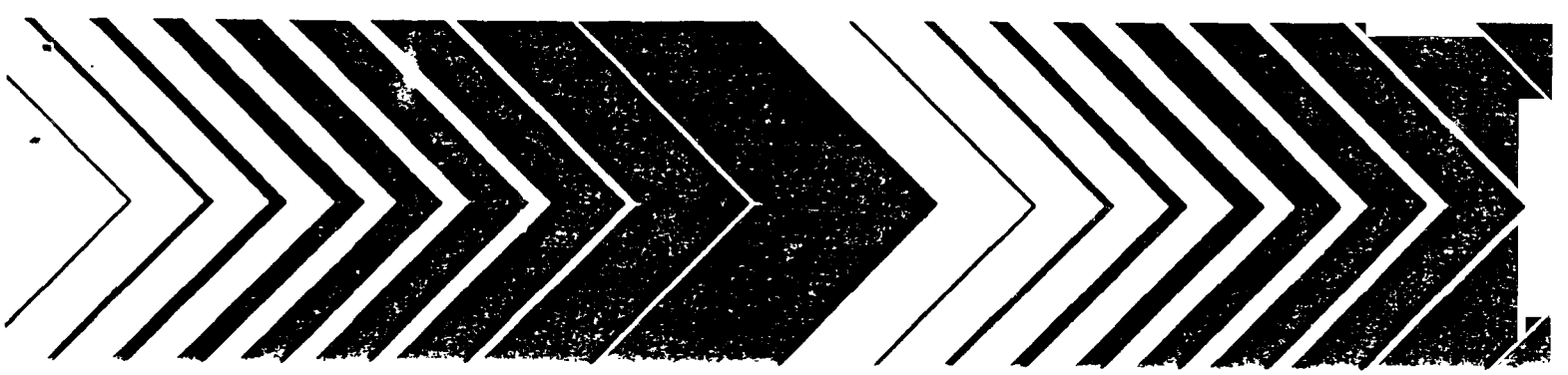
Office of Health and
Environmental Assessment
Washington DC 20460

EPA-600/8-88/080F
June 1988

Research and Development

EPA

Summary Review of Health Effects Associated With Monochloroethane: Health Issue Assessment



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Summary Review of Health Effects Associated With Monochloroethane: Health Issue Assessment

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
Office of Health and Environmental Assessment
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CONTENTS

TABLES

PREFACE

The Office of Health and Environmental Assessment has prepared this summary health assessment for use by the Office of Air Quality Planning and Standards to support decision making regarding possible regulation of monochloroethane as a hazardous air pollutant.

In the development of this document, the scientific literature has been inventoried, key studies have been evaluated, and the summary and conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed-effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels. The relevant literature for this document has been reviewed through June 1986.

Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in many instances on assumption rather than specific data. This information is not intended, nor should it be used, to support any conclusions regarding risk to public health.

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1. SUMMARY AND CONCLUSIONS

Monochloroethane (C_2H_5Cl, CAS No. 75-00-3, also referred to as chloroethane or ethyl chloride) is a volatile monochloro derivative of ethane that is present in the environment as a result of releases from anthropogenic sources. It has been found in the atmosphere, in drinking water, in oyster tissue, and in estuarine sediment samples.

Monochloroethane enters the atmosphere in emissions from chemical production and use, and municipal incinerators, as a result of its use as a chemical solvent, and as a by-product from the combustion of various commercial products (e.g., neoprene materials, polyvinyl chloride compositions, polyurethane rigid foam, and creosote-treated wood). Annual losses into the atmosphere in the United States have been estimated at 0.01 million tons, a level sufficiently high to raise questions concerning the environmental and human health impacts of such releases.

Monochloroethane has been identified in air samples taken at a number of locations around the United States. Atmospheric concentrations as high as 1248 parts per trillion (ppt) have been measured in some urban areas. The average atmospheric concentration, based on the combined data collected in several field studies, was reported to be 96 ppt in samples from urban and suburban areas and 18 ppt in samples from source-related areas. In one field study, the public's exposure to monochloroethane through inhalation was estimated to average from 2.4 to 13.5 μg/day.

The major atmospheric sink for monochloroethane is the troposphere, where the primary degradation pathway involves reactions with the hydroxyl radical. Laboratory studies indicate that the major oxidation products are carbon dioxide, carbon monoxide, formaldehyde, formyl chloride, and acetyl chloride. Formyl chloride, the principal carbon-chlorine product, may undergo further degradation in the atmosphere to form hydrogen chloride. The hydrogen chloride is removed from the atmosphere by precipitation, and thus may contribute to some degree to the acidification of surface waters.

Monochloroethane is unreactive towards O_3. Photodissociation is not expected to occur in the visible and near ultraviolet region of the spectrum. Laboratory studies, however, indicate that photodegradation occurs at shorter wavelengths. Ethylene and hydrogen are the major photodecomposition products at wavelengths of <147 nm. Ethane, ethylene, vinyl chloride, and n-butane are the major products produced at higher wavelengths. In a laboratory simulation of conditions that might occur in urban atmospheres, formaldehyde and hydrogen chloride were the major products formed when monochloroethane in air underwent photochemical decomposition in the presence of nitrogen oxides.

Although monochloroethane is very volatile, its chemical reactivity, as indicated by rate data for its reaction with hydroxyl radicals, is relatively low, and on this basis, it is not expected to participate to any great extent in photochemical smog formation. However, because laboratory studies indicate that photochemical decomposition reactions result in the release of such respiratory irritants as hydrogen chloride and formaldehyde, further evaluation is needed to determine to what extent such reactions occur under natural conditions.

The mean atmospheric residence times reported for monochloroethane, as calculated from hydroxyl radical rate data, range from 0.04 to 0.4 years: consequently, some regional and continental transport through the atmosphere might be expected.

Because of its high volatility, the major route of exposure to monochloroethane is inhalation. The compound is readily absorbed into the blood through the lungs and rapidly eliminated in exhaled breath. Blood/air partition coefficients of 2.3 and 2.5 have been reported. Little information is available concerning tissue distribution of absorbed monochloroethane. One study found that the highest levels were in perirenal fatty tissue. The log octanol/water partition coefficient has been calculated to be 1.49 and 1.54, indicating a relatively low potential for bioaccumulation. The available evidence suggests that the compound undergoes only a limited amount of metabolic breakdown to the expected by-products: acetaldehyde, acetic acid, and ethanol.

It has been suggested that because monochloroethane is not metabolized to a great extent, and because it is rapidly eliminated, it is not likely to have severe toxic effects on specific organ systems unless concentrations are extremely high. Histopathological changes in lungs, liver, and kidney have

been observed in animals, but only at concentrations >20,000 ppm, and severe toxic effects, such as hyperemia, edema, and hemorrhages in the internal organs, brain, and lungs were produced only at concentrations above 40,000 ppm.

Humans exposed to monochloroethane have exhibited central nervous system depression, headaches, dizziness, incoordination, inebriation, unconsciousness, abdominal cramps, respiratory tract irritation, respiratory failure, cardiac arrhythmias, cardiac arrest, skin irritation and freezing, allergic eczema, and eye irritation. Studies have shown that exposure to 13,000 ppm (1.3 percent) monochloroethane in air results in only a slight subjective feeling of intoxication after 17 min. Inhalation of 19,000 ppm produces weak analgesia within 12 minutes: 25,000 ppm produces slight incoordination after 15 min: and 33,600 ppm produces incoordination, cyanosis, and nausea after 8.5 min. Respiratory arrest has been observed at a monochloroethane concentration of 60,000 ppm. Concentrations producing acute toxic effects are several orders of magnitude above the highest measured ambient level of monochloroethane (1.25 ppm). In comparison, the current United States occupational exposure standard for monochloroethane is 1000 ppm for an 8-hr time-weighted average.

No conclusive information was found concerning the subchronic and chronic toxicity of monochloroethane to humans. One animal study indicated that exposures for 4 hr per day for six months to air concentrations as low as 0.57 mg/L (220 ppm) resulted in changes in liver function, decreased arterial blood pressure, lowered phagocytic activity of leukocytes, lipid degenerative changes in the liver, and some dystrophic changes in the lungs. However, these results were disputed by several other subchronic and chronic studies in which there was no evidence of histopathological lesions even at concentrations as high as 10,000 ppm.

Monochloroethane vapor was found to be mutagenic to various Salmonella strains when tested with and without the addition of metabolic activation systems. It was inactive in an in vitro cell transformation assay using BALB/c-3T3 cells in the absence of exogenous metabolic activation. Based on the in vitro mutagenic activity of monochloroethane (with and without metabolic activation), and in view of the demonstrated carcinogenicity, DNA-protein adduct-forming ability, and mutagenic activity of acetaldehyde, a predicted metabolite of monochloroethane, there is suggestive evidence that monochloroethane may have carcinogenic potential. However, there were no standard chronic carcinogenicity studies found in the literature which report direct clinical,

epidemiological, or experimental evidence for monochloroethane. According to EPA cancer assessment guidelines, this compound should be considered to be in Group D. NTP is currently preparing a technical report on a new inhalation bioassay for this compound. The report is being internally peer reviewed by NTP as of June 1988.

Monochloroethane was reported to be nonteratogenic in a recent study. Detailed results of the study are not yet available. No other information was found on the developmental or reproductive toxicity of the compound.

There is only limited information on the potential genotoxicity and teratogenicity of the compound and no experimental data on carcinogenicity. A major concern that has arisen relates to the known mutagenicity and carcinogenicity of acetaldehyde, the predicted main metabolite of monochloroethane. Thus, further understanding of the potential for long-term adverse health effects may be dependent on the pharmacokinetics and degree of metabolism of monochloroethane.

Further study is also needed to determine to what degree the photochemical oxidation products of monochloroethane (hydrogen chloride and formaldehyde) contribute to the overall degradation of air quality, particularly in urban areas where the concentrations are highest.

2. INTRODUCTION

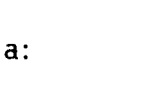
The purpose of this review is to briefly summarize the available information concerning the potential health effects associated with exposure to monochloroethane (CAS No. 75-00-3). Available data on pharmacokinetics, acute and chronic toxicity, teratogenicity, mutagenicity, and carcinogenicity are covered in this report. Physical and chemical properties and air quality data, including sources, distribution, fate, and ambient concentrations in the United States, are also included to allow a preliminary evaluation of the effects of monochloroethane on human health at ambient conditions commonly encountered by the general public.

Monochloroethane (also referred to as chloroethane or ethyl chloride) is a monochloro derivative of ethane with a molecular formula of C_2H_5Cl and a molecular weight of 64.5. It is a colorless liquid with a burning taste and an ether-like odor. It is very volatile and forms a gas at room temperature (vapor pressure 900 to 1000 mm Hg at 20°C). The major physical and chemical properties of monochloroethane are summarized in Table 2-1.

Monochloroethane is produced commercially by the free radical chlorination of ethane, by the hydrochlorination of ethanol or ethylene, or by the action of chlorine on ethylene in the presence of copper or iron chlorides (Fishbein, 1979a,b; Processes Research, Inc., 1972). About 90 to 95 percent of the monochloroethane produced in the United States is made by the hydrochlorination of ethylene (Morris and Tasto, 1979). In 1976, United States production of monochloroethane was 670 million pounds (U.S. International Trade Commission, 1976, as reported in National Institute of Occupational Safety and Health, 1978). United States production of monochloroethane in 1984 was 290,232,000 pounds (U.S. International Trade Commission, 1985). As listed by Hughes (1983), the major manufacturers of monochloroethane in the United States are

Dow Chemical U.S.A., Freeport, TX
E.I. du Pont de Nemours & Company, Inc., Deepwater, NJ
Ethyl Corporation, Houston, TX
Hercules Incorporated, Hopewell, VA
PPG Industries, Incorporated, Lake Charles, LA

TABLE 2-1. CHEMICAL AND PHYSICAL PROPERTIES OF MONOCHLOROETHANE

CAS Registry Number:	75-00-3	
NIOSH RTECS No.	KH7 5250	Tatken and Lewis, 1983
Chemical Name:	Ethane, chloro- (8CI) (9CI)	
Synonyms:	Aethylchlorid [German]: Aethylis: Aethylis chloridum: Anodynon: Chelen: Chlororethaan [Dutch]: Chlorene: Chlorethyl: Chloridum: Chloroaethan [German]: Chloroethane: Chlorured'ethyle [French]: chloryl: chloryl anesthetic: Cloretilo: Chloroetano [Italian]: Cloruro di etile [Italian]: Dublofix: Ethane, chloro-: Ether chloratus: Ether hydrochloric: Ether muriatic: Ethyl chloride: Etylu chlorek [Polish]: Hydrochloric ether: Kelene: Monochloroethane: Muriatic ether: Narcotile: NCI-C06224: UN 1037	RTECS: TDB: CAS: MESH: USPDDN: DOT, as reported in DIALOG (CHEMNAME) 1986
Chemical Formula:	C_2H_5Cl	
Structural Formula:		
Molecular Weight:	64.52	
Physical State:	Gas at ordinary temperature and pressure, liquid at low temperatures or high pressures	Windholz et al., 1983
Melting Point:	-138.7°C	Windholz et al., 1983
Boiling Point:	12.3°C at 760 mm Hg	Windholz et al., 1983
Solubility:		
(a) Water:	0.574 g/100 mL at 20°C	Windholz et al., 1983
(b) Non-aqueous solvents:		
Alcohol:	48.3 g/100 mL	Windholz et al., 1983
Ether:	Miscible	Windholz et al., 1983
Partition Coefficient (log P): (Octanol/Water):	1.54 (calc.)	Leo et al., 1971
Flash Point:	(-50°C (closed cup))	Windholz et al., 1983
Critical Pressure:	52.0 atm	Windholz et al., 1983

(continued on the following page)

TABLE 2-1. (continued)

Density (specific gravity):	0.9214 (d_4^0)	Windholz et al., 1983
	0.8978 (d_4^{20})	Weast et al., 1985
Vapor Pressure:	457 mm Hg at 0°C)	Verschueren, 1983
	700 mm Hg at 10°C	Verschueren, 1983
	710.4 mm Hg at 10.5°C	Boublik et al., 1984
	905.4 mm Hg at 20°C	Shen, 1982
	1,000 mm Hg at 20°C	Verschueren, 1983
	1.9 atm at 30°C	Verschueren, 1983
Diffusion Coefficient:	0.09789 at 10°C	Shen, 1982
	0.10402 at 20°C	Shen, 1982
	0.11031 at 30°C	Shen, 1982
Henry's Law Constant:	0.011 atm m^3 mol^{-1}	Singh et al., 1984
Vapor Density:	2.22 (air = 1)	Windholz et al., 1983
	2.76 kg/m^3 at 20°C	Konietzko, 1984
Vapor Volume:	46 cu ft (1 gal evapor.)	Alliance of American Insurers, 1980
Evaporation Rate:	<1.0 (ether = 1)	Alliance of American Insurers, 1980
	50% of 1 ppm evapor. in 21 min	Dilling, 1977
OH^- Reactivity:	49 (methane = 1)	Pitts et al., 1977
Vapor Hazard Index[a]:	1	Pitt, 1982
Refractive Index (nD20):	1.3676	Weast et al., 1985-86
Conversion Factors:	1 mg/m^3 = 0.37 ppm	Verschueren, 1983
	1 ppm = 2.69 mg/m^3	Verschueren, 1983
Odor:	Etheric	Verschueren, 1983
Odor Threshold:	10-12 mg/m^3 (recog.)	Verschueren, 1983
	4.2 ppm (v/v)	Amoore and Hautala, 1983
Critical Temperature:	187.2°C	Windholz et al., 1983

Monochloroethane is used primarily in the production of tetraethyl lead and ethylcellulose (Hughes, 1983). Small amounts may also be used in the production of ethylbenzene, alkyl catalysts and pharmaceuticals, as local anesthetics, in aerosols, and as a dye vehicle (Hughes, 1983; Fishbein, 1979). Although it has been reported to be useful as a solvent and refrigerant, it is probably no longer used for such purposes (Hughes, 1983).

According to the National Institute of Occupational Safety and Health (1978), monochloroethane is used in the following industries:

Medical and health services
Automotive dealers and service stations
Wholesale trade
Electric, gas and sanitary services
Machinery, except electrical
Special trade contractors
Fabricated metal products
Printing and publishing
Rubber and plastics products
Food and kindred products

Pre-1978 figures indicated that 113,000 workers were exposed to monochloroethane (SRI, 1978, as reported in the National Institute of Occupational Safety and Health, 1978; Parker et al., 1979). The occupational exposure limit for monochloroethane as adopted by the U.S. Occupational Safety and Health Administration is 1000 ppm (2600 $\mu g/m^3$) for an 8-hr time-weighted average (TWA) (Code of Federal Regulations, 1979). The OSHA IDLH level (immediately dangerous to life or health) is 20,000 ppm. The occupational exposure limit in other countries ranges from 100 to 1250 ppm (International Labour Office, 1980). The TLV-TWA adopted by the American Conference of Governmental Industrial Hygienists (1985) (ACGIH) is also 1000 ppm. Although the ACGIH has a TLV-STEL (short-term exposure limit) of 1250 ppm for monochloroethane, this standard is being deleted by ACGIH, and in the absence of a specific TLV-STEL, the generic ACGIH standard for excursion limits above the TLV-TWA would apply. This standard states that "short-term exposures should exceed three times the TLV-TWA for no more than a total of 30 minutes during the work day and under no circumstances should they exceed five times the TLV-TWA," (American Conference of Governmental Industrial Hygienists, 1985).

The U.S. Environmental Protection Agency has listed chlorinated ethanes, thus including monochloroethane, as priority pollutants (Arbuckle and Vanderver,

1983). Monochloroethane has a production volume of approximately 180 x 10^6lbs/yr, is very volatile, and has been identified in air samples taken from around the United States (see Section 3). In addition, it has been found in drinking water (Kopfler et al., 1975), and in oyster tissue and sediment samples taken from an estuarine locality (Ferrario et al., 1985). Because of its occurrence in various environmental media, and particularly in urban atmospheres, the potential exists for significant environmental and/or human health effects.

3. AIR QUALITY AND ENVIRONMENTAL FATE

3.1 SOURCES

There are no known natural sources of monochloroethane. The general public is exposed to the compound as a result of losses from anthropogenic sources (Singh et al., 1979). It has been found in emissions from chemical manufacturing plants (Processes Research, Inc., 1972; Shamel et al., 1975), and from municipal waste incinerators (Busso, 1971, as reported in Graedel, 1978). It may be lost to the atmosphere during its use as a chemical solvent (U.S. Environmental Protection Agency, 1975a, as reported in Graedel, 1978). It has also been identified as a combustion product of such materials as neoprene, polyvinyl chloride compositions, polyurethane rigid foam, and creosote-treated wood (Hartştein and Forshey, 1974).

Singh et al. (1981) reported that 0.01 million tons (22×10^6 lbs) of monochloroethane are released into the atmosphere every year in the United States. Processes Research, Inc. (1972) estimated that emissions during production would average 32 to 42 pounds per ton of final product. Using pre-1975 data, Brown et al. (1975) reported that 1 percent, or 5.8 million pounds per year, of the total United States production of monochloroethane would be lost during production processes. In addition, it was reported that 5 percent, or 28.8 million pounds per year, went to nonintermediate dispersive uses. The total release rate was therefore reported to be 34.6 million pounds per year.

Monochloroethane can also enter the atmosphere as a result of evaporative losses from the hydrosphere. The compound is released into aqueous environmental media in industrial effluents. Perry et al. (1979) found it in 2 of 63 effluents from chemical manufacturing plants. Concentrations were below 10 µg/L. The evaporative half-life of monochloroethane from water was reported by Dilling (1977) to be 23.1 min, indicating a relatively rapid transport to the atmosphere. Half-lives of 16.8 and 21 min have also been reported (Neely, 1976).

Partitioning of monochloroethane between the atmosphere and hydrosphere was calculated by Dilling (1982, 1977) from vapor pressure and water solubility data using the following formula:

$$H = \frac{C_{air}}{C_{water}} = \frac{16.04 \times P \times M}{T \times S}$$

where:

H = partition coefficient
C = concentration
P = vapor pressure (mm Hg)
M = molecular weight
T = temperature (°Kelvin)
S = solubility (mg/L)

According to Dilling, a coefficient of 1.0 indicates that, in the absence of degradation reactions, and with sufficient time and complete mixing, a compound would be distributed almost entirely (>99 percent) to the atmosphere (Dilling, 1982). A compound with a partition coefficient of 0.01 would be distributed to the atmosphere in amounts >50 percent. Dilling (1977) reported a partition coefficient of 0.46 for monochloroethane, indicating substantial distribution to the atmosphere.

3.2 DISTRIBUTION

The major atmospheric sink for monochloroethane is the troposphere, where the primary degradation pathway involves reactions with the hydroxyl radical (Singh et al., 1979). The amount entering the stratosphere has been estimated to be approximately 0.6 percent of the amount released at ground level (Singh et al., 1979).

Considering that the mean atmospheric residence times reported for monochloroethane range from 0.04 to 0.4 years and the fact that air masses move across the North American continent in about one week (Altshuller, 1980a), it is possible that under certain conditions there would be some regional and continental transport of monochloroethane through the atmosphere. Further study is needed to determine the distribution patterns at various distances from major source localities.

3.3 AMBIENT CONCENTRATIONS

The average global concentration of monochloroethane from dispersive losses was computed to be about 0.5 ppt, and the average concentration in the northern hemisphere was estimated to be about 1 ppt (Altshuller, 1980b). The compound has been identified in air samples taken from various localities around the United States, particularly in urban and industrial areas such as Houston, TX, Baltimore, MD, Belle, WV, Edison, NJ, and the Los Angeles basin (Pellizzari, 1977b; Pellizzari et al., 1976). In rural areas concentrations are generally only a few ppt. The maximum reported atmospheric level was 1248 ppt in Houston, TX. Average and maximum levels reported for several United States localities are given in Table 3-1.

TABLE 3-1. ATMOSPHERIC LEVELS OF MONOCHLOROETHANE

Concentration (ppt)	Locality	Reference
<5	Rural Washington State	Grimsrud and Rasmussen, 1975
510	Iberville Parish, LA	Pellizzari, 1977a
227 (avg.) 1248 (max.)	Houston, TX	Singh et al., 1981
46 (avg.) 182 (max.)	St. Louis, MO	Singh et al., 1981
41 (avg.) 125 (max.)	Denver, CO	Singh et al., 1981
87 (avg.) 312 (max.)	Riverside, CA	Singh et al., 1981
110 (avg.) 312 (max.)	Staten Island, NY	Singh et al., 1983
86 (avg.) 229 (max.)	Pittsburgh, PA	Singh et al., 1983
66 (avg.) 296 (max.)	Chicago, IL	Singh et al., 1983

[a]As reported in Pellizzari et al. (1979).

3.3.1 Exposure levels

On the basis of measured ambient concentrations of monochloroethane, averaged over 9 to 11 days (Table 3-1) during the summer of 1980, Singh et al. (1981) calculated that the general public's exposure to the chemical through inhalation would average 13.5 µg/day in Houston, TX, 2.7 µg/day in St. Louis, MO, 2.4 µg/day in Denver, Co, and 5.1 µg/day in Riverside, CA. These doses were calculated based on the breathing rate for a 70 kg man.

3.4 FATE

The U.S. Environmental Protection Agency (1975b) reported that monochloroethane emitted to the atmosphere is relatively rapidly lost through photochemical reactions. The following sections deal with the various types of these reactions.

3.4.1 Reactions With ·OH Radicals

Although monochloroethane was reported to be relatively unreactive towards hydroxyl radicals (Brown et al., 1975), this is now generally considered to be the major mechanism accounting for the removal of the compound from the atmosphere (Singh et al., 1979). The rate constants for the reaction have been given as 2.57×10^{-13} cm^3/molecule·sec at 265°K (Singh et al., 1979), 3.9×10^{-13} cm^3/molecule·sec at 296°K (Howard and Evenson, 1976) and 300°K (Guesten et al., 1984), and 4.4×10^{-13} cm^3/molecule·sec at 302.5°K (Butler et al., 1978).

The half-life for the reaction with ·OH was reported by Brown et al. (1975) to be about one year. However, Howard and Evenson (1976) estimated that the atmospheric lifetime of monochloroethane would be about 1 month, and other studies have indicated that the mean atmospheric residence time would be 0.3 years (Singh et al., 1979), 0.4 years (Altshuller, 1980a,b), 0.2 or 0.6 yr (for ·OH concentrations of 6 x 105/cm^3, and 2 x 105/cm^3) (Snelson et al., 1978), and 0.041 to 0.16 years (for ·OH concentration of 2 x 106/cm^3 to 5 x 105/cm^3) (Dilling, 1982).

Altshuller (1980a) reported that a 1 percent depletion of monochloroethane by ·OH radicals would take 6.6 days in January and 0.4 days in July at 40° N latitude. Altshuller also noted that the atmospheric depletion of organics by reaction with ·OH radicals would vary with latitude due to higher concentrations of ·OH radicals in the lower latitudes.

The likely oxidation products resulting from hydroxyl radical attack on monochloroethane and other chlorinated ethanes were identified by Spence and Hanst (1978) in a laboratory study in which hydroxyl radical abstraction of hydrogen from the chloroethane molecule was simulated by using chlorine atoms to abstract the hydrogen. The chlorine atoms were generated by the UV photodissociation of molecular chlorine. Monochloroethane and 1,1,1-trichloroethane were the least reactive of the species studied. The oxidation products of monochloroethane were carbon dioxide, carbon monoxide, formaldehyde, formyl chloride, and acetyl chloride. Formyl chloride was the principal carbon-chlorine product formed. Spence and Hanst (1978) noted that in the atmosphere many of the chlorinated oxidation products would be further attacked to produce hydrogen chloride, carbon dioxide, and carbon monoxide.

3.4.2 Reactions With Ozone

Brown et al. (1975) reported that monochloroethane was unreactive towards O_3; the half-life for the reaction was given as 10 years.

3.4.3 Photodegradation

According to Callahan et al. (1979), photodissociation of monochloroethane in the "terrestrial environment" would not be expected to occur since the compound has no chromophores which absorb in the visible or near-ultraviolet region of the spectrum. However, several laboratory studies have shown that the compound undergoes photodegradation when subjected to shorter-wavelength ultraviolet light. Ethylene was found to be the major decomposition product at wavelengths of <147 nm (Ichimura et al., 1976; Tiernan and Hughes, 1968; Cremieux and Herman, 1974). Shold and Ausloos (1979) reported that hydrogen, in addition to ethylene, was a dominant decomposition product at such short wavelengths. At slightly longer wavelengths the major products observed were ethane, ethylene, vinyl chloride, and n-butane.

Under laboratory conditions, and in the presence of nitrogen oxides, photochemical decomposition of monochloroethane in air resulted in the formation of formaldehyde and hydrogen chloride (Kanno et al., 1977).

4. PHARMACOKINETICS

4.1 ABSORPTION

Because monochloroethane is highly volatile, the major route of exposure is by inhalation. The compound is readily absorbed into the body through the lungs (Konietzko, 1984). Adriani (1960) reported that at 38°C five volumes of vapor dissolve in one volume of blood. According to Killian and Weese (1954, as reported in Konietzko, 1984), approximately 75 percent is bound to cell constituents in the blood and 25 percent to the plasma. Buch and Buch (1980, as reported in Konietzko, 1984) calculated that the Ostwald solubility coefficient of monochloroethane in a blood/air system was 2.5: the oil/blood partition coefficient was 960. Similarly, Morgan et al. (1972) reported that the partition coefficient in a blood serum/air system was 2.3, while that for an olive oil/gas system was 26. The blood/air coefficient is relatively low compared to that for other chlorinated ethanes, indicating that the compound would be rapidly excreted (Morgan et al., 1972: Konietzko, 1984). The major portion of an inhaled dose is eliminated unchanged in exhaled breath, but minute traces may remain in the blood for some time (Adriani, 1960). Some of the compound is also excreted in the urine, feces, and sweat (Adriani, 1960).

4.2 DISTRIBUTION AND TISSUE LEVELS

Adriani (1960) reported that monochloroethane had a high lipid solubility (data not given): however, the octanol/water partition coefficient has been calculated to be only 1.54 (Leo et al., 1971). The highest concentrations of the compound have been found in perirenal fatty tissue and the lowest in cerebrospinal fluid: the concentration in the brain was twice that in the blood (Killian and Weese, 1954, as reported in Konietzko, 1984; no other data reported). Adriani (1960) reported that the concentration of monochloroethane in the blood was 20 mg/100 mL in cases of light anesthesia and 30 mg/100 mL in cases of deep anesthesia. A blood level of 40 mg/100 mL was reported to be

lethal. Monochloroethane was one of a number of halogenated organic compounds found in samples of human milk collected from women residing in several United States urban areas (Pellizzari et al., 1982).

4.3 METABOLISM

Van Dyke and Wineman (1971) evaluated the dechlorination of a number of chloroethanes and chloropropanes, using hepatic microsome preparations from rats. For most of the compounds studied, dechlorination appeared to be achieved through an enzyme system similar in function to a mixed-function oxidase system requiring oxygen and NADPH, but which was only slightly dependent on, or not rate-limited by, cytochrome P-450. For monochloroethane, enzymatic losses of chlorine amounted to less than 0.5 percent of the initial amount of radiolabel used. It was reported, however, that some dechlorination (not quantified) occurred in the absence of NADP, suggesting an alternate pathway of metabolism or a nonenzymatic breakdown of the compound.

Loew et al. (1973) attempted to relate the extent of metabolism of a series of chloroethanes with the molecular energy conformational or electronic properties of the compounds. Electronic properties, particularly the electron deficiency of the most electron-deficient carbon orbital were found to be predictive of the extent of dechlorination. This indicated that the initial rate determining step in the dechlorination process was a nucleophilic attack at the carbon atom orbital. It was suggested that the carbon-chlorine bond is cleaved and the chlorine displaced by an anion such as OH^-. The relatively low level of enzymatic dechlorination of monochloroethane was supported by these calculations.

Loew et al. (1984) reviewed the available information on the metabolism of a number of chloroethanes and noted that in most cases the initial oxidative metabolites were found to be chlorophenols which then formed chloroaldehydes as a result of loss of HCl. A similar metabolic pathway was suggested for monochloroethane, with the predicted metabolic by-products of acetic acid and ethanol (formed from acetaldehyde and monochloroethanol). Slight metabolic conversion of monochloroethane to ethanol was reported by Elfskind (1929, as reported in Konietzko, 1984), but only following high anesthetic doses.

By calculating the relative heat of reaction for the various metabolic steps leading from the chloroethanes to the chloroacetaldehydes, Loew et al.

(1984) found that the data indicated that the initial hydroxylation of chloroethanes by the cytochrome P-450 system occurs by a radical oxene mechanism through the intermediacy of aliphatic hydrocarbon radical formation. These data were used to predict that the metabolism of monochloroethane would be comparable to that for 1,1,1-trichloroethane, a compound which is not extensively metabolized, compared to other chloroethanes.

5. GENOTOXICITY AND CARCINOGENICITY

5.1 GENOTOXICITY

Riccio et al. (1983; see also Milman et al., 1984, as reported in MEDLARS II [Cancerline] 1986) reported that monochloroethane vapor was found to be mutagenic to various Salmonella strains when tested in desiccators both with and without the addition of metabolic activation systems.

5.2 CARCINOGENICITY

According to Fishbein (1979a,b), no information was available as of 1979 concerning the potential carcinogenicity of monochloroethane. In recent computerized searches of major bibliographic data bases (MEDLARS II, Chemical Abstracts) covering the period from 1976 to 1986, no epidemiological, clinical, or experimental studies on the potential carcinogenicity of monochloroethane were found. Tu et al. (1985) reported that chloroethane was inactive in an in vitro cell transformation assay using BALB/c-3T3 cells in the absence of an exogenous metabolic activation system.

Loew et al. (1984) reviewed the available information on the carcinogenicity of a series of chloroethanes and compared the data with the observed and predicted extent of metabolic conversion of the parent compounds to the suspected active carcinogenic metabolites (i.e., aldehydes). Carcinogenicity was found to be correlated to several electrophilic properties of the active metabolites. Because of the low electrophilicity of acetaldehyde, the predicted main intermediate metabolite of monochloroethane, it was predicted by Loew et al. that monochloroethane would not be carcinogenic. However, several laboratory studies have shown that acetaldehyde does induce carcinomas in the nasal cavity and larynx of rodents (Feron et al., 1982; Woutersen et al., 1984). There is also evidence that acetaldehyde is a weak mutagen in certain in vitro genotoxicity assays (see Lam et al., 1986 for review), and that it forms DNA-protein adducts in vitro and in vivo (Lam et al., 1986). As Lam

et al. (1986) noted, the concentrations of acetaldehyde required for the formation of DNA-protein adducts and those producing carcinogenic effects in rodents are also cytotoxic concentrations that cause considerable cellular degeneration, stratified squamous metaplasia, and hyperplasia. These investigators were of the opinion that both cytotoxicity and DNA - protein crosslink formation may have been responsible for the observed carcinogenicity. In addition, they also point out that the known tumor promoter peroxyacetic acid, a compound which forms when acetaldehyde is exposed to air, may have also contributed to the development of the nasal tumors.

Because acetaldehyde has been identified as a carcinogen in the aforementioned animal studies, and structure-activity relationships can be hypothesized with other chlorinated ethanes that show carcinogenic activity, monochloroethane might be viewed as having a potential to be carcinogen. There is however, no presently available data to resolve the uncertainties regarding the presence or lack of a carcinogenic potential. More specific information is needed on the extent of metabolism of monochloroethane and on the nature of the carcinogenic potential of acetaldehyde, a metabolite. Under the circumstances, the weight-of-evidence for monochloroethane's carcinogenic potential is inadequate for assessment. Using the EPA cancer assessment guidelines, a group D classification is appropriate.

NTP has recently tested ethyl chloride (monochloroethane) and is presently peer reviewing the technical report prior to submitting the report to the clearinghouse for final review. In this new bioassay, rats and mice were exposed to ethyl chloride by inhalation. The technical report number will be number 346 when it is made available. The carcinogenicity evaluation should be updated when these new data are available.

6. DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

In a recent laboratory study monochloroethane was reported to be nonteratogenic (detailed results are not available) (Submitting Company, 1986). No other information was found on the developmental or reproductive toxicity of the compound.

7. OTHER TOXIC EFFECTS

7.1 ACUTE TOXICITY

7.1.1 Humans

As summarized by Parker et al. (1979; see also NIOSH, 1978), specific adverse effects reported in humans exposed to monochloroethane have included central nervous system depression, headaches, dizziness, incoordination, feeling inebriated, unconsciousness, abdominal cramps, respiratory tract irritation, respiratory failure, cardiac arrhythmias, cardiac arrest, skin irritation and freezing, allergic eczema, and eye irritation.

In the past, monochloroethane had been used as a general anesthetic (Adriani, 1970). Von Oettingen (1958) reported that deaths due to cardiac or respiratory failure were not uncommon following such use. Anesthetic doses of the compound result in cerebral cortex blocks, depression of respiration and vasomotor control, an increase followed by a decrease in the heart rate, and a reduction in blood pressure. Respiratory arrest has been observed at a monochloroethane concentration of 60,000 ppm (Adrian, 1967, as reported in Konietzko, 1984). Lawson (1965) suggested that monochloroethane affects the heart by vagal stimulation and by direct myocardial depression.

The toxic effects of exposure to monochloroethane in humans were evaluated by Davidson (1926) (see Table 7-1). Exposure to 13,000 ppm (1.3 percent) monochloroethane in air resulted in only a slight subjective feeling of intoxication after 17 min. Inhalation of 19,000 ppm produced weak analgesia within 12 minutes: 25,000 ppm produced slight incoordination: and 33,600 ppm produced incoordination, cyanosis, and nausea. There was an initial increase in reaction times following all exposure levels.

Sayers et al. (1929) reported that two breaths of a 4 percent vapor caused marked dizziness, an oily taste in the mouth, slight eye irritation, and a cramplike effect on the stomach. Three or four breaths of a 2 percent vapor caused dizziness and slight stomach cramps.

TABLE 7-1. ACUTE TOXICITY OF MONOCHLOROETHANE VAPOR TO HUMANS

Concentration (mg/L)	Concentration (ppm)	Exposure period	Effects
34.3	13,000	17 min	Slight subjective symptoms of intoxication
50.4	19,000	1 min	Initial signs of intoxication
		12 min	Slight analgesia
52.8	20,000	.....	After 4 inhalations, dizziness and slight abdominal cramps
66.0	25,000	50 sec	Initial signs of intoxication
		15 min	Slight incoordination
88.7	33,600	30 sec	Initial signs of intoxication
		5 min	Incoordination
		8.5 min	Cyanosis, nausea
105.6	40,000	.....	After 2 inhalations, stupor, irritation of eyes, and stomach cramps

Source: Adapted from Davidson (1926) and Lehmann and Flury (1943).

Eczematous reactions were observed in three individuals exposed to monochloroethane (van Ketel, 1976). All three subjects, however, had also exhibited severe allergic reactions when exposed to deodorant sprays and other chemicals, such as trichloromonofluoromethane. Torkelson and Rowe (1981) suggest that allergic reactions to monochloroethane are probably quite rare except in highly sensitized individuals.

Konietzko (1984) states that because monochloroethane is not metabolized to a great extent, and because it is rapidly eliminated, it is not likely to have severe toxic effects on specific organ systems at low concentrations.

7.1.2 Animals

Sayers et al. (1929) evaluated the acute toxicity of monochloroethane to guinea pigs (see Table 7-2). Vapor concentrations of 23 percent (230,000 ppm) for 8 min, 15.3 percent (153,000 ppm) for 30 min, 8 percent (80,000 ppm) for 90 min, and 4 percent (40,000 ppm) for 540 min caused some deaths. Histopathological changes in lungs, liver, and kidney occurred in some test animals. A

TABLE 7-2. ACUTE TOXICITY OF MONOCHLOROETHANE VAPOR TO GUINEA PIGS

Concentration (%)	Time (min)	Effects
24.1	5	Loss of equilibrium: unconscious
23.2	10	Unconscious, 1 death
15.3	40	Some deaths in 30 to 39 min: some survived 40 min
12.7	90	Some deaths in 65 to 90 min
9.1	30	1 death in 1 day, lungs hemorrhagic and edematous, liver and pancreas congested
8.0	90	All died in 1 to 3 days, histopathological degeneration of lungs, liver, kidney, spleen
5.1	40	1 death in 2 days, lungs congested
4	122	All survived: abnormal breathing, loss of equilibrium
	270	All survived, slight congestion in lungs and spleen
	540	Some deaths in 45 min to 2 days
2	270	All survived
	540	All survived, slight histopathological changes in lungs, liver, pancreas, and kidneys in some animals
1	810	All survived, no symptoms

Source: Adapted from Sayers et al. (1929).

concentration of 3.6 percent (36,000 ppm) was reported to be narcotic in rodents (Frey, 1912; Konig, 1933, as reported in Konietzko, 1984). At concentrations above 10 percent (100,000 ppm), all test animals were anesthetized (Elfskind, 1928, as reported in Konietzko, 1984). Nuckolls (1933) reported that guinea pigs exposed to 2.0 to 2.5 percent (20,000 and 25,000 ppm) monochloroethane for 2 hr were unable to stand, had forced and irregular breathing, showed frequent violent retching, and gradually became unconscious.

Troshina (1964, as reported in Biol. Abstr. 63:17017f) reported a 2-hr LC_{50} of 152 mg/L (57,600 ppm) for rats. Hyperemia of the internal organs, cerebral edema, and hemmorrhages in the brain and lung were found in histological studies.

In tests on dogs, Van Liere et al. (1966) found that high concentrations of monochloroethane (levels not reported) caused a severe drop in blood pressure and decreases in uterine motility and in muscle tonus.

Monochloroethane is an agent for sensitizing the heart to epinephrine (Reinhardt et al., 1971). Dogs anesthetized with monochloroethane exhibited cardiac irregularities when injected with epinephrine (Hermann and Vial, 1934; Morris et al., 1953). Monochloroethane and other volatile anesthetics may cause cardiac failure by permanently damaging myocardial ultrastructures involved in excitation-contraction coupling (Doering, 1975).

When placed in the eye of a rabbit, monochloroethane produced corneal opacity which was attributed to chemically induced epithelial damage (Vannas, 1954). When sprayed for 5 sec on the bared sclera in rabbit eyes, there was a transient elevation in intraocular pressure followed by transient hypotony (Puscariu and Cerkez, 1926).

7.2 SUBCHRONIC TOXICITY

7.2.1 Humans

Reversible cerebellar dysfunction was reported in one case of a 28-yr-old woman who had used monochloroethane as a narcotic for several months (Hes et al., 1979). The neurological signs included ataxia, nystagmus and scanning dysarthria, dysdiadochokinesis of each arm, and sluggish lower limb reflexes. A slight disturbance in liver function and hepatomegaly were also noted.

7.2.2 Animals

Troshina (1964, as reported in Biol. Abstr. 63:17017f) reported that in rats repeated 2-hr exposures for 60 days to 14 mg/L (5300 ppm) monochloroethane caused a decrease in phagocytic activity of leukocytes, lowered hippuric acid formation in liver, and histopathological changes in the liver, brain, and lungs.

The National Toxicology Program (1981, as reported in Landry et al., 1982) reported that 90-day inhalation exposures of rats and mice to 0, 2500, 5000, 10,000, or 19,000 ppm monochloroethane resulted in no identifiable histopathological changes. (The final report for the NTP study has not yet been published).

Landry et al. (1982) conducted a two-week long inhalation study evaluating the toxic effects of monochloroethane on male and female Fischer 344 rats and male beagle dogs. Exposures were for 6 hr per day, 5 days per week to 0, 1600, 4000, or 10,000 ppm monochloroethane. There were no treatment-related effects on body weights, clinical chemistry, hematology, urinalysis, neurology (dogs only), gross pathology, or histopathology. There was, however, a slight but significant increase in liver-to-body weight ratios of male rats exposed to 4000 and 10,000 ppm. In separate 6-hr tests on male rats and male B6C3F1 mice, liver non-protein sulfhydryl concentrations (an indicator of potential toxicity and/or biological reactivity) were slightly but significantly less than control levels in rats and mice exposed to 4000 ppm and in rats exposed to 10,000 ppm. This effect was not considered to be a sign of toxicity, but rather an indication of "adaptive tissue reaction and detoxification processes."

7.3 CHRONIC TOXICITY

7.3.1 Humans

Troshina (1966, as reported in Biol. Abstr. 64: 20506b) reported that some workers occupationally exposed to monochloroethane exhibited some pathological changes in the sympathetic nervous system and decreased phagocyte activity of leukocytes. Shirokov (1976, as reported in MEDLARS II, 1986) reported that women occupationally exposed to ethylenediamine and various chlorinated hydrocarbons, including monochloroethane, exhibited gynecological abnormalities such as inflammatory diseases of the cervix and uterine appendages, colpitis (vaginitis), conditional anomalies of internal genitalia, and signs of genital infantilism. No indication was given (in the MEDLARS abstract) as to whether the study determined if the observed effects were due to exposure to all or only some of the chemicals.

7.3.2 Animals

In a study conducted by Adams et al. (1939, as reported in Landry et al., 1982), rats and rabbits exposed to 10,000 ppm monochloroethane for 5 days per week for 6.5 months exhibited normal weight gains and showed no evidence of histopathological lesions. In contrast, Troshina (1966, as reported in Biol. Abstr. 64: 20506b) exposed rats for 4 hr per day to only 0.57 mg/L (220 ppm)

monochloroethane for six months and found changes in liver function, decreased arterial blood pressure, lowered phagocytic activity of leukocytes, lipid degenerative changes in the liver, and some dystrophic changes in the lungs.

7.4 BIOCHEMICAL EFFECTS

Takano and Miyazaki (1982) reported that monochloroethane was one of fourteen chlorinated ethanes and ethylenes that inhibited glutamate and malate oxidation in rat mitochondria. Of the compounds tested, monochloroethane produced the lowest level of inhibition.

In a study conducted by Loprinzi and Verma (1984), topically applied monochloroethane had a variable and unpredictable effect on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ornithine decarboxylase activity in human skin.

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TECHNICAL REPORT DATA
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1. REPORT NO. 600/8-88/080F	2.
3. RECIPIENT'S ACCESSION NO.	
4. TITLE AND SUBTITLE: Summary Review of Health Effects Associated with Monochloroethane: Health Issue Assessment	5. REPORT DATE: June 1988
	6. PERFORMING ORGANIZATION CODE: 600/23
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.: ECAO-R-0091
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Environmental Criteria and Assessment Office (MD-52), Office of Health and Environmental Assessment, ORD, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711	10. PROGRAM ELEMENT NO.: A101
	11. CONTRACT/GRANT NO.: DW 899329-01-0
12. SPONSORING AGENCY NAME AND ADDRESS: Office of Health and Environmental Assessment (RD-689), Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460	13. TYPE OF REPORT AND PERIOD COVERED: Tier 1
	14. SPONSORING AGENCY CODE: 600/21
15. SUPPLEMENTARY NOTES	

16. ABSTRACT

Monochloroethane (ethyl chloride) is released into the environment from anthropogenic sources and has been identified in air samples from locations around the U.S. The major route of exposure is inhalation. Histopathological changes in the lungs, liver and kidneys have been observed in animals at concentrations >20,000 ppm. Severe toxic effects were seen at concentrations >40,000 ppm. Humans exposed to high concentrations exhibited CNS, cardiac, and respiratory effects. There is no conclusive information about chronic toxicity of monochloroethane to humans, and it is in EPA's Group D as to carcinogenicity. Monochloroethane was found to be non-teratogenic in one animal study.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT: Release Unlimited	19. SECURITY CLASS *(This Report)*: Unclassified	21. NO. OF PAGES
	20. SECURITY CLASS *(This page)*: Unclassified	22. PRICE