DATE: December 2, 1980

SUBJECT: Background Document: Resource Conservation and Recovery Act Subtitle C

FROM: Nancy Hanson for
Angela Wilkes, Publications Officer
Office of Solid Waste (WH-562)

TO: EPA Regional and Headquarters Librarians

Background Documents 1941.28 "Listing of Hazardous Wastes (Section 3001 Parts 261.31 and 261.32)" and 1941.29 "Appendix A-Health and Environmental Effect Profiles" will be sent in replacement of existing documents of the same title. Please note this change. Thank you.

WH-562: AWilkes:jll:12-2-80

FORM 1320-6 (REV. 3-76)

Preface

These health and environmental effect profiles have been compiled to support the listing of approxmately 170 of the hazardous constituents identified on Appendix VIII in the regulations (40 CFR, Part 261). These profiles are also being used to support the listing of hazardous wastes in Subpart D of Part 261, due to the presence in the wastes, of these hazardous constituents. Many of these profiles have been summarized from the water quality criteria documents prepared in support of various programs under the Clean Water Act. In each case, however, the document is based on information and references available to the Agency and which are referenced in each individual document.

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No. 1

Acetaldehyde

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

ACETALDEHYDE

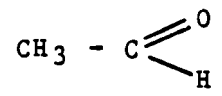
Summary

An increased incidence of malignant neoplasms was reported in workers in an aldehyde factory. Acetaldehyde was found in concentration of 1 to 7 mg/m^3 but there was no indication that acetaldehyde was the causative factor for the cancers.

Equivacol results were obtained from a number of mutugenicity assays.

I. INTRODUCTION

Acetaldehyde (CH_3COH) is a clear, flammable liquid with a pungent, fuity odor. It has the following physical/chemical properties (Hawley, 1977; U.S. EPA, 1976a):

Chemical Structure:	
CAS No.:	75-07-0
Molecular Formula:	C_2H_4O
Boiling Point:	20.2°C
Melting Point:	-123.5°C
Vapor Pressure:	740 mm (20°C)
Density:	0.7834 at 18°C/4°C
Octanol/Water Partition Coefficient:	0.43
Vapor Density:	1.52
Solubility:	soluble in water and most organic solvents

A review of the production range (includes importation) statistics for acetaldehyde (CAS No. 75-07-0) which was listed in the initial TSCA Inventory (1977) has shown that between 1 billion and 2 billion pounds of this chemical were produced/imported in 1977.*/

Acetaldehyde is used mainly as a chemical intermediate in the production of paraldehydes, acetic acid, acetic anhydride, and a variety of other chemicals (Hawley, 1977).

II. EXPOSURE

The NIOSH National Occupational Hazard Survey estimates that 2,430 workers are exposed to acetaldehyde annually (1976).

A. Environmental Fate

The available data do not indicate a potential for persistance and accumulation in the environment. While there is little information on the environmental fate of acetaldehyde, the BOD/COD of 0.72 confirms that acetaldehyde will readily biodegrade (Verschueren, 1978).

As to its fate in air, aldehydes are expected to photodissociate rapidly and competively with their oxidation for a half-life of 2 to 3 hours. Aldehydes do not persist in the atmosphere but the fact that acetaldehyde is a component of vehicle exhaust may be significant in its contribution to smog (U.S. EPA, 1977b).

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*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulation (40 CFR 710).

B. Bioconcentration

Acetaldehyde has an octanol/water partition coefficient of 0.43 indicating that it is highly hydrophilic and should not accumulate (U.S. EPA, 1976).

C. Environmental Occurrence

Acetaldehyde is a normal intermediate product in the respiration of higher plants; it occurs in traces in ripe fruits and may form in alcoholic beverages after exposure to air. It has been reported that acetaldehyde is found in leaf tobacco, cigarette smoke, and automobile and diesel exhaust (U.S. EPA, 1977a). Acetaldehyde has been reported in both finished drinking water supplies and effluents from sewage treatment plants in several locations throughout the U.S. (EPA, 1976b).

III. PHARMACOKINETICS

Acetaldehyde which is the first occurring metabolite of ethanol in mammals is produced in the liver and is often found in various tissues after the consumption of alcohol (Obe and Ristow, 1977). It is an intermediate product in the metabolism of sugars in the body and hence occurs in traces in blood (EPA, 1977b).

IV. HEALTH EFFECTS

A. Carcinogenicity

Watanabe and Sugimoto (1956) administered 0.5-5% acetaldehyde subcutaneously to rats for a period of 489 to 554 days. Four of the 14 animals developed spindle cell carcinomas at the site of injection.

An increased incidence of malignant neoplasms has been observed in workers at an aldehyde factory who were exposed to acetaldehyde,

butyraldehyde, crotonaldehyde, aldol, several alcohols, and longer chain aldehydes. Acetaldehyde was found in concentrations of 1-7 mg/m^3. Of the 220 people employed in this factory, 150 has been exposed for more than 20 years. During the period 1967 to 1972, tumors were observed in nine males (all of whom were smokers). The tumor incidences observed in the workers exceeded incidences of carcinomas of the oral cavity and bronchogenic lung cancer expected in the general population and, for the age group 55-59 years, the incidence of all cancers in chemical plant workers. There is no indication that acetaldehyde was the causative factor in the excess incidence of cancer (Bittersohl, 1974; Bittersohl, 1975).

Acetaldehyde has been found positive in a variety of mutagenicity tests: siter chromatid exchange in cultured human lymphocytes and a Chinese hamster (ovary) cell line (Ristow and Obe, 1978; Obe and Ristow, 1977); S. typhimirium (Ames Test); (Pol A^-) E. coli (Rosenkranz, 1977); and WP2 uvrA trp^-) E. coli (Veghelyi et al., 1978). It has, however, also been reported negative by other investigators: S. typhimurium, with and without activation (Cotruvo et al., 1977; Commoner, 1976; Laumbach et al., 1977); Saccharomyces cerevisiae test for recombination (Cotruvo et al., 1977); and Bacillus subtilis repair essay (Laumbach et al., 1977). Thus, of ten reports of in vitro tests for the mutagenicity of acetaldehyde, 5 were positive and 5 were negative. Acetaldehyde was also found to cross-link isolated calf thymus DNA (Ristow and Obe, 1978).

C. Other Toxicity

1. Acute

A table summarizing the acute toxicity of acetaldehyde in rats and mice is found below:

Species	Dose	Route	Result	Reference
rat	16,000ppm x 4 hrs.	ihl	lethal	Smyth, 1956
rat	4,000ppm x 4 hrs.	ihl	lethal	NIOSH, 1977
rat	640 mg/kg	s.c.	LD_{50}	Skog, 1950
rat	20,000ppm x 30 min.	ihl	LC_{50}	Skog, 1950
rat	1,930 mg/kg	oral	LD_{50}	NIOSH, 1977
mouse	560 mg/kg	s.c.	LD_{50}	Skog, 1950
mouse	1,232 mg/kg	oral	LD_{50}	NIOSH, 1977

D. Other Relevant Data

Acetaldehyde is a mucous membrane irritant in humans (Verschueren, 1978).

V. AQUATIC EFFECTS

A. Acute

The 24-hour median threshold limit (TLm) for acetaldehyde pinperch is 70 mg/l. The 96-hour TLm in sunfish is 53 mg/l (Verschueren, 1978).

VI. EXISTING GUIDELINES

A. Humans

The American Conference of Governmental and Industrial Hygienists (ACGIH) has adopted a Threshold Limit Value (TLV) of 100 ppm for acetaldehyde. The OSHA standard in air is a Time Weighted Average (TWA) of 200 ppm.

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No. 2

Acetonitrile

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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ACETONITRILE

SUMMARY

Depending on the amount absorbed, acetonitrile may cause disorders in the central nervous system, liver, kidneys, cardiovascular system and gastrointestinal system, regardless of the route of administration. These effects are attributed to the metabolic release of cyanide from the acetonitrile molecule, although the parent molecule itself may cause these effects.

This Hazard Assessment Profile was based largely on information obtained from NIOSH and its Criteria for a Recommended Standard: Occupational Exposure to Nitriles, (NIOSH, 1978).

The NIOSH 1972-1974 National Occupational Hazards Survey estimates that about 26,000 workers are occupationally exposed to nitriles.

Major occupational exposures to nitrile occur by inhalation of vapor or aerosols and by skin absorption. Adverse effects of nitriles are also found from eye contact.

There is no available evidence to indicate that acetonitrile has mutagenic or carcinogenic activity. Two studies have reported teratogenic effects in rats.

Unlike the immediate onset of cyanide toxicity, nitrile poisoning displays a delayed onset of symptoms.

I. INTRODUCTION

Acetonitrile (CH_3CN) is a mononitrile and falls into the saturated aliphatic class of nitriles. It is a colorless liquid and has a vapor pressure of 73 mm Hg at 20° C. It has a molecular weight of 41.05 and a specific gravity of 0.786 (NIOSH, 1978).

When heated to decomposition, nitriles emit toxic fumes containing cyanides (Sax, 1968).

Acetonitrile was introduced to the commerical market in 1952, and its industrial uses lie in the manufacture of plastics, synthetic fibres, elastomers, and solvents. Acetonitrile is used as a solvent in the extractive distillation that separates olefins from diolefins, butadiene from butylene, and isoprene from isopentane.

In 1964, 3.5 million pounds of acetonitrile were consumed industrially.

II. EXPOSURE

A. Water and Food

Pertinent data were not found in the available literature.

B. Inhalation

Acetonitrile can be readily absorbed from oral mucosa (McKee, et al. 1962; Dalhamn, et al. 1968).

In the workplace, acute poisoning and death have been reported following the inhalation of acetonitrile (Dequidt, et al. 1974).

Studies have demonstrated that acetonitrile is absorbed by lung tissue (Dequidt, et al. 1974; Grabois, 1955; Amdur, 1959).

C. Dermal

Dermal exposures to acetonitrile have caused adverse reactions including death in some cases (NIOSH, 1978).

Acetonitrile has been reported to have been absorbed through the intact skin of rabbits, yielding a dermal LD_{50} of 980 mg/kg (Pozzani, et al. 1959).

III. PHARMACOKINETICS

A. Absorption

Acetonitrile is a component of cigarette smoke and is absorbed by the oral tissues (McKee, et al. 1962; Dalhamn, et al. 1968).

Humans have been shown to absorb acetonitrile directly through the skin and respiratory tract (Zeller, et al. 1969; Amdur, 1959; Dequidt, et al. 1974).

B. Distribution

Studies by McKee, et al. (1962) and Dalhamn, et al. (1968) show that acetonitrile from cigarette smoking is retained by the lungs.

Tissue distribution studies indicated that mononitriles (and acetonitrile, in particular) are distributed uniformly in the internal organs of humans and that cyanide metabolites are found predominantly in the spleen, stomach and skin, and to a lesser extent, in the liver, lungs, kidneys, hearts, brain, muscle, intestines, and testes (Dequidt, et al. 1974).

Haguenoer, et al. (1975) exposed three rats to 2,800 or 25,000 ppm acetonitrile by inhalation. At 25,000 ppm, all three rats died after 30 minutes. Chemical analysis

of the organs showed that the mean concentration of acetonitrile in muscle was 136 µg/100 g of tissue and 2,438 µg/100 g of kidney tissue. High acetonitrile excretion or possible renal blockage were postulated as the causes for the high renal concentration.

Nitriles and their metabolic products have been detected in urine, blood and tissues (McKee, et al. 1962).

C. Metabolism

Since human and animal studies report symptoms characteristics of cyanide poisoning, it is reasonable to assume that a portion of the effects of exposure to acetonitrile is due to the release of the cyanide ion from the parent compound (Zeller, et al. 1969; Amdur, 1959; Pozzani, 1959).

After absorption, nitriles may be metabolized to an alpha cyanohydrin or to inorganic cyanide, which is oxidized to thiocyanate and is excreted in the urine. The C=N group may be converted into a carboxylic acid derivative and ammonia, or may be incorporated into cyanocobalamine. Ionic cyanide also reacts with carboxyl groups and with disulfides (McKee, et al. 1962).

Haguenoer, et al (1975) injected white male Wistar rats with varying levels of acetonitrile ranging from 600 mg/kg to 2,340 mg/kg. At autopsy, the internal organs showed that the combined hydrogen cyanide consisted essentially of thiocyanates, cyanohydrins and cyanocobalamines.

D. Excretion

Acetonitrile is found in the morning urine of cigarette smokers. Concentrations of acetonitrile range from 2.2

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D. Excretion

Acetonitrile is found in the morning urine of cigarette smokers. Concentrations of acetonitrile range from 2.2

µg/100 ml urine for those smoking three cigarettes per day up to 20 µg/100 ml urine for heavy smokers (up to 2.5 packs per day). The results showed that acetonitrile, once absorbed into the body, can be excreted unchanged in the urine (McKee, et al. 1962).

Acetonitrile is also excreted unchanged in exhaled air (Haguenoer, et al. 1975).

IV. EFFECTS

A. Carcinogenicity

Dorigan, et al. (1976) failed to show significant carcinogenic effects in a two-year exposure study conducted with rats.

B. Mutagenicity

Pertinent data were not found in the available literature.

C. Teratogenicity

Intraperitoneal (i.p.) administration of acetonitrile to pregnant rats produced fetal malformations (Dorigan, et al. 1976). Schmidt, et al. (1976) have determined skeletal abnormalities in rats following i.p. exposure to acetonitrile.

D. Other Reproductive Effects

Pertinent data were not found in the available literature.

E. Chronic Toxicity

In an experiment to stimulate chronic occupational exposure (seven hours per day, five days per week), 30 rats were exposed to a concentration of 655 ppm acetonitrile for

90 days. The rats exhibited bronchial inflammation, desquamatization and hypersecretion of mucus, and hepatic and renal lesions. Monkeys exposed by the same regimen, but to 350 ppm acetonitrile for 91 days, experienced bronchitis and moderate hemorrhage of the superior and inferior sagittal sinuses of the brain (Pozzani, et al. 1959).

Dogs exposed to acetonitrile at a concentration of 300 ppm for 91 days showed a reduction in body weight as well as a reduction in hemoglobin and hematocrit values (Pozzani,, et al. 1959).

Monkeys exposed to 660 ppm acetonitrile per day showed poor coordination during the second week of exposure and a monkey exposed to 330 ppm showed hyperexcitability toward the end of the 13th week (Pozzani, et al. 1959).

The same investigators reported chronic LD_{50} values of 0.85 and 0.95 ml/kg for female rats which i.p. administration of acetonitrile.

G. Other Relevant Information

Dogs exposed with lethal quantities of acetonitrile (16,000 ppm for four hours) showed blood cyanide levels ranging from 305-433 µg/100 ml of blood after three hours (Pozzani, et al. 1959).

V. AQUATIC TOXICITY

A. Acute

Observed 96-hour LC_{50} values for the fathead minnow (Pimephales promelas) are 1020 mg/l in hardwater and 1000 ml/l in softwater (Bringmann, 1976). For bluegills, (Lepomis macrochirus) and guppies (Lebistes reticulatus), the

respective 96-hour values in softwater are 1850 mg/l and 1650 mg/l (Jones, 1971; Henderson, et al. 1960).

B. Chronic, Plant Effects, and Residue

Pertinent data were not found in the available literature.

C. Other Relevant Information

Acetonitrile has been observed to damage the bronchial epithelium of fish (Belousov, 1969). This compound, when added to the aqueous environment of roaches and filberts, disrupted blood circulation and protein metabolism and induced hyperemia, hemorrhages, and the appearance of small granules in the heart, brain, liver, and gills of fish. The hepatic glycogen level decreased sharply. CH_3CN induced-death apparently resulted from circulatory disturbances and necrobiotic changes in the cerebral neurons (Belousov, 1972).

Acetonitrile at a concentration of 100 mg/l inhibited nitrification in saprophytic organisms (Chekhovskaya, 1966).

VI. EXISTING GUIDELINES

A. Human

A federal occupational standard exists for acetonitrile and is based on the TLV for workplace exposure previously adopted by American Conference of Governmental and Industrial Hygienists. This TLV is 40 ppm (70 mg/m^3) and is an eight-hour TWA.

B. Aquatic

Pertinent data were not found in the available literature.

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No. 3

Acetophenone

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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ACETOPHENONE

Summary

Acetophenone is present in various fossil fuel processes and products, particularly coal and petroleum products. It is used as a flavoring agent in products for human consumption and as an intermediate in organic synthetic processes, particularly plastics manufacturing.

No data on the potential for carcinogenic, mutagenic, or teratogenic effects or on the chronic toxicity of acetophenone were found in the available literature.

There are no existing OSHA, NIOSH, or ACGIH standards or guidelines. Acetophenone is a skin irritant and has been shown to cause severe eye irritation in rabbits at microgram quantities. Acetophenone is highly toxic to aquatic life

I. INTRODUCTION

Acetophenone (1-phenylethanone, phenyl methyl ketone, acetylbenzene, benzoyl methide, hypnone, $C_6H_5COCH_3$; molecular weight 120.15) is a liquid with a melting point of 20.5°C and is slightly soluble in water. Acetophenone is used to impart a pleasant jasmine or orange-blossom-like odor to perfumes, as a catalyst for the polymerization of olefins, and in organic syntheses, especially as a photosynthesizer (Windholz, 1976). Additionally, it is used as a tobacco flavoring, as a solvent or intermediate in the synthesis of pharmaceuticals, and as a by-product of the coal processing industry. Acetophenone is present in gasoline exhaust at less than 0.1 to 0.4 ppm (Verschueren, 1977).

II. EXPOSURE

No data on levels of acetophenone in food or water or on other potential (inhalation or dermal) exposures were found in the readily available literature.

III. PHARMACOKINETICS

Information on the absorption, distribution, metabolism, or excretion of acetophenone was not found in the readily available literature, despite the fact that it is used in pharmaceutical preparations and in tobacco, perfume, and other products for human comsumption.

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity, and Chronic Toxicity

Readily available data are extremely limited. One paper suggests the possible mutagenicity of acetophenone due to its ability to cause DNA breakage in bacterial systems following DNA photosensitization (Rahn, et al. 1974). Because of the particular sensitivity of the bacterial system to DNA breakage, this information by itself is insufficient to establish acetophenone as a mutagenic agent.

There is no additional data readily available on the potential for carcinogenic, mutagenic, or teratogenic activity by acetophenone. No data are available on chronic toxicity.

B. Acute Toxicity

Skin irritaion was observed in the rabbit at 10 mg/24 hrs. using the draize procedure and at 515 mg when applied to the skin in the absence of the absorbent gauze patch. Severe eye irritation was obtained in the rabbit following application of 771 ug of acetophenene. The oral LD_{50} in rats was 900 mg acetophenone/kg, while the lethal dose following intraperitoneal injection in mice was 200 mg/kg (NIOSH, 1978). Acetophenone is a hypnotic in high concentrations and was used as an anesthetic in the last century before less toxic substances were found (Kirk and Othmer, 1963).

C. Other Relevant Information

Based upon the retention time in a gas chromatographic/mass spectrographic column, Veith and Austin (1976) suggest a potential for bioaccumulation of acetophenone. There is no additional information available to verify this situation, however.

Microbial metabolism of acetophenone as the sole source of carbon and energy has been demonstrated in pure culture (Cripps, 1975).

V. AQUATIC TOXICITY

Based upon reported values in the literature, acetophenone has been shown to be highly toxic to aquatic life, (U.S. EPA, 1979). LC_{50} values for fathead minnow are reported for the following time periods: 1 hour, greater than 200 mg/l; 24 hours, 200 mg/l; 48 hours, 163 mg/l; 72 hours, 158 mg/l; and 96 hours, 155 mg/l (U.S. EPA, 1976).

Acetophenone has been reported to be a major constituent (36 percent) of a weathered bunker fuel. This suggests that it may be present in large quantity following spills of some bunker fuels (Guard, et al. 1975).

Bunker fuels are highly variable form refinery to refinery; thus, a blanket statement as to percentage composition of acetophenone or other constituents cannot be made.

VI. EXISTING GUIDELINES AND STANDARDS

There are no existing guidelines and standards from OSHA, NIOSH, or ACGIH. Similarily, no ambient water quality standards for acetophenone exist.

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No. 4

Acetyl Chloride

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

ACETYL CHLORIDE

Summary

Acetyl chloride is an irritant and a corrosive. Cutaneous exposure results in skin burns, while vapor exposure causes extreme irritation of the eyes and mucous membranes. Inhalation of two ppm acetyl chloride has been found irritating to humans. Death or permanent injury may result after short exposures to small quantities of acetyl chloride. An aquatic toxicity rating has been estimated to range from 10 to 100 ppm.

However, acetyl chloride reacts violently with water. Thus, its half-life in ambient water should be short and exposure from water should be nil. The degradation products should likewise pose no exposure problems if the pH of the water remains stable.

ACETYL CHLORIDE

I. INTRODUCTION

Acetyl chloride (ethanoyl chloride; CH_3COCl; molecular weight, 78.50) is a colorless, fuming liquid with a pungent odor, a boiling point of 51-52°C, and a melting point of -112°C (Windholz, 1976). It is used as an acetylating agent in testing for cholesterol and in the qualitative determination of water in organic liquids. It is miscible with benzene, chloroform, ether or glacial acetic acid (Windholz, 1976). In the presence of water or alcohol, however, acetyl chloride hydrolyzes violently to form hydrogen chloride and acetic acid. Phosgene fumes, which are highly toxic, are emitted when acetyl chloride is heated to decomposition (Sax, 1975).

The 1975 U.S. annual production of acetyl chloride was approximately 4.54×10^5 grams (SRI, 1976). During transportation, this chemical should be stored in a cool, well-ventilated place, out of direct sunlight, and away from areas of high fire hazard; it should periodically be inspected (Sax, 1975). Acetyl chloride must be protected from water (Windholz, 1976).

II. EXPOSURE

Acetyl chloride reacts violently with water (see above). Thus, its half-life in ambient water should be short and exposure from water should be nil. The degradation products should likewise pose no exposure problems if the pH of the water remains stable. Internal exposure to acetyl chloride will most likely occur through inhalation of the vapor, or, on rare occasions, through ingestion. Skin absorption is very unlikely although severe burns would be expected.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature.

IV. EFFECTS

Acetyl chloride is an irritant and a corrosive. Cutaneous exposure results in skin burns. Vapor exposure causes extreme irritation of the eyes and mucous membranes (Windholz, 1976). Inhalation of 2 ppm acetyl chloride was found irritating to humans (Handbook of Organic Industrial Solvents, 1961). Death or permanent injury may result after very short exposures to small quantities of acetyl chloride (Sax, 1975).

Because the toxicity of acetyl chloride might be expected to pattern that of its breakdown product hydrogen chloride (HCL), LC_{LO} value (the lowest concentration of a substance in air which has been reported to cause death in humans or animals) for HCl might be indicative of its toxicity. This value in humans is 1000 ppm for one minute (Mason, 1974).

Pertinent information could not be located in the available literature regarding the carcinogenicity, mutagenicity, teratogenicity and chronic toxicity of acetyl chloride.

V. AQUATIC TOXICITY

Acetyl chloride has been shown to be toxic to aquatic organisms in the ranges of 10 to 100 ppm (Hann and Jensen, 1974). No other information has been found in the literature.

VI. EXISTING GUIDELINES AND STANDARDS

No standards for acetyl chloride have been reported. However, a ceiling limit of 5 ppm has been reported for hydrogen chloride (the most irratating hydrolysis product of acetyl chloride) in industrial exposures. (Mason, 1974).

ACETYL CHLORIDE

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No. 5

Acrolein

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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ACROLEIN

SUMMARY

Acrolein has not been shown to be a carcinogen or cocarcinogen in inhalation experiments. Acrolein is mutagenic in some assay systems. Information on teratogenicity is not available. The only reported chronic effect of acrolein in humans is irritation of the mucous membranes. Chronic exposure of Syrian golden hamsters to acrolein in the air caused reduced body weight gains and inflammation and epithelial metaplasia in the nasal cavity. In addition, females had decreased liver weight, increased lung weight, and slight hematologic changes.

Acrolein has been demonstrated to be acutely toxic in freshwater organisms at concentrations of 57 to 160 µg/l. A single marine fish tested was somewhat more resistant with a 48-hour LC_{50} of 240 µg/l. Toxicity to marine invertebrates was comparable to that of freshwater organisms.

ACROLEIN

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Acrolein (U.S. EPA, 1979).

Acrolein (2-propenal; CH_2=CHCHO; molecular weight 56.07) is a flammable liquid with a pungent odor. It has the following physical and chemical properties (Weast, 1975; Standen, 1967):

Melting Point	-86.95°C
Boiling Point Range	52.5 - 53.5°C
Vapor Pressure	215mm Hg at 20°C
Solubility	Water: 210.8 percent by weight at 20°C
Density	0.8410 at 20°C
Production (Worldwide)	59 kilotons (Hess, et al. 1978)
Capacity (Worldwide)	102 kilotons/year
Capacity (United States)	47.6 kilotons/year

Acrolein is used as a biocide, crosslinking agent, and tissue fixative. It is used as an intermediate throughout the chemical industry.

The fate of acrolein in water was observed in natural channel waters (Bowmer and Higgins, 1976). No equilibrium was reached between dissipating acrolein and degradation products, with the dissipating reaction apparently being continued to completion. Degradation and evaporation appear to be the major pathways for loss, while a smaller amount is lost through absorption and uptake in aquatic organisms and sediments (Bowmer and Sainty, 1977; Hopkins and Hattrup, 1974).

II. EXPOSURE

There is no available evidence that acrolein is a contaminant of potable water or water supplies (U.S. EPA, 1979).

Acrolein is a common component of food. It is commonly generated during cooking or other processing, and is sometimes produced as an unwanted

by-product in the fermentation of alcoholic beverages (Izard and Libermann, 1978; Kishi, et al. 1975; Hrdlicka and Kuca, 1965; Boyd, et al. 1965; Rosenthaler and Vegezzi, 1955). However, the data are insufficient to develop a conclusive measure of acrolein exposure from food processing or cooking.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for acrolein to be 790 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

Atmospheric acrolein is generated as a combustion product of fuels and of cellulosic materials (e.g., wood and cigarettes), as an intermediate in atmospheric oxidation of propylene, and as a component of the volatiles produced by heating organic substrates (U.S. EPA, 1979). Acrolein is present in urban smog; average concentrations of 0.012 - 0.018 mg acrolein/m^3 and peak concentrations of 0.030 - 0.032 mg acrolein/m^3 were noted in the air of Los Angeles (Renzetti and Bryan, 1961; Altshuller and McPherson, 1963). Diesel exhaust emissions contained 12.4 mg acrolein/m^3; trace amounts of acrolein were present in samples taken from an area of traffic; and no acrolein was detected in ambient air from an open field (sensitivity of measurement was below one part per million) (Bellar and Sigsby, 1970). Acrolein content of smoke from tobacco and marijuana cigarettes ranged from 85 to 145 ug/cigarette (Hoffman, et al. 1975; Horton and Guerin, 1974). Acrolein was detected at levels of 2.5 - 30 mg/m^3 at 15 cm above the surface of potatoes or onions cooking in edible oil (Kishi, et al. 1975).

III. PHARMACOKINETICS

A. Absorption

Total respiratory tract retention of acrolein in anesthetized dogs was 77 to 86 percent (Egle, 1972).

B. Distribution

Pertinent data were not found in the available literature.

C. Metabolism

Relatively little direct information is available on the metabolism of acrolein. In vitro, acrolein can serve as a substrate for alcohol dehydrogenases from human and horse liver (Pietruszko, et al. 1973). In vivo studies in rats indicate that a portion of subcutaneously administered acrolein is converted to 3-hydroxylpropylmercapturic acid (Kaye and Young, 1972; Kaye, 1973). Acrolein undergoes both spontaneous and enzymatically catalyzed conjugation with glutathione (Boyland and Chasseaud, 1967; Esterbauer, et al. 1975). The low pH's encountered in the upper portions of the gastrointestinal tract probably would rapidly convert acrolein to saturated alcohol compounds (primarily beta propionaldehyde) (U.S. EPA, 1979). As several of the toxic effects of acrolein are related to the high reactivity of the carbon-carbon double bond, saturation of that bond should result in detoxification (U.S. EPA, 1979).

D. Excretion

In rats given single subcutaneous injections of acrolein, 10.5 percent of the administered dose was recovered in the urine as 3-hydroxypropylmercapturic acid after 24 hours (Kaye and Young, 1972; Kaye, 1973).

IV. EFFECTS

A. Carcinogenicity

One-year and lifespan inhalation studies with hamsters indicate that acrolein is not a carcinogen or cocarcinogen (Feron and Kruysse, 1977; National Cancer Institute, 1979).

B. Mutagenicity

Both positive and negative results have been obtained in mutagenicity assays. Acrolein induced sex-linked mutations in Drosophila melanogaster (Rapoport, 1948) and was mutagenic for DNA polymerase-deficient Escherichia coli (Bilimoria, 1975) and Salmonella typhimurium (Bignami, et al. 1977). Mutagenic activity was not detected in the dominant lethal assay in ICR/Ha Swiss mice (Epstein, et al. 1972) or in a strain of E. coli used for detecting forward and reverse mutations (with or without microsomal activation) (Ellenberger and Mohn, 1976; 1977). Acrolein was weakly mutagenic for Saccharomyces cerevisiae (Izard, 1973).

C. Teratogenicity

Pertinent data were not found in the available literature.

C. Other Reproductive Effects

Exposure of male and female rats to 1.3 mg/m^3 acrolein vapor for 26 days did not have a significant effect on the number of pregnant animals or the number and mean weight of fetuses (Bouley, et al. 1976).

E. Chronic Effects

Little information is available on the chronic effects of acrolein on humans. An abstract of a Russian study indicates that occupational exposure to acrolein (0.8 to 8.2 mg/m^3), methylmercaptan (0.003 to 5.6 mg/m^3), methylmercaptopropionaldehyde (0.1 to 6.0 mg/m^3), formaldehyde (0.05 to 8.1 mg/m^3), and acetaldehyde (0.48 to 22 mg/m^3) is associated

with irritation of the mucous membranes. This effect is most frequent in women working for less than one and greater than seven years (Kantemirova, 1975). Acrolein is known to produce irritation of the eyes and nose (Albin 1962; Pattle and Cullumbine, 1956; Sim and Pattle, 1957) and is thought to be responsible, at least in part, for the irritant properties of photochemical smog (Altshuller, 1978; Schuck and Renzetti, 1960) and cigarette smoke (Weber-Tschopp, et al. 1976a; 1976b; 1977).

In the only published chronic toxicity study on acrolein in animals (Feron and Kruysse, 1977), male and female Syrian golden hamsters were exposed to acrolein at 9.2 mg/m^3 in air, seven hours per day, five days per week, for 52 weeks. During the first week only, animals evidenced signs of eye irritation, salivated, had nasal discharge, and were very restless. During the exposure period, both males and females had reduced body weight gains compared to control groups. Survival rate was unaffected. Slight hematological changes, increased hemoglobin content and packed cell volume, decreases in liver weight (-16 percent), and increases in lung weights (+32 percent) occurred only in females. In both sexes, the only pathological changes in the respiratory tract were inflammation and epithelial metaplasia in the nasal cavity.

In a study of subacute oral exposure, acrolein was added to the drinking water of male and female rats at 5 to 200 mg acrolein/l for 90 days (Newell, 1958). No hematologic, organ-weight, or pathologic changes could be attributed to acrolein ingestion.

F. Other Relevant Information

Acrolein is highly reactive with thiol groups. Cysteine and other compounds containing thiol groups antagonize the toxic effects of acrolein

(Tillian, et al. 1976; Low, et al. 1977; Sprince, et al. 1978; Munsch, et al. 1973;1974; Whitehouse and Beck, 1975). Ascorbic acid also antagonizes the toxic effects of acrolein (Sprince, et al. 1978).

The effects of acrolein, on the adrenocortical response of rats unlike those of DDT and parathion, are not inhibited by pretreatment with phenobarbital and are only partially inhibited by dexamethason (Szot and Murphy, 1970). Pretreatment of rats with acrolein significantly prolongs hexobarbital and pentobarbital sleeping time (Jaeger and Murphy, 1973).

V. AQUATIC TOXICITY

A. Acute Toxicity

A relatively narrow range of acute toxicity to six species of freshwater fish has been reported for acrolein (U.S. EPA, 1979). LC_{50} values ranged from 61 to 160 µg/l with fathead minnows, (Pimephales promelas), being most sensitive and largemouth bass, (Micropterus salmoides), the most resistant of the species tested. Results from 7 static bioassays varying from 24 to 96 hours in duration were reported. The freshwater invertebrate Daphnia magna was as sensitive to acrolein as freshwater fish with 48-hour static LC_{50} values of 59 and 80 µg/l being reported in two individual studies. The longnose killifish, (Fandulus similis), was the only marine species tested for acute toxicity of acrolein; a 48-hour flow-through LC_{50} of 150 µg/l was obtained. The eastern oyster, (Crassostrea virginica), and adult brown shrimp, (Penacus aztecus), were the most sensitive species tested an EC_{50} value of 55 µg/l based on 50% decrease in shell growth of oysters and an EC_{50} value of 100 based on loss of equilibrium of brown shrimp (Butler, 1965). Adult barnacles were more resistant in static assays with 48-hour LC_{50} values of 1,600 and 2,100 µg/l being reported.

B. Chronic Toxicity

In a chronic life cycle test with the freshwater fathead minnow, Pimephales promelas, survival of newly hatched second generation fry was reduced significantly at 42 but not 11 µg/l, leading to a chronic value of 21.8 µg/l (Macek, et al. 1976). A comparable value of 24 µg/l was obtained from reduced survival of three generations of Daphnia magna. Chronic data for marine organisms was not available.

C. Plant Effects

Pertinent data relating the phytotoxicity of freshwater marine plants could not be located in the available literature.

D. Residues

A bioconcentration factor of 344 was obtained for radio labeled acrolein administered to bluegills, (Lepomis macrochivas). A biological half-life greater than seven days was indicated (U.S. EPA. 1979).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by the U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on the use of subacute toxicological data for rats (no observable effect level of 1.56 mg/kg body weight) and an uncertainty factor of 1000, the U.S. EPA (1979) has derived a draft criterion of 6.50 µg/l for acrolein in ambient water. This draft criterion level corresponds to the calculated (U.S. EPA, 1979) acceptable daily intake of 109 µg.

The ACGIH (1977) time-weighted average TLV for acrolein is 0.1 ppm (0.25 mg/m^3). The same value is recommended by OSHA (39 FR 23540). This

standard was designed to "minimize, but not entirely prevent, irritation to all exposed individuals" (ACGIH, 1974).

The FDA permits acrolein as a slime-control substance in the manufacture of paper and paperboard for usage in food packaging (27 FR 46) and in the treatment of food starch (28 FR 2676) at not more than 0.6 percent acrolein.

B. Aquatic

The draft criterion for protecting freshwater organisms is 1.2 µg/l as a 24-hour average not to exceed 2.7 µg/l. For marine life, the draft criterion has been proposed as 0.88 µg/l, not to exceed 2.0 µg/l.

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No. 7

Acrylonitrile

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated acrylonitrile and has found sufficient evidence to indicate that this compound is carcinogenic.

ACRYLONITRILE

Summary

Acrylonitrile is the most extensively produced aliphatic nitrile and ranks 45th on the list of high-volume chemicals produced in the U.S. Chronic exposure to acrylonitrile produces mild liver damage and functional disorders of the central nervous system, cardiovascular and hemopoietic systems. Acrylonitrile has shown mutagenic activity in Drosophila and bacteria. This compound is teratogenic in rats whether exposure is by inhalation or ingestion in drinking water. There are both animal and epidemiologic data to suggest that acrylonitrile may be a human carcinogen.

The fathead minnow has an observed 96-hour LC_{50} value ranging from 10,100 to 18,100 µg/l depending on test condition and a 30-day LC_{50} value of 2,600 µg/l. For the freshwater invertebrate, Daphnia magna, a reported 48-hour LC_{50} value is 7,550 µg/l with no adverse effects to concentrations as high as 3,600 µg/l in a life cycle test. A saltwater fish has an observed 96-hour LC_{50} of 24,500 µg/l. A bluegill in a 28-day study bioconcentrated acrylonitrile 48-fold with a half-life of 4-7 days.

ACRYLONITRILE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Acrylonitrile (U.S. EPA, 1979).

Acrylonitrile (CH_2=CHCN) is an explosive, flammable liquid having a normal boiling point of 77°C and a vapor pressure of 80 mm Hg (20°C). Currently, 1.6 billion pounds per year of acrylonitrile are manufactured in the United States. The major use of acrylonitrile is in the manufacture of copolymers for the production of acrylic and modacrylic fibers. Acrylonitrile has been used as a fumigant; however, all U.S. registrations for this use were voluntarily withdrawn as of August 8, 1978 (U.S. EPA, 1979).

II. EXPOSURE

A. Water

While no data on monitoring of water supplies for the presence of acrylonitrile were found in the literature, potential problems may exist. Possible sources of acrylonitrile in the aqueous environment are: (a) dumping of chemical wastes, (b) leaching of wastes from industrial landfills, (c) leaching of monomers from polymeric acrylonitrile, and (d) precipitation from rain. Acrylonitrile is short-lived in the aqueous environment; a 10 ppm solution was completely degraded after 6 days in Mississippi River water (Midwest Research Institute, 1977).

B. Food

There is no data on the levels of acrylonitrile in food. However, acrylonitrile may contaminate food by leaching of the monomer from polyacrylonitrile containers (National Resources Defense Council, 1976). The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for

acrylonitrile to be 110 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on steady-state bioconcentration studies in bluegills.

C. Inhalation

NIOSH (1978) estimated that 125,000 workers are exposed to acrylonitrile each year. Acrylonitrile may be liberated to the atmosphere via industrial processes or by the burning of polyacrylonitrile fiber (Monsanto, 1973). Data could not be found in the available literature regarding the concentrations of acrylonitrile in ambient air.

III. PHARMACOKINETICS

A. Absorption

When orally administered to rats, essentially all of the acrylonitrile is absorbed (Young, et al. 1977).

B. Distribution

In rabbits, after administration of a 30 mg/kg dose, acrylonitrile rapidly disappeared from the blood; only 1 mg/kg remained after 4 hours (Hashimoto and Kanai, 1965). In rats the metabolites of acrylonitrile distributed to the stomach wall, erythrocytes, skin, and liver (Young, et al. 1977).

C. Metabolism

Earlier reports (Giacosa, 1883; Meurice, 1900) indicated that most aliphatic nitriles are metabolized to cyanide which is then detoxified to thiocyanate. A more recent report concluded that acrylonitrile exerts its toxicity by the metabolic release of cyanide ion, and that the relative ability of various species to convert CN^- to SCN^- determined their susceptibility to the toxic action of acrylonitrile (Brieger, et al. 1952). Other facts, however, suggest that acrylonitrile toxicity is due in part to the

acrylonitrile molecule itself or other unknown metabolite(s) rather than just to the cyanide functional group (U.S. EPA, 1979). In a comprehensive tracer study with rats Young, et al. (1977) found three uncharacterized metabolites as well as CO_2 after acrylonitrile administration. Also, cyanoethylated mercapturic acid conjugates have been detected after administration of acrylonitrile (U.S. EPA, 1979).

D. Excretion

Urinary excretion of thiocyanate after acrylonitrile administration ranges from 4-33 percent of the administered dose depending on the species (U.S. EPA, 1979). Urinary excretion also depends on route of administration (Gut, et al. 1975).

IV. EFFECTS

A. Carcinogenicity

In two studies rats received acrylonitrile in the drinking water at concentrations of 0, 35, 100 and 300 mg/l, which is equivalent to daily dosages of approximately 4, 10, 30 mg/kg body weight respectively, excess mammary tumors and tumors of the ear canal and nervous system were noted (Norris, 1977; Quast, et al. 1977). Both the intermediate and the highest doses produced increased tumor incidences. In rats administered acrylonitrile in olive oil by stomach tube at 5 mg/kg body weight 3 times per week for 52 weeks, a slight enhancement of the incidence of mammary tumors, forestomach papillomas and acanthomas, skin carcinomas, and encephalic tumors has been reported (Maltoni, et al. 1977). Also, exposure of rats by inhalation (40, 20, 10, and 5 ppm for 4 hours daily, 5 times/week) for 52 weeks caused increases in tumor incidence (Maltoni, et al. 1977). It should be pointed out that possible impurities found in the acrylonitrile used by various investigators might determine the carcinogenic effect. The specific role of these impurities has not yet been determined (U.S. EPA, 1979).

Retrospective studies on workers in a textile fiber plant (O'Berg, 1977) and on workers in the polymerization recovery and laboratory areas of a B.F. Goodrich plant (Monson, 1977) have shown higher than expected incidences of cancers of all sites in workers exposed to acrylonitrile. The greatest increase was noted with lung cancer. It should be noted that these workers were exposed to other chemicals in their working environment.

B. Mutagenicity

Acrylonitrile is a weak mutagen in Drosophila melanogaster (Benes and Sram, 1969); although toxicity limited this testing. Milvy and Wolff (1977) reported mutagenic activity for acrylonitrile in Salmonella typhimurium with a mammalian liver-activating system. In Escherichia coli mutagenic activity was observed without an activating system (Venitt, et al. 1977).

C. Teratogenicity

Studies in pregnant rats demonstrated that acrylonitrile administered by gavage at 65 mg/kg/day caused fetal malformations (Murray, et al. 1976). These malformations included acaudea, short-tail, short trunk, missing vertebrae, and right-sided aortic arch. In a subsequent study, Murray, et al. (1978) concluded that in pregnant rats exposed to 0, 40, or 80 ppm of acrylonitrile by inhalation, teratogenic effects in the offspring were seen at 80 ppm but not 40 ppm. Significant maternal toxicity was found at both 80 and 40 ppm, as well as in the previous study at 65 mg/kg/day.

D. Other Reproductive Effects

Pregnant rats receiving 500 ppm acrylonitrile in their drinking water showed reduced pup survival, possibly due to a maternal toxicity (Beliles and Mueller, 1977).

E. Chronic Toxicity

Knoblock, et al. (1972) observed a perceptible change in peripheral blood pattern, functional disorders in the respiratory and cardiovascular systems, and the excretory system, as well as signs of neuronal lesions in the central nervous system of rats and rabbits breathing acrylonitrile (50 mg/m^3 air) for 6 months. Babanov, et al. (1972) reported that inhalation of acrylonitrile vapor (0.495 mg/m^3, 5 hours/day, 6 days/week) for 6 months resulted in central nervous system disorders, increased erythrocyte count, and decreased leukocyte count in rats. Workers exposed for long periods of time to acrylonitrile have subjective complaints including headache, fatigue, nausea and weakness, as well as clinical symptoms of anemia, jaundice, conjunctivitis and abnormal values of specific gravity of whole blood, blood serum and cholinesterase values, urobilinogen, bilirubin, urinary protein and sugar (Sakarai and Kusimoto, 1972). In another study, functional disorders of the central nervous system, cardiovascular and hemopoietic systems were noted (Shustov and Mavrina, 1975). Sakarai and Kasumoto (1972) concluded that acrylonitrile exposures at levels of 5-20 ppm caused mild liver injury and probably a cumulative general toxic effect.

F. Other Relevant Information

HCN and CO were found to enhance acrylonitrile toxicity in experimental animals (Yamamoto, 1976) as well as in workers engaged in acrylonitrile production (Ostrovskaya, et al. 1976).

V. Aquatic Toxicity

A. Acute Toxicity

The 96-hour LC_{50} values of fathead minnows (Pimephales promelas) were 10,100 and 18,100 µg/l for flow-through and static tests, respectively, and 14,300 and 18,100 µg/l for hard (380 mg/l) and soft (29 mg/l) waters,

respectively (Henderson, et al. 1961). A reported 48-hour LC_{50} for Daphnia magna is 7,550 µg/l (U.S. EPA, 1978). The saltwater pinfish (Lagodon rhomboides) has an observed 96-hour LC_{50} value of 24,500 µg/l in a static concentration unmeasured test (Daugherty and Garrett, 1951).

B. Chronic Toxicity

Daphnia magna has been exposed for its life cycle and the results indicate no adverse effects at concentrations as high as 3,600 µg/l (U.S. EPA, 1978). Henderson, et al. (1961) observed a 30-day LC_{50} value of 2,600 µg/l with Pimephales promelas (fathead minnows). No chronic test data are available for saltwater species.

C. Plant Effects

Pertinent data could not be located in the available literature on the sensitivity of plants to acrylonitrile.

D. Residues

In the only reported study, the bluegill (Lepomis macrochirus) was exposed for 28 days and the determined whole body bioconcentration factor was 48, with a half-life between 4-7 days (U.S. EPA, 1978).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The American Conference of Governmental Industrial Hygienists threshold limit value (TLV) (ACGIH, 1974) for acrylonitrile is 20 ppm. In January, 1978, the Occupational Safety and Health Administration (OSHA) announced an emergency temporary standard for acrylonitrile of 2 ppm averaged

over an eight-hour period. Based on rat data (Norris, 1977; Quast, et al. 1977; Maltoni, et al. 1977), and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of acrylonitrile in ambient water which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams of fish and shellfish.		0.008×10^{-4} ng/l	0.08×10^{-4} ng/l	0.8×10^{-4} ng/l
Consumption of fish and shellfish only.		0.016×10^{-4} ng/l	0.16×10^{-4} ng/l	1.6×10^{-4} ng/l

B. Aquatic

For acrylonitrile, the draft criterion to protect freshwater aquatic life is 130 µg/l as a 24-hour average, and the concentration should not exceed 300 µg/l at any time. To protect saltwater species, the draft criterion is 130 µg/l as a 24-hour average, with the concentration not to exceed 290 µg/l at any time (U.S. EPA, 1979).

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No. 8

Aldrin

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated aldrin and has found sufficient evidence to indicate that this compound is carcinogenic.

ALDRIN

Summary

Aldrin is a man-made compound belonging to the group of cyclodiene insecticides. The chronic toxicity of low doses of aldrin include shortened lifespan, liver changes, and teratogenic effects. The induction of hepatocellular carcinoma in both male and female mice from the administration of aldrin leads to the conclusion that it is likely to be a human carcinogen. Aldrin has not been found mutagenic in several test systems although it did induce unscheduled DNA synthesis in human fibroblasts. The World Health Organization acceptable daily intake level for aldrin is 0.1 µg/kg/day.

Aldrin is rapidly converted to dieldrin by a number of fresh and salt-water species. The overall toxicity of aldrin is similar to dieldrin. The 96-hour LC_{50} values for freshwater fish vary from 2.2 to 37 µg/l with invertebrates being one order of magnitude less sensitive. Both marine fish and plants were susceptible to levels of aldrin corresponding to those of freshwater fish.

ALDRIN

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Aldrin and Dieldrin (U.S. EPA, 1979a).

Aldrin is a white crystalline substance with a melting point of 104°C. It is soluble in organic solvents. The chemical name for aldrin is 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,:5,8-exo-dimethano-naphthalene. Aldrin is biologically altered in the environment to dieldrin, a more stable and equally toxic form. For information concerning dieldrin refer to the dieldrin hazard profile or the draft Ambient Water Quality Criteria Document for Aldrin and Dieldrin (U.S. EPA, 1979a,b).

Aldrin was primarily used as a broad spectrum insecticide until 1974 when the U.S. EPA restricted its use to termite control by direct soil injection, and non-food seed and plant treatment (U.S. EPA, 1979a). From 1966 to 1970 the use of aldrin in the United States dropped from 9.5×10^3 to 5.25×10^3 tons (U.S. EPA, 1979a). This decrease in use has been attributed primarily to increased insect resistance to aldrin and to development of substitute materials. Although the production of aldrin in the United States is restricted, formulated products containing aldrin are imported from Europe (U.S. EPA, 1979a).

II. EXPOSURE

A. Water

Aldrin has been applied to vast areas of agricultural land, and aquatic areas in the United States and in most parts of the world. As a result, this pesticide is found in most fresh and marine waters (U.S. EPA, 1979a). Levels of aldrin, ranging from 15 to 18 ng/l or as high as 407 ng/l

have been found in waters of the United States (U.S. EPA, 1976; Leichtenberg, et al. 1970). The half-life of aldrin in water one meter in depth has been estimated to be 10.1 days (MacKay and Wolkoff, 1973).

B. Food

The estimated daily dietary intake of aldrin in 16 to 19 year old males was estimated to be 0.001 mg in 1965 and only a trace amount in 1970 (Natl. Acad. Sci., 1975).

No direct measured bioconcentration factor for aldrin can be obtained because it is rapidly converted to dieldrin by aquatic organisms (U.S. EPA, 1979a). The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor of aldrin at 32. This estimate is based on the octanol/water partition coefficient for aldrin.

C. Inhalation

Aldrin enters the air through various mechanisms such as spraying, wind action, water evaporation, and adhesion to particles (U.S. EPA, 1979a). Ambient air levels of 8 ng/m^3 of aldrin have been reported (Stanley, et al. 1971).

D. Dermal

Dermal exposure to aldrin is limited to workers employed during its manufacture and use as a pesticide. Wolfe, et al. (1972) reported that exposure in workers is mainly through dermal absorption rather than inhalation. The ban on the manufacture of aldrin in the United States has greatly reduced the risk of exposure.

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature concerning the absorption of aldrin (U.S. EPA, 1979a).

B. Distribution

The distribution of aldrin in humans or animals has not been extensively studied because aldrin is readily converted to dieldrin *in vivo* via epoxidation (U.S. EPA, 1979a). For example, the blood plasma levels of aldrin were lower than the corresponding blood plasma levels of dieldrin in six workers just after chronic exposure to aldrin for five weeks (Mick, et al. 1971).

C. Metabolism

The epoxidation of aldrin to dieldrin has been reported in many organisms including man (U.S. EPA, 1979a). The reaction is NADPH-dependent and the enzymes are heat-labile (Wong and Terriere, 1965). The metabolic products of aldrin include dieldrin, as well as aldrin diol, and polar metabolites excreted in the urine and feces (U.S. EPA, 1979a).

D. Excretion

Aldrin is excreted mainly in the feces and to some extent in the urine in the form of several polar metabolites (U.S. EPA, 1979a). Ludwig, et al. (1964) reported nine times as much radioactivity in the feces as in the urine of rats chronically administered ^{14}C-aldrin. A saturation level was reached in these animals and concentrations of radioactivity in the body decreased rapidly when feeding was terminated.

Specific values for the half-life of aldrin in humans were not found in the available literature. However, in humans exposed to aldrin and/or dieldrin the half-life of dieldrin in the blood was estimated to be 266 days (Jager, 1970). In another study with 12 volunteers ingesting various doses of dieldrin, Hunter, et al. (1969) estimated the average dieldrin half-life to be 369 days.

IV. EFFECTS

A. Carcinogenicity

Aldrin has induced liver tumors in males and females in various strains of mice according to reports of four separate feeding studies (Davis and Fitzhugh, 1962; Davis, 1965; 43 FR 2450; Song and Harville, 1964). According to reports of five studies in two different strains of rats, aldrin failed to induce a statistically significant carcinogenic response at all but one site (Deichmann, et al. 1967, 1970; Fitzhugh, et al. 1964; Cleveland, 1966; 43 FR 2450).

The only information concerning the carcinogenic potential of aldrin in man is an occupational study by Versteeg and Jager (1973). The workers had been employed in a plant producing aldrin and dieldrin with a mean exposure time of 6.6 years. An average time of 7.4 years had elapsed since the end of exposure. No permanent adverse effects including cancer were observed.

B. Mutagenicity

Aldrin was found not to be mutagenic in two bacterial assays (S. typhimurium and E. coli) with metabolic activation (Shirasu, et al. 1977). Aldrin did, however, produce unscheduled DNA synthesis in human fibroblasts with and without metabolic activation (Ahmed, et al. 1977).

C. Teratogenicity

Aldrin administered in single oral doses to pregnant hamsters caused significant increases in hamster fetal death and increased fetal anomalies (i.e., open eye, webbed foot, cleft palate, and others). When a similar study was done in mice at lower doses, teratogenic effects were also observed, although these effects were less pronounced (Ottolenghi, et al. 1974).

D. Other Reproductive Effects

Deichmann (1972) reported that aldrin and dieldrin (25 mg/kg diet) fed to mice for six generations affected fertility, gestation, viability, lactation and survival of the young.

E. Chronic Toxicity

The other effects produced by chronic administration of aldrin to mice, rats, and dogs include shortened lifespan, increased liver to body weight ratios, various changes in liver histology, and the induction of hepatic enzymes (U.S. EPA, 1979a).

F. Other Relevant Information

Since aldrin and dieldrin are metabolized by way of mixed function oxidase (MFO), any inducer or inhibitor of the MFO enzymes should affect the metabolism of aldrin and dieldrin (U.S. EPA, 1979a).

When aldrin is administered with DDT, or after a plateau has been reached in dogs with chronic DDT feeding, the retention of DDT by the blood and fat increases considerably (Deichmann, et al. 1969). Clark and Krieger (1976) found that tissue accumulation of ^{14}C-aldrin was significantly increased when an inhibitor of the epoxidation of aldrin to dieldrin was administered prior to ^{14}C-aldrin.

V. AQUATIC TOXICITY

A. Acute Toxicity

Aldrin is rapidly converted to dieldrin in the environment. However, a number of acute studies haved been done with aldrin, although the test concentrations have not been measured after the bioassays. Reported 96-hour static LC_{50} values are as follows: bluegill (Lepomis macrochirus) 4.6 to 15 µg/l (Henderson, et al. 1959; Macek, et al. 1969); rainbow trout (Salmo gairdneri) 2.2 to 17.7 µg/l (Macek, et al. 1969; Katz, 1961); and

fathead minnows (Pimephales promelas) 32 and 37 µg/l (Henderson, et al. 1959). Acute toxicity varies greatly in freshwater invertebrates. In bioassays in which the aldrin concentrations were not measured, the observed 48-hour LC_{50} value for Daphnia pulex was 28 µg/l (Sanders and Cope, 1966), and the observed 96-hour LC_{50} values ranged from 4,300 to 38,500 µg/l for scud, Gammarus spp. (Sanders, 1969, 1972; Gaufin, et al. 1965).

In flow-through exposures to aldrin, the 48 and 96-hour LC_{50} values for six saltwater fish species ranged from 2.0 to 7.2 µg/l. Invertebrate LC_{50} values ranged from 0.37 to 33.0 µg/l (U.S. EPA, 1979a).

B. Chronic Toxicity

No entire cycle or embryo-larval tests have been reported for any fresh or saltwater species (U.S. EPA, 1979a).

C. Plant Effects

An aldrin concentration of 10,000 µg/l reduced the population growth in 12 days for water meal, Wolffia papulifera (Worthley and Schott, 1971). The productivity of a phytoplankton community was reduced 85 percent after four hour exposure to 1,000 µg/l aldrin (Butler, 1963).

D. Residues

No freshwater or saltwater residue studies have been reported for aldrin (U.S. EPA, 1979a).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The current exposure level for aldrin set by the Occupational Safety and Health Administration is a time-weighted average of 250 $\mu g/m^3$ for skin absorption (37 FR 22139). In 1969, the U.S. Public Health Service Advisory Committee recommended that the drinking water standard for aldrin be 17 $\mu g/l$ (Mrak, 1969). The U.N. Food and Agricultural Organization/World Health Organization acceptable daily intake for aldrin is 0.1 $\mu g/kg/day$ (Mrak, 1969).

The carcinogenicity data of the National Cancer Institute (1976) (43 FR 2450) were used to calculate the draft water quality criterion for aldrin which keeps the lifetime cancer risk for humans below 10^{-5}. The concentration for aldrin is 4.6×10^{-2} ng/l (U.S. EPA, 1979a).

B. Aquatic

Draft criterion has not been proposed directly for aldrin because of its rapid conversion to dieldrin (U.S. EPA, 1979a).

ALDRIN

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No. 9

Allyl Alcohol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

ALLYL ALCOHOL

Summary

Allyl alcohol is a severe irritant to the mucous membranes at high concentrations. Hepatotoxicity has been seen after oral and inhalation exposures, however, results indicate that this effect may not be cumulative. Allyl alcohol is also absorbed percutaneously.

Information on the carcinogenic, mutagenic, teratogenic or other reproductive effects of allyl alcohol was not found in the available literature.

Data concerning the effects of allyl alcohol to aquatic organisms were not found in the available literature.

I. INTRODUCTION

This profile is based on computerized searches of Toxline, Biosis and Chemical Abstracts, and a review of other available appropriate information sources as available.

Allyl alcohol (molecular weight-58.08) is a limpid liquid with pungent odor. It is soluble in water, alcohol and ether, has a melting point of -50°C and a boiling point of 96-97°C (Sax, 1979).

The major uses of allyl alcohol are in the manufacture of allyl compounds, war gas, resins, and plasticizers (Windholz, 1976). Sixty kt. are used in this country per year, of which 50 kt. are used to manufacture glycerol (Kirk and Othmer, 1963).

After several years of storage, allyl alcohol polymerizes into a substance that is soluble in chloroform but not water. When treated with ether this substance becomes brittle (Windholz, 1976).

II. EXPOSURE

Pertinent data were not found in the available literature on air or water exposure.

Esters of allyl alcohol are used as food flavorings. Natural derivatives of allyl alcohol are widely distributed in vegetable material (Lake, et al. 1978).

III. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data were not found in the available literature.

B. Metabolism

It has been suggested that allyl alcohol is completely metabolized and that acrolein might be an intermediate metabolite (Browning, 1965). The rate of metabolism in rats was found to be about 23 mg/kg/hr. during constant intravenous infusion (Carpanini, et al. 1978).

C. Excretion

Allyl alcohol was not found in the urine of animals that had been dosed subcutaneously or intravenously with the compound (Browning, 1965). Other pertinent data were not found in the available literature.

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity, and Reproductive Effects

Information on the carcinogenic effects of allyl alcohol was not found in the available literature.

B. Chronic Toxicity

Lake, et al. (1978) administered allyl alcohol to rats by gastric intubation. The rats were dosed daily for 1, 10, or 28 days. Liver homogenates from treated animals were analyzed for enzyme activity. Administration for one day produced marked periportal necrosis, but repeated administration for 10 or 28 days did not seem to increase the damage.

Allyl alcohol administration in the drinking water at a dose of 72 mg/kg/day caused weight loss, transient pulmonary rales, crustiness of the eyelids, and local areas of liver necrosis (Browning, 1965).

Rats exposed to 40, 60, or 100 ppm of allyl alcohol by inhalation showed signs of acute mucous membrane irritation, such as gasping and nasal discharge. At the 100 ppm dose, the animals died after 10 exposures (Browning, 1965). No gross toxicity was seen at 5 or 10 ppm, 5 days a week for 13 months in rats, rabbits, guinea pigs, and dogs. However, mild reversible degenerative changes in the liver and kidney were seen at the seven ppm dose. A dose of 50 ppm was lethal to rats after 30 days (Torkelson, et al. 1959).

Carpanini, et al. (1978) gave rats doses of allyl alcohol 50, 100, 200, or 800 ppm im the drinking water for 15 weeks. Weight loss was seen in males given 100, 200, or 800 ppm and females given 800 ppm. Food consumption values were lower than the controls in males at 200 ppm and 800 ppm and females at 800 ppm. A dose-related decrease in water consumption was seen in all treated animals. Minor changes were seen in the liver, kidneys, and lungs of both treated and control groups upon histological examination.

C. Acute Toxicity

Oral LD_{50}'s of allyl alcohol have been found to be 64-100 mg/kg for rats, 96-139 mg/kg for mice, and 52-71 mg/kg for rabbits; 43 mg/kg was lethal to dogs. Intraperitoneal LD_{50}'s were 42 mg/kg for rats and 60 mg/kg for mice. In rabbits an LD_{50} of 53-89 mg/kg was found by percutan- eous absorption (Carpanini, et al. 1978). Inhalation of 1000 ppm was lethal to rabbits and monkeys after 3 to 4 hours. Erythema of the conjunctiva and swelling of the cornea are seen in the eye after exposure to allyl alcohol, however, no permanent damage was noted. Application to the skin caused only mild erythema. Intravenous injection produced a drop in blood pressure. Injection of 40 minims in a 20 percent saline solution caused fluctuations in the blood pressure, of rabbits resulting in violent convulsions. Vomiting, diarrhea, convulsions, apathy, ataxia, lacrimation and coma are seen after oral administration. Few cases of serious injury due to inhalation have been reported, however, because concentrations that would cause severe damage in a short period of time are painful to the eyes and nose. Five ppm are detectable by irritation and 2 ppm by odor (Browning, 1965).

Moderate air contamination has been found to cause lacrimation, pain around the eyes and blurred vision in man lasting up to 48 hours (Carpanini, et al. 1978).

D. Other Relevant Information

Allyl alcohol has an unusual effect on the central nervous system of mice and rats. The effect is seen as apathy, unwillingness to move, anxiety, and no interest in escaping. It is apparently different from narcosis seen with other agents (Dunlap, et al. 1958).

V. AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES

The recommended maximum atmospheric concentration (8 hours) is 2 ppm (Indust. Hyg. Assoc., 1963).

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No. 10

Antimony

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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ANTIMONY

Summary

The adverse health effects most commonly associated with exposure to antimony are pulmonary, cardiovascular, dermal, and certain effects on reproduction, development, and longevity. Cardiovascular changes have been well-established with exposure to antimony and probably represent the most serious threat to human health. Antimony has not been associated with carcinogenic effects. The lowest observed effect level for antimony in the drinking water of rats was 5 ppm. A draft criterion of 145 µg/l has been recommended for antimony in water based on an acceptable daily intake of antimony from water, fish, and shellfish for man of 294 µg.

Antimony is highly toxic to aquatic organisms at a concentration ranging from 19 mg/l to 530 mg/l. Chronic values for antimony in freshwater organisms range from 0.8 mg/l to 5.4 mg/l.

ANTIMONY

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Antimony (U.S. EPA, 1979). The health hazards of antimony and its compounds have also been recently reviewed by the National Institute for Occupational Safety and Health (NIOSH, 1978).

Antimony (Sb; molecular weight 121.8) is a silvery, brittle, solid belonging to group VB of the periodic table and lies between arsenic and bismuth. It is classified as both a metal and a metalloid, and its principal oxidation states are +3 and +5. Antimony has a boiling point of 1366°C and a melting point of 636°C. Most inorganic compounds of antimony are either only slightly water soluble or decompose in aqueous media.

Antimony reacts with both sulfur and chlorine to form the tri-and pentavalent sulfides and chlorides. Oxidation to antimony trioxide (stibine), the major commercial oxide of antimony, is achieved under controlled conditions.

Consumption of antimony in the United States is on the order of 40,000 metric tons per year (Callaway, 1969), of which half is obtained from recycled scrap and the balance mainly imported. Use of antimony in the United States is directed chiefly to the manufacture of ammunition, storage batteries, matches and fireworks, and in the fire-proofing of textiles.

II. EXPOSURE

A. Water

Schroeder (1966) compiled data from surveys of municipal water supplies in 94 cities and reported that levels averaged less than 0.2 µg/l in finished water. In a related study, Schroeder and Kraemer (1974) noted that tap water levels of antimony can be elevated in soft water supplies due to leaching from plumbing.

B. Food

Because of the wide range of antimony levels in various types of foods, it is not possible to accurately estimate an average dietary intake. Tanner and Friedman (1977) concluded that dietary intake of antimony is negligible, based upon trace metal food monitoring data from the U.S. Food and Drug Administration. However, in earlier studies, calculated average dietary intakes were reported at 100 µg per day for man (Schroeder, 1970) and in the range of 0.25 to 1.28 mg per day for institutionalized children (Murthy, et al. 1971). In one study on antimony levels in Italian diets a mean daily value of several micrograms was reported (Clemente, 1976).

C. Inhalation

Antimony is not generally found in ambient air at measurable concentrations. National Air Sampling Network data for 1966 showed possibly significant levels at only four urban stations (0.042 to 0.085 $\mu g/m^3$) (Schroeder, 1970; Woolrich, 1973).

D. Other Routes

The total body burden of antimony arising from all environmental media is apparently very small relative to other trace metals (i.e., lead, mercury, cadmium) in the environment. Clemente (1976) published

limited data on fecal and urinary levels of antimony in selected Italian populations and concluded that daily intakes were less than 2.0 µg/day. In addition, data on the bioconcentration potential of antimony in fish (U.S. EPA, 1978) indicate that no bioaccumulation is likely to occur. The U.S. EPA (1979) has calculated the weighted average bioconcentration factor (BCF) for antimony to be 1.4 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on 25-day bioconcentration studies in bluegill.

III. PHARMACOKINETICS

Absorption of antimony in man and animals is mainly via the respiratory and gastro-intestinal tracts. The extent of absorption is dependent on factors such as solubility, particle size, and chemical forms (Felicetti, et al. 1974a; 1974b). Absorption via the GI tract is of the order of several percent with antimony trioxide, a relatively insoluble compound , and presumably would be much greater with soluble antimonials.

Blood is the main carrier for antimony, the extent of partition between blood compartments depending on the valence state of the element and the animal species studied (Felicetti, et al. 1974a). The rodent exclusively tends to concentrate trivalent antimony for long periods in the erythrocyte (Djuric, et al. 1962). Whatever the species, it can generally be said that pentavalent antimony is borne by plasma and trivalent antimony in the erythrocyte. Clearance of antimony from blood to tissues is relatively rapid, and this is especially true in the case of parenteral administration and the use of pentavalent antimony (Casals, 1972; Abdalla and Saif, 1962; El-Bassouri, et al. 1963).

The tissue distribution and subsequent excretion of antimony is a function of the valence state.

In animals, trivalent antimony aerosols lead to highest levels in the lung, skeleton, liver, pelt, and thyroid while pentavalent aerosols show a similar distribution, with the exception of slower uptake by the liver (Felicetti, et al. 1974a; 1974b; Thomas, et al. 1973).

Parenteral administration to animals shows trivalent antimony accumulating in the liver and kidney as well as in pelt and thyroid (Molkhia and Smith, 1969; Waitz, et al. 1965).

In man, non-occupational or non-therapeutic exposure shows very low antimony levels in various tissues with little evidence of accumulation (Abdalla and Saif, 1962). Chemotherapeutic use leads to highest accumulation in liver, thyroid, and heart for trivalent antimony.

The biological half-life of antimony in man and animals is a function of route of exposure, chemical form, and oxidation state. The rat appears to be unique in demonstrating a long biological half-time owing to antimony accumulation in the erythrocyte. In other species, including man, moderate half-times of the order of days have been demonstrated. While most soft tissues do not appear to accumulate antimony, the skin does show accumulation, perhaps because of its high content of sulfhydryl groups. With respect to excretion, injection of trivalent antimony leads mainly to urinary excretion in guinea pigs and dogs, and mainly fecal clearance in hamsters, mice and rats.

Pentavalent antimony is mainly excreted via the kidney in most species owing to its higher levels in plasma.

Unexposed humans excrete less than 1.0 μg antimony daily via urine, while occupational or clinical exposure may result in markedly increased amounts.

IV. EFFECTS

A. Carcinogenicity

Antimony has not been tested for carcinogenic activity using an appropriately designed chronic bioassay protocol. However, Shroeder (1970) indicated that the chronic administration of antimony at 5 ppm in the drinking water of rats, had no apparent tumorigenic effect. However, the shortened life span of treated animals (average 106 to 107 days less than controls) limits the usefulness of these data. Similar results were also observed in a study with mice chronically exposed to antimony at 5 ppm in the drinking water (Kanisawa and Schroeder, 1969).

A single epidemiologic investigation has been conducted into the role of antimony in the development of occupational lung cancer (Davies, 1973). This retrospective study, which was limited in scope, provided no definitive information to support the possible role of antimony in lung cancer development.

B. Mutagenicity

Antimony has not been tested for activity in standard mutagenicity bioassays.

C. Teratogenicity

Little information is available concerning possible teratogenic effects of antimony. In one study, Casals (1972) observed no effects, i.e., no fetal abnormalities, following administration of a solution of antimony dextran glycoside containing 125 or 250 mg Sb/kg to pregnant rats on days 8 to 15 of gestation.

D. Other Reproductive Effects

Aiello (1955) observed a higher rate of premature deliveries among female workers engaged in antimony smelting and processing. In

addition, dysmenorrhea was frequently reported among women workers. Similarly, Belyaeva (1967) reported that a greater incidence of gynecological disorders was found among antimony smelter workers than in a control group (77.5 percent vs. 56 percent; significance unknown). Spontaneous late abortions occurred in 12 percent of the exposed females compared to 4.1 percent among controls. Average urine levels of antimony for exposed workers, however, were extremely high, ranging from 2.1 to 2.9 mg/100 ml. Antimony was also found in breast milk (3.3$\pm$ 2 mg/10), placental tissue (3.2 to 12.6 mg/100 mg), amniotic fluid (6.2 to 2.8 mg/100 mg), and umbilical cord blood (6.3 $\pm$ 3 mg/100 ml).

In studies with rats exposed either to antimony dust (50 mg/kg, i.p.) or to antimony trioxide dust (250 mg/m^3, 4 hours per day for 1.5 to 2 months), Belyaeva (1967) reported increased reproductive failure, fewer offspring, and damage to the reproductive tissues (ovary and uterus).

E. Chronic Toxicity

The toxic effects of exposure to antimony have been repeatedly observed in both humans and experimental rodents. Pulmonary, cardiovascular, dermal, and certain effects on reproduction, development, and longevity are among the health effects most commonly associated with antimony exposure.

Cardiovascular changes have been well established following exposure to antimony and probably represent the most serious human health effects demonstrated thus far (U.S. EPA, 1979). Air concentrations of

antimony trisulfide exceeding 3 mg/cu m were associated with the induction of altered ECG patterns and some deaths attributed to myocardial damage among certain antimony workers (Brieger, et al. 1954). Also, in parallel studies on animals, Brieger and coworkers (1954) observed ECG alterations in rats and rabbits exposed to antimony in air at levels of 3.1 to 5.6 mg/m^3, 7 hours/day, 5 days/week for at least 6 weeks.

Gross and coworkers (1955) presented evidence for growth retardation occurring when rats were chronically fed diets containing two percent antimony trioxide. Other investigators (Schroeder, et al. 1970; Kanisawa and Schroeder, 1969) reported that oral exposure to 5 ppm of antimony in drinking water had no effect on the rate of growth of either rats or mice. However, the 5 ppm exposure level was effective in producing slight but significant lifespan shortening in both rats and mice, and altered blood chemistries in exposed rats. Therefore, the 5ppm exposure level has been considered the "lowest observed effect level" in animals that likely approximates the "no effect" level for antimony-induced effects on growth and longevity.

V. AQUATIC TOXICITY

A. Acute Toxicity

The data base for antimony and freshwater organisms is small and indicates that plants may be more sensitive than fish or invertebrate species.

A 96-hour LC_{50} of 22,000 µg/l was reported for antimony trichloride with the fathead minnow, whereas the value for bluegills and antimony trioxide is above 530,000 µg/l (U.S. EPA, 1979). For Daphnia magna a 48-hour LC_{50} value of 19,000 µg/l and a 64-hour EC_{50} value of 19,800 µg/l have been reported for antimony trichloride. Another 48-hour

EC_{50} value for antimony trioxide and Daphnia magna has been reported to be above 530,000 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

No adverse effects on the fathead minnow were observed during an embryo-larval test with antimony trioxide at the highest test concentration of 7.5 µg/l (U.S. EPA, 1978). However, a comparable test with antimony trichloride produced limits of 1,100 and 2,300 µg/l for a chronic value of 800 µg/l. A life cycle test with Daphnia magna and antimony trichloride produced limits of 4,200 and 7,000 µg/l for a chronic value of 5,400 µg/l (U.S. EPA, 1979). Pertinent information could not be located in the available literature regarding chronic effects of antimony on saltwater organisms.

C. Plants Effects

The 96-hour EC_{50} values for chlorophyll a inhibition and reduction in cell number of the freshwater alga, Selenastrum capricornutum are 610 and 630 µg/l, respectively. This indicates that aquatic plants may be more sensitive than fish or invertebrate species (U.S. EPA, 1978). No inhibition of chlorophyll a reduction or in cell numbers of the marine alga, Skeletonema costatum, were observed at concentrations as high as 4,200 µg/l (U.S. EPA, 1978).

D. Residues

There was no bioconcentration of antimony by the bluegill above control concentrations during a 28 day exposure to antimony. No data have been reported on bioconcentration of antimony in marine species.

VI EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of

public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Existing occupational standards for exposure to antimony are reviewed in the recently released NIOSH criteria document, Occupational Exposure to Antimony (U.S. Department of Health, Education and Welfare, 1978). As stated in the NIOSH (1978) document, the American Conference of Governmental Industrial Hygienists (ACGIH), in 1977, listed the TLV for antimony as 0.5 mg/m^3 along with a notice of intended change to a proposed TLV of 2.0 mg/m^3 for soluble antimony salts. The proposed TLV was based mainly on the reports of Taylor (1966) and Cordasco (1974) on accidental poisoning by antimony trichloride and pentachloride, respectively. Proposed limits of 0.5 mg/m^3 for handling and use of antimony trioxide and 0.05 mg/m^3 for antimony trioxide production were included in the ACGIH (1977) notice of intended changes.

The Occupational Safety and Health Administration earlier adopted the 1968 ACGIH TLV for antimony of 0.5 mg/m^3 as the Federal standard (29 CFR 1910.1000). This limit is consistent with limits adopted by many other countries as described in Occupational Exposure Limits for Airborne Toxic Substances - A tabular Compilation of Values from Selected Countries, a publication released by the International Labour Office in 1977. The NIOSH (1978) document also presented table of exposure limits from several countries, reproduced here as Table 1; the typical standard adopted was 0.5 mg/m^3.

TABLE 1

HYGIENIC STANDARDS OF SEVERAL COUNTRIES FOR
ANTIMONY AND COMPOUNDS IN THE WORKING ENVIRONMENT

Country	Standard (mg/m^3)	Qualifications
Finland	0.5	Not stated
Federal Republic of Germany	0.5	8-hour TWA
Democratic Republic of Germany	0.5	Not stated
Rumania	0.5	Not stated
USSR	0.5	For antimony dust
	0.3	For fluorides and chlorides (tri-and pentavalent); obligatory control of HF and HCl
	1.0	For trivalent oxides and sulfides
	1.0	For pentavalent oxides and sulfides
Sweden	0.5	Not stated
USA 8-hour TWA		0.5
Yugoslavia	0.5	Not stated

Modified from Occupational Exposure Limits in Airborne Toxic Substances, International Labour Office.

The 0.5 mg/m^3 level was also recommended as the United States occupational exposure standard by the NIOSH (1978) criteria document, based mainly on estimated no-effect levels for cardiotoxic and pulmonary effects.

Based upon the data presented in the Ambient Water Quality Criteria Document for Antimony (U.S. EPA, 1979), a recommended draft criterion of 145 $\mu g/l$ has been established. This value is based upon an acceptable daily intake for man of 294 ug, derived from experimental animal studies in which 5 ppm of antimony produced a slight shortening of lifespan with no other deserved effects. An uncertainty factor of 100 was used in extrapolating from animal data to human health effects.

B. Aquatic

The draft criterion for Antimony to protect freshwater aquatic life as derived using the Guidelines is 120 µg/l as a 24 hour average and the concentration should not exceed 1,000 µg/l at any time.

A saltwater criterion was not derived (U.S. EPA, 1979)

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No. 11

Arsenic

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated arsenic and has found sufficient evidence to indicate that this compound is carcinogenic.

ARSENIC

SUMMARY

Epidemiological studies have shown increased death rates from lung cancer in workers exposed to arsenic, probably through inhalation. Other human studies have shown increased skin cancers in non-occupationally exposed populations. Increased incidence of lymphomas and hemangioendotheliomas are also occasionally reported.

Arsenicals have produced mutagenic effects in plants, bacteria, *in vitro* leukocyte cultures, and in the lymphocytes of exposed humans. The teratogenic effects of arsenicals have been demonstrated in many animal species. An increased frequency of abortions in pregnant women exposed to arsenic has been reported in a single study (U.S. EPA, 1979).

The chronic toxic effects of arsenic involve skin hyperkeratosis, liver damage, neurological disturbances (including hearing loss), and a gangrenous condition of the extremities (Blackfoot disease). An increased mortality from cardiovascular disease resulting from chronic arsenic exposure has been suggested in two studies.

The data base for the toxicity of arsenic to aquatic organisms is more complete for freshwater organisms, where concentrations as low as 128 µg/l have been acutely toxic to freshwater fish. A single marine species produced an acute value in excess of 8,000 µg/l. Based on one chronic life cycle test using *Daphnia magna*, a chronic value for arsenic was estimated at 853 µg/l.

ARSENIC

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Arsenic (U.S. EPA, 1979).

Arsenic is a gray, crystalline metalloid with a molecular weight of 74.92, a density of 5,727, a melting point (at 28 atmospheres) of 817°C, and a boiling point (sublimates) of 613°C (Weast, 1975). Arsenic exists in a variety of valence states; the most common forms include pentavalent (arsenate), trivalent (arsenite), and -3 valency (arsine). Properties of some inorganic arsenic compounds are shown in Table 1.

Conditions of low pH, low oxidation-reduction potential, and low dissolved oxygen in water favor formation of the lower valency states (arsenite and arsine); more basic, oxygenated waters favor the presence of arsenate. Inorganic arsenic can be converted to organic alkyl-arsenic acids and to methylated arsines under both aerobic and anaerobic conditions (U.S. EPA, 1979).

Arsenic and its compounds are used in the manufacture of glass, cloth, and electrical semiconductors, as fungicides and wood preservatives, as growth stimulants for plants and animals, and in veterinary applications (U.S. EPA, 1976).

Production is currently 1.8×10^4 metric tons per year (U.S. EPA, 1979).

Arsenic will persist in some form in the environment. Inorganic arsenate is thermodynamically favored under normal conditions over arsenite in water and is a more soluble form (Ferguson and Gavis, 1972). Both arsenate and arsenite may be precipitated from water by adsorption onto iron and alum-

Table 1. Properties of Some Inorganic Arsenic Compounds
(Standen, 1967; U.S. EPA, 1976)

Compound	Formula	Water Solubility	Specific Properties
Arsenic trioxide	As_2O_3	12×10^6 µg/l @ 0°C 21×10^6 µg/l @ 25°C	Dissolves in water to form arsenious acid (H_3AsO_3: $K = 8 \times 10^{-10}$ @ 25°C)
Arsenic pentoxide	As_2O_5	2300×10^6 µg/l @ 20°C	Dissolves in water to form arsenic acid (H_3AsO_4: $K_1 = 2.5\ 10^{-4}$ $K_2 = 5.6 \times 10^{-8}$; $K_3 = 3 \times 10^{-13}$)
Arsenic hydride	AsH_3	20 ml/100 g cold water	This compound and its methyl derivatives are considered to be the most toxic.
Arsenic(III) sulfide	As_4S_6	520 µg/l @ 18°C	Burns in air forming arsenic trioxide and sulfur dioxide; occurs naturally as orpiment.
Arsenic sulfide	As_4S_4		Occurs naturally as realgar.
Arsenic(V) sulfide	As_4S_{10}	1400 µg/l @ 0°C	

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inum compounds (U.S. EPA, 1979). Methylated arsines appear to be volatile and sparingly soluble. Waters containing high organic matter may bind arsenic compounds to colloidal humic matter (U.S. EPA, 1979).

II. EXPOSURE

Arsenic appears to be ubiquitous in the environment. The earth's crust contains an average arsenic concentration of 5 mg/kg (U.S. EPA, 1976). The major sources of arsenic in the environment are industrial, such as those in the smelting of non-ferrous ores and in coal-fired power plants that utilize fuel containing arsenic. Substantial arsenic contamination of water can occur from the improper use of arsenical pesticides (U.S. EPA, 1979).

Based on available monitoring data, the U.S. EPA (1979) has estimated the uptake of arsenic by adult humans from air, water, and food:

Source	mg/day	
	Maximum Conditions	Minimum Conditions
Atmosphere	.125	.001
Water	4.9	0.002
Food Supply	.9	.007
Total	5.925	.010

Contaminated well water, seafood, and air near smelting plants all present sources of high potential arsenic intake.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor (BCF) for arsenic to be 2.3 in the edible portions of fish and shellfish consumed by Americans. This estimate was based on bioconcentration studies in freshwater fish.

III. PHARMACOKINETICS

A. Absorption

The main routes by which arsenic can enter the body are inhalation and ingestion. Particle size and solubility greatly influence the biological fate of inhaled arsenic. Falk and Kotin (1961) have reported that the optimal range of particle size for deposition in the lower tracheobronchial tree is 0.1 to 2 μ. Larger particles are trapped by the mucous membranes of the nose and throat and swallowed; following this, the particles may be absorbed from the gastrointestinal tract (U.S. EPA, 1979).

Human inhalation studies in terminal lung cancer patients (Holland, et al. 1959) have indicated that 4.8 to 8.8 percent of inhaled arsenic-74 in cigarette smoke may be absorbed. Radioactive arsenite inhaled in an aerosol solution by two patients showed 32 and 62 percent absorption, respectively. Pinto, et al. (1976) studied arsenic excretion in 24 workers exposed to the compound during copper smelting; urinary arsenic levels were found to correlate significantly with average airborne arsenic concentrations.

Water soluble arsenicals are readily absorbed through the gastrointestinal tract. Studies with radioactive arsenate administered orally to rats have shown 70 to 90 percent absorption from the gastrointestinal tract (Urakubo, et al. 1975; Dutkiewicz, 1977). Arsenic trioxide is only slightly soluble in water and is not well absorbed. Theoretically, trivalent arsenicals should be less readily absorbed than pentavalent forms due to reactivity with membrane components

and lower solubility (U.S. EPA, 1979). However, investigators have reported high absorption of trivalent arsenic from the gastrointestinal tract in humans (Bettley and O'Shea, 1975; Crecelius, 1977).

The absorption of arsenicals following dermal exposure has been described in rats (Dutkiewicz, 1977) and humans (Robinson, 1975; Garb and Hine, 1977).

Arsenic has been detected in the tissues (Kadowaki, 1960) and cord blood of newborns (Kagey, et al. 1977), and thus transfers across the placenta in humans.

B. Distribution

Injection of radiolabelled arsenite in terminally ill patients produced widespread distribution of the compound (WHO, 1973). Hunter, et al. (1942) studied the distribution of radioactive arsenicals in humans following oral and parenteral administration and found arsenic in the liver, kidney, lungs, spleen, and skin during the first 24 hours after administration. Levels of arsenic are maintained for long periods in bone, hair and nails (Kadowaki, 1960; Liebscher and Smith, 1968).

Tissue distribution of pentavalent arsenic has been described in only a few animal studies; these studies indicate only minor differences in distribution between trivalent and pentavalent arsenicals (WHO, 1973).

C. Metabolism

Studies with brain tumor patients given injections of trivalent arsenic indicate that about 60 percent of the total urinary arsenic was in the pentavalent state the first day after dosing (Mealey, et al. 1959). Braman and Foreback (1973) have analyzed human urine samples and detected high amounts of methylated forms (dimethyl arsenic acid and methyl arsenic acid). Analysis of the urine of one patient who ingested arsenic-contaminated wine indicated that 8 percent of the initial dose was excreted as inorganic arsenic, 50 percent was excreted as dimethyl arsenic acid, and 14 percent was excreted as methyl arsenic acid (Crecelius, 1977).

The half-lives of inorganic and organic (methylated) arsenicals in one patient have been reported as 10 and 30 hours, respectively (Crecelius, 1977).

D. Excretion

Arsenic is excreted primarily in the urine, with small amounts removed in the feces and through normal hair loss and skin shedding (U.S. EPA, 1979). Reports of minor arsenic loss in sweat have also been made (Vellar, 1969).

Small amounts of radioactive arsenic (.003 to .35 percent) have been detected in expired air following administration to rats (Dutkiewicz, 1977) and chickens (Overby and Fredrickson, 1963).

IV. EFFECTS

A. Carcinogenicity

Epidemiological studies have shown an increased mortality rate from respiratory cancer in workers exposed to

arsenic during smelting operations (Lee and Fraumani, 1969; Pinto and Bennett, 1963; Snegireff and Lombard, 1951; Kuratsune, et al. 1974). A retrospective study of Dow Chemical employees indicated that workers exposed primarily to lead arsenate and calcium arsenate showed increased death rates from lung cancer and malignant neoplasms of the lymphatic and hematopoietic systems (except leukemia) (Ott, et al. 1974).

A similar trend was noted in a study of retired Allied Chemical workers (Baetjer, et al. 1975).

High rates of development of skin cancers have been reported in several studies of populations exposed to high concentrations of arsenic in drinking water (Geyer, 1898; Bergogilio, 1964; Tseng, et al. 1968).

Hemangioendothelioma of the liver associated with exposure to arsenicals through ingestion has been reported in several case studies (Roth, 1957; Regelson, et al. 1968).

Extensive experiments in animal systems with arsenicals administered in the diet or drinking water, or applied topically or by intratracheal instillation failed to show positive tumorigenic effects (U.S. EPA, 1979). However, two recent reports have shown effects in animals. Schrauzer and Ishmael (1974) indicated that feeding of sodium arsenite in drinking water accelerated the rate of spontaneous mammary tumor formation. Osswald and Goerttler (1971) found an increase in leukemias and lymphomas in mice injected repeatedly with sodium arsenate.

Animal studies on the skin tumor-promoting or co-carcinogenic effects of arsenicals have produced negative results (Raposo, 1928; Baroni, et al. 1963; Boutwell, 1963).

B. Mutagenicity

An increased incidence of chromosomal aberrations has been found in persons exposed to arsenic occupationally and medically (Petres, et al. 1970; Nordenson, et al. 1978; Burgdorf, et al. 1977).

In vitro chromosomal changes following exposure to arsenicals have been reported in root meristem cultures (Levan, 1945) and in human leukocyte cultures (Petres and Hundeiker, 1968; Petres, et al. 1970, 1972; Paton and Allison, 1972).

Arsenate has been found to increase the frequency of chromosome exchanges in Drosophila. Several organic arsenicals have a synergistic effect with ethylmethane sulfonate in producing chromosome abnormalities in barley (Moutshcen and Degraeve, 1965).

Sodium arsenate, sodium arsenite, and arsenic trichloride produced positive mutagenic effects in a recombinant strain of Bacillus subtillus (Nishioka, 1975). Loforth and Ames (1978) were unable to show mutagenic effects of trivalent and pentavelent arsenicals in the Ames Salmonella assay. Arsenite exposure decreased the survival of E. coli after UV damage of cellular DNA (Rossman, et al. 1975).

C. Teratogenicity

Nordstrom, et al. (1978) have reported an increase in the frequency of spontaneous abortions in pregnant women living in the vicinity of a copper smelting plant; the exposure environment was complex, involving several heavy metals and sulfur dioxide.

Sodium arsenate has been shown to induce teratogenic effects in the chick embryo (Ridgway and Karnofsky, 1952), in golden hamsters (Ferm and Carpenter, 1968; Ferm, et al. 1971), in mice (Hood and Bishop, 1972), and rats (Beaudoin, 1974). Malformations noted included exencephaly, anencephaly, renal agenesis, gonadal agenesis, eye defects, and rib and genitourinary abnormalities. Sodium arsenite injected intraperitoneally into mice produced a lower incidence of malformations than an equivalent dose of sodium arsenate (Hood and Bishop, 1972; Hood, et al. 1977). Thacker, et al. (1977) has noted that a higher oral dose of sodium arsenate is needed to produce teratogenic effects in mice, when compared to intraperitoneal doses.

Feeding of three generations of mice with low doses of sodium arsenite in the chow failed to produce teratogenic effects, but did decrease litter size (Schroeder and Mitchener, 1971).

D. Other Reproductive Effects

Pertinent information could not be located in the available literature regarding other reproductive effects.

E. Chronic Toxicity

A variety of chronic effects of arsenic exposure has been noted. This includes a characteristic palmar-

plantar hyperkeratosis and a gangrenous condition of the hands and feet called Blackfoot disease (U.S. EPA, 1979). Several clinical reports of liver damage in patients treated with arsenical medication have been published (WHO, 1979). An increased mortality from cardiovascular disease has been noted in two epidemiological studies of smelter workers exposed to high airborne arsenic (Lee and Fraumeni, 1969; U.S. EPA, 1979). Neurological disturbances, including hearing loss, in workers exposed to arsenicals have been reported (WHO, 1979).

Effects of arsenicals on the hematopoietic system following chronic exposure have also been noted (WHO, 1979). These include disturbed erythropoiesis and granulocytopenia, which may lead to impaired resistance to viral infections.

V. AQUATIC TOXICITY

A. Acute Toxicity

Seven static and seven flow-through bioassays from 48 to 96-hours in duration provide a range of LC_{50} values for freshwater fish of 290 to 150,000 µg/l. Hughes and Davis (1967) demonstrated the most sensitive species as being bluegill fingerlings, Lepomis macrochirus, while Sorenson (1976) reports that the most resistant species was the green sunfish, Lepomis cyanellus. Both species were tested in static tests. Sanders and Cope (1966) provided the data for freshwater invertebrates in static bioassays. The cladoceran, Simocephalus serrulatus, was the most sensitive with an 48-hour LC_{50} value of 812 µg/l, while the stonefly, Ptaronarcys californica, was the most resistant species with an

LC_{50} value of 22,040 µg/l. In marine organisms, the chum salmon, Onchorhynchus keta, had a 48-hour flow-through LC_{50} value of 8,331 µg/l (Alderdice and Brett, 1957). Two marine invertebrates were tested in 96 or 48-hour static-renewal or static assays and produced the following LC_{50} values: bay scallop, Argopecten irradiana, with 3,490 µg/l; and the embryos of the American oyster, Crassostrea virginica, with a value of 4,330 µg/l.

B. Chronic Toxicity

One chronic life cycle freshwater test has provided a chronic value of 853 µg/l for arsenic to Daphnia magna. Pertinent data could not be located in the available literature for the chronic toxicity of arsenic to marine organisms.

C. Plant Effects

The lowest effective concentration recorded was 100 percent kill levels of 2,320 µg/l for four species of freshwater algae.

D. Residues

Bioconcentration factors for five freshwater invertebrate species and two fish species ranged from less than 1 to 17 (U.S. EPA, 1979).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Criteria for organic and inorganic arsenicals have been derived. However, due to public comment questioning the relevancy and accuracy of the studies used in the development of these criteria, further review is necessary before final recommendation.

The OSHA time-weighted average exposure criterion for arsenic is 10 $\mu g/m^3$.

B. Aquatic

For arsenic, the draft criterion for freshwater organisms is 57 µg/l, not to exceed 130 µg/l. For marine organisms, the draft criterion is 29 µg/l, not to exceed 67 µg/l (U.S. EPA, 1979).

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No. 12

Asbestos

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated asbestos and has found sufficient evidence to indicate that this compound is carcinogenic.

ASBESTOS

Summary

Numerous studies indicate that asbestos fibers introduced into the pleura, peritoneum, and trachea of rodents have induced malignant tumors. The strongest evidence for the carcinogenicity of ingested asbestos is provided by epidemiology of human populations occupationally exposed to high concentrations of airborne asbestos dust. Inhalation exposure to asbestos dust is accompanied by ingestion because a high percentage of the inhaled fibers are removed from the lung by mucociliary action and subsequently swallowed. Peritoneal mesothelioma, often in great excess, and modest excesses of stomach esophagus, colonrectal, and kidney cancer have been linked to occupational exposure to asbestos.

Pertinent data on the acute or chronic effects of asbestos to aquatic organisms were not found in the available literature.

ASBESTOS

I. INTRODUCTION

This profile is based primarily upon the Ambient Water Quality Criteria Document for Asbestos (U.S. EPA, 1979). In addition, valuable information is available from recent reviews by the International Agency for Research on Cancer (IARC, 1977) and the National Institute for Occupational Safety and Health (NIOSH, 1977).

Asbestos is a broad term applied to numerous fibrous mineral silicates composed of silicon, oxygen, hydrogen, and metal cations such as sodium, magnesium, calcium, or iron. There are two major groups of asbestos, serpentine (chrysotile or "white asbestos") and amphibole. Although chrysotile is considered to be a distinct mineral, there are five fibrous amphiboles: actinolite, amosite ("brown asbestos"), anthophyllite, crocidolite ("blue asbestos"), and tremolite. The chemical composition of different asbestos fibers varies widely, and typical formulas are presented in Table 1. Some typical physical properties of three different mineral forms of asbestos are presented in Table 2.

TABLE 1

TYPICAL FORMULAS FOR ASBESTOS FIBERS

1.	Serpentines	chrysotile	$Mg_3Si_2O_5(OH)_4$
2.	Amphiboles	amosite	$(Mg,Fe)_7Si_8O_{22}(OH)_2$
		crocidolite	$Na/_2(Mg,Fe)_5Si_8O_{22}(OH)_2$
		anthophyllite	$(Mg,Fe)_7Si_8O_{22}(OH)_2$
		tremolite	$Ca_2Mg_5Si_8O_{22}(OH)_2$
		actinolite	$Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2$

TABLE 2

TYPICAL PHYSICAL PROPERTIES OF CHRYSOTILE (WHITE ASBESTOS), CROCIDOLITE (BLUE ASBESTOS), AND AMOSITE

	Units	Chrysotile (white asbestos)	Crocidolite (blue asbestos)	Amosite
Approximate diameter of smallest fibers	micron	0.01	0.08	0.1
Specific gravity	-	2.55	3.37	3.45
Average tensile strength	lb./inch^2	3.5×10^5	5×10^5	1.75×10^5
Modulus of elasticity	lb./inch^2	23.5×10^6	27.0×10^6	23.5×10^6

Asbestos minerals, despite a relatively high fusion temperature, are completely decomposed at temperatures of 1,000°C. Both the dehydroxylation temperature and decomposition temperature increase with increased MgO content among the various amphibole species (Speil and Leineweber, 1969).

The solubility product constants for various chrysotile fibers range from 1.0×10^{-11} to 3×10^{-12}. Most materials have a negative surface charge in aqueous systems. However, since chrysotile has a positive (+) charge, it will attract, or be attracted to, most dispersed materials. The highly reactive surface of asbestos causes many surface reactions which are intermediate between simple absorption and a true chemical reaction. The absorption of various materials on the surface of chrysotile supports the premise that the polar surface of chrysotile has a greater affinity for polar molecules (e.g., H_2O, NH_3) than for non-polar molecules (Speil and Leineweber, 1969).

Of all the asbestos minerals, chrysotile is the most susceptible to acid attack. It is almost completely destroyed within one hour in 1 N HCL at 95°C. Amphibole fibers are much more resistant to mineral acids (Lindell, 1972).

The resistance of the asbestos fibers to attack by reagents other than acid is excellent up to temperatures of approximately 100°C with rapid deterioration observed at higher temperatures. Chrysotile is completely decomposed in concentrated KOH at 200°C. In general, organic acids have a tendency to react slowly with chrysotile (Speil and Leineweber, 1969).

Chrysotile is the major type of asbestos used in the manufacture of asbestos products. These products include asbestos cement pipe, flooring products, paper products (e.g., padding), friction materials (e.g., brake linings and clutch facings), roofing products, and coating and patching compounds. In 1975, the total consumption of asbestos in the U.S. was 550,900 thousand metric tons (U.S. EPA, 1979).

Of the 243,527 metric tons of asbestos discharged to the environment, 98.3 percent was discharged to land, 1.5 percent to air, and 0.2 percent to water (U.S. EPA, 1979). Solid waste disposal by consumers was the single largest contribution to total discharges. Although no process water is used in dry mining of asbestos ore, there is the potential for runoff from asbestos waste tailings, wet mining, and iron ore mining. Mining operations can also contribute substantially to asbestos concentrations in water by air and solid waste contamination. In addition to mining and industrial discharges of asbestos, asbestos fibers, which are believed to be the result of rock outcroppings, are found in rivers and streams.

II. EXPOSURE

A. Water

Asbestos is commonly found in domestic water supplies. Of 775 recent samples analyzed by electron microscopy under the auspices of the U.S. EPA, 50 percent showed detectable levels of asbestos, usually of the chrysotile variety (Millette, 1979). Nicholson and Pundsack (1973) measured average asbestos levels of 0.3 - 1.5 µg/l in drinking water from two Eastern United States river systems. Levels of 2.0 to 172.7 x 10^6 fibers/l have been reported in Canadian tap water, the highest levels being found in unfiltered tap water near a mining area (Cunningham and Pontefract, 1971). In other studies of Canadian drinking water levels of 0.1 to 4 x 10^6 fibers/l have been reported (Kay, 1973). The U.S. EPA (1979) has concluded that about 95 percent of water consumers in the United States are exposed to asbestos fiber concentrations of less than 10^6 fibers/l. The mass concentrations of chrysotile asbestos in the water of cities with less than 10^6 fibers/l are likely to be less than 0.01 µg/l, corresponding to an adult daily intake of less than 0.02 ug. Pertinent data on the ability of aquatic organisms to bioconcentrate asbestos from water were not located in the available literature.

B. Food

There are scant data on the contribution of food products to population asbestos exposure. However, asbestos fibers and talc, which sometimes contains asbestos as an impurity, may be used in the manufacture of certain processed foods such as sugar, coated rice, vegetable oil and lard (IARC, 1977). Cunningham and Pontefract (1971) reported that certain beers and wines could contain asbestos fibers at levels similar to those found in drinking water systems (10^6 to 10^7 fibers/l).

C. Inhalation

Asbestos is present in virtually all metropolitan areas. Concentrations of asbestos in urban atmosphere are usually less than 10 ng/m^3, but may reach 100 ng/m^3 (Nicholson, et al. 1971; Nicholson and Pundesack, 1973; Sebastien, et al. 1976; IARC, 1977). Construction sites and buildings fireproofed with loose asbestos material showed the most significant contamination with individual measurements as high as 800 ng/m^3 (Nicholson, et al. 1975).

III. PHARMACOKINETICS

There are contradictory data concerning whether ingested asbestos fibers are capable of passage across the gastrointestinal mucosa (Gross, et al. 1974; Cooper and Cooper, 1978; Cunningham and Pontefract, 1973; Cunningham, et al. 1977). Most ingested asbestos particles are excreted in the feces (Cunningham, et al. 1976). However, at least one recent study (Cook and Olson, 1979) indicates that ingestion of drinking water containing amphibole fibers may result in the appearance of these fibers in the urine, thus providing evidence for passage of asbestos across the human gastrointestinal tract.

Ingestion of asbestos fibers is accompanied by swallowing of many fibers cleared from the respiratory tract by mucociliary action. More than half the asbestos inhaled will likely be swallowed (U.S. EPA, 1979). The deposition of asbestos fibers in the lung is a function of their diameter rather than length, as about 50 percent of particles with a mass median diameter of less than 0.1 um will be deposited on nonciliated pulmonary surfaces. Deposition on nasal and pharyngeal surfaces becomes important as mass median diameter approaches 1 μm and rises rapidly to become the dominant deposition site for airborne particles 10 um in diameter or greater

(Brain and Volberg, 1974). Portions of inhaled asbestos fibers which are not cleared by microciliary action may remain trapped in the lung for decades (Pooley, 1973; Langer, 1973). However, the chrysotile content of the lung does not build up as significantly as that of the amphiboles for similar exposure circumstances (Wagner, et al. 1974).

IV. EFFECTS

A. Carcinogenicity

All commercial forms of asbestos have demonstrated carcinogenic activity in mice, rats, hamsters, and rabbits. Intraperitoneal injection of various asbestos fibers has produced mesotheliomas in rats and mice (Maltoni and Annoscia, 1974; Pott and Friedrichs, 1972; Pott, et al. 1976). In rats, chronic inhalation of various types of asbestos have produced lung carcinomas and mesotheliomas (Reeves, et al. 1971, 1974; Gross, et al. 1967; Wagner, et al. 1974; Davis, et al. 1978). Intrapleural injection of asbestos fibers has produced mesotheliomas in rats, hamsters, and rabbits (Donna, 1970; Reeves, et al. 1971; Stanton and Wrench, 1972; Stanton, 1973; Wagner, et al. 1973, 1977; Smith and Hubert, 1974). The oral administration of asbestos filter material reportedly caused malignancies in rats (Gibel, et al. 1976) although other feeding studies have produced equivocal results.

Occupational exposure to chrysotile, amosite, anthophyllite, and mixed fibers containing crocidolite has resulted in high incidences of human lung cancers (Selikoff, et al. 1979; Seidman, et al. 1979; Enterline and Henderson, 1973; Henderson and Enterline, 1979; IARC, 1977). Occupational exposure to crocidolite, amosite, and chrysotile have also been associated with a large incidence of pleural and peritoneal mesatheliomas. An excess of gastrointestinal cancers has been associated in some studies with exposure to amosite, chrysotile, or mixed fibers containing crocidolite (Seli

koff, 1976; Selikoff, et al. 1979; Elmes and Simpson, 1971; Henderson and Enterline, 1979; Nicholson, et al. 1979; Seidman, et al. 1979; Newhouse and Berry, 1979; McDonald and Liddell, 1979; Kogan, et al. 1972).

In the general environment, mesotheliomas have occurred in persons living near asbestos factories and crocidolite mines and in the household contacts of asbestos workers (Wagner, et al. 1960; Newhouse and Thomson, 1965). In addition, several studies have implicated asbestos in drinking water with the development of cancer of the lung and digestive tract cancers (Mason, et al. 1974; Levy, et al. 1976; Cooper, et al. 1978, 1979). There is convincing evidence to support the contention that asbestos exposure and cigarette smoking act synergistically to produce dramatic increases in lung cancer over that from exposure to either agent alone (Selikoff, et al. 1968; Berry, et al. 1972).

In a study by Hammond, et al. (1979) involving 17,800 insulation workers, the death rate for non-smokers was 5.17 times that of a non-smoking control population. The death rate was 53.24 times that of the non-smoking control population or 4.90 times the death rate for a comparable group of non-exposed smokers. Cancers of the larynx, pharynx and buccal cavity in insulators were also found to be associated with cigarette smoking, together with some non-malignant asbestos effects such as fibrosis and deaths due to asbestosis.

B. Mutagenicity

In cultured Chinese hamster cells, chrysotile and crocidolite have produced genetic damage and morphologic transformation (Sincock and Seabright, 1975; Sincock, 1977). On the other hand, chrysotile, amosite, and anthophyllite showed no mutagenic activity toward tester strains of E. coli or S. typhimurium (Chamberlain and Tarmy, 1977).

C. Teratogenicity

Pertinent data on the possible teratogenic effects of asbestos were not located in the available literature, although transplacental passage of asbestos fibers has been reported (Cunningham and Pontefract, 1971, 1973).

D. Other Reproductive Effects

It is not known whether asbestos exposure may impair fertility or interfere with reproductive success (U.S. EPA, 1979).

E. Chronic Toxicity

The chronic ingestion of chrysotile by rats (0.5 mg or 50 mg daily for 14 months) produced no effects on the esophagus, stomach, or cecum tissue, but histological changes were seen in the ileum, particularly of the villi (Jacobs, et al. 1978).

The long-term disease entity, asbestosis, results from the inhalation of asbestos fibers and is a chronic, progressive pneumoconiosis. It is characterized by fibrosis of the lung parenchyma and produces shortness of breath as the primary symptom. Asbestos has accounted for numerous cases of occupational disablement during life as well as a considerable number of deaths among worker groups. In groups exposed at lower concentrations such as the families of workers, there is less incapacitation and although asbestosis can occur, deaths have not been reported (Anderson, et al. 1976).

Extrapulmonary chronic effects reported include "asbestos corns" from the penetration of asbestos fibers into the skin. No chronic nonmalignant gastrointestinal effects have been reported.

V. AQUATIC TOXICITY

Pertinent data concerning the effects of asbestos to either freshwater or marine organisms were not located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The current Occupational Safety and Health Administration (OSHA) standard for an 8-hour time-weighted average (TWA) occupational exposure to asbestos is 2 fibers longer than 5 microns in length per milliliter of air (2f/ml or 2,000,000 f/m^3). Peak exposures of up to 10 f/ml are permitted for no more than 10 minutes (Fed. Reg., 1972). This standard has been in effect since July 1, 1976, when it replaced an earlier one of 5 f/ml (TWA). Great Britain also has a value of 2 f/ml as the accepted level, below which no controls are required (BOHS, 1968). The British standard, in fact, served as a guide for the OSHA standard (NIOSH, 1972).

The British standard was developed specifically to prevent asbestosis among working populations; data were felt to be lacking that would allow for determination of a standard for cancer (BOHS, 1968). Unfortunately, among occupational groups, cancer is the primary cause of excess death for workers (see "Carcinogenicity" section) with three-fourths or more of asbestos-related deaths caused from malignancy. This fact has led OSHA to propose a lower TWA standard of 0.5 f/ml (500,000 f/m^3) (Fed. Reg., 1975). The National Institute for Occupational Safety and Health (NIOSH), in their criteria document for the hearings on a new standard, have proposed a value of 0.1 f/ml (NIOSH, 1977). In the discussion of the NIOSH proposal, it was stated that the value was selected on the basis of the sensitivity of analytical techniques using optical microscopy and that 0.1 f/ml may not neces

sarily protect against cancer. Recognition that no information exists that would define a threshold for asbestos carcinogenesis was also contained in the preamble of the OSHA proposal. The existing standard in Great Britain has been questioned by Peto (1978), who estimates that asbestos disease may cause the death of 10 percent of workers exposed at 2 f/ml for a working lifetime.

The existing federal standard for asbestos emissions into the environment prohibits "visible emissions" (U.S. EPA, 1975). No numerical value was specified because of difficulty in monitoring ambient air asbestos concentrations in the ambient air or in stack emissions. Some local government agencies, however, may have numerical standards (e.g., New York, 27 ng/m^3).

No standards for asbestos in foods or beverages exist even though the use of filtration of such products through asbestos filters has been a common practice in past years. Asbestos filtration, however, is prohibited or limited for human drugs (U.S. FDA, 1976).

The draft recommended water quality criterion for asbestos particles (U.S. EPA, 1979) is derived from the substantial data which exists for the increased incidence of peritoneal mesothelioma and gastrointestinal tract cancer in humans exposed occupationally to asbestos. This derivation assumes that much or all of this increased disease incidence is caused by fibers ingested following clearance from the respiratory tract. Several studies allow the association of approximate airborne fiber concentrations to which individuals were exposed with observed excess peritoneal and gastrointestinal cancer. All of the inhaled asbestos is assumed to be eventually cleared from the respiratory tract and ingested.

The draft criterion calculated to keep the individual lifetime cancer risk below 10^{-5}, is 300,000 fibers of all sizes/liter. The corresponding mass concentration for chrysotile asbestos is approximately 0.05 ug/l. This criterion has not yet gone through the process of public review; therefore, there is a possibility that the criterion may be changed.

B. Aquatic

Because no data are available on the aquatic toxicity of asbestos, the U.S. EPA (1979) derived no aquatic criteria.

ASBESTOS

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No. 13

Barium

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

BARIUM

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SUMMARY

Water-soluble barium compounds are highly toxic to man. Fish and lower species of marine organisms have been shown to bioaccumulate barium. The concentration of barium in sea water ranges around 20 ug/L, while that of drinking water averages about 6 ug/L.

Soluble barium salts have a high acute toxicity. Small amounts of barium can accumulate in the skeleton of humans and animals. Barium salts are strong muscle stimulants: acute intoxication generally results in uncontrolled contractions followed by partial or complete paralysis. Cardiac disturbances including arrythmias can also occur. Barium dusts are irritant to nose, throat and eyes. Baritosis (pneumoconiosis) occurs following chronic inhalation of (fine) barium dusts. Barium sulfate used in barium enemas, swallows and artificial orthopedic bones can result in tissue injury following solubilization of the barium sulfate and/or soluble impurities. Potassium acts as an antagonist for barium induced cellular disturbances. The TWA for exposure to soluble barium compounds is 0.5 mg/m^3.

I. INTRODUCTION

Barium (Ba; atomic weight 137.34) is a yellowish-white metal of the alkaline earth group. It is relatively soft and ductile and may be worked readily. Barium has a melting point of 729°C and a boiling point of 1640°C; its density is 3.51 g/cm^3 (Kunesh 1978).

Barium characteristically forms divalent compounds. At room temperature, it combines readily and exothermically with oxygen and the halogens. It reacts vigorously with water to form barium hydroxide, $Ba(OH)_2$ (Kunesh 1978).

Barium occurs in nature chiefly as barite, crude $BaSO_4$, and as witherite, a form of $BaCO_3$, both of which are highly insoluble salts. Only barite is mined in this country (Kirkpatrick 1978).

A review of the production range (includes importation) statistics for barium (CAS. No. 7440-39-3) which are listed in the initial TSCA Inventory, (U.S. EPA 1979) has shown that between 100,000 and 900,000 pounds of this chemical were produced/imported in 1977*.

*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

C. Environmental Occurrence

The flow of barium in the United States has been traced for the year 1969, during which time consumption of barium totaled 1.87 billion pounds. It was estimated that 30.8 million pounds of barium were emitted to the atmosphere. Nearly 18 percent of the emissions resulted from the processing of barite, more than 28 percent from chemical production, 26 percent from the combustion of coal, and 23 percent from the manufacture of miscellaneous end products (U.S. EPA 1972).

The concentration of barium in sea water is generally accepted as about 20 ug/L, with lower concentrations in the surface waters than at greater depths. Barium ions are generally removed from solution quite rapidly by adsorption, sedimentation and precipitation (U.S. EPA 1973). Concentrations of barium in this country's drinking water supplies generally range from less than 0.6 ug/L to about 10 ug/L, although a few midwestern and western states have had upper limits of 100 to 300 ug/L (U.S. EPA 1976).

Due to the common use of barite as a weighting agent in drilling muds, the resultant contamination of sediments near drilling sites was studied. The average content of barium in benthic sediments from the Southern California Bight was 637 parts per million (ppm), with a range from 43 to 1899 ppm. This area includes active drilling sites where barium contamination is expected. The concentration values were compared with the average 879 ppm barium found in mainland intertidal sediments and the 388 ppm determined in the channel island intertidal sediments. The lower barium content of the island sediments was attributed to the volcanic soil of the islands; however, the higher barium concentration of the mainland could not be traced to either natural or anthropogenic origin. Due to variations in soil sources it is questionable whether barium concentrations determined elsewhere could be used as reference values for this study (Chow 1978).

In two studies correlating trace metal concentrations in the environment with that in scalp hair of the inhabitants, barium was measured in the house dust collected in four communities. Geometric mean values of barium determined in house dust samples from the New York City area were as follows: 65.2 ug Ba/g dust in Riverhead, 137.6 ug/g in Queens, and 312.4 ug/g in the Bronx (USEPA, 1978b). The geometric mean value for barium measured in house dust in Ridgewood, New Jersey was 330.0 ug/g (U.S. EPA 1978c).

Barium and its compounds are used industrially as weighting agents in oil and gas well drilling muds; as coloring agents in glass, ceramics, paint, and pigments; as filler in rubber; and as antismoking agents in diesel fuel (U.S. EPA 1972; NAPCA 1969). In medicine, barium sulfate is used as an x-ray contrast medium because of its extreme insolubility and its ability to absorb x-rays (Kirkpatrick 1978; U.S. EPA 1978a).

II. EXPOSURE

A. Environmental Fate

Due to the high reactivity of barium, it is not found in its elemental state in the environment. In sea water, the naturally present sulfate and carbonate tend to precipitate any water-soluble barium components. Thus, the sediment usually has a higher concentration of barium than its corresponding water source (Guthrie 1979).

B. Bioconcentration

Due to the toxicity of soluble barium salts to man, the bioaccumulation of the element has been a concern. Barium can be concentrated in goldfish by a factor of 150. Concentration factors for barium listed in one study are 17,000 in phytoplankton, 900 in zooplankton, and 8 in fish muscle (U.S. EPA 1973). Thus, ingestion of fish by man can be a source of barium exposure.

Another study conducted on various species of marine organisms produced the following results (Guthrie 1979): Barnacles bioaccumulated about five times greater concentration of barium than was in the water, while oysters and clams contained concentrations of the element similar to that present in the water. Crabs and polychaetes were also analyzed for barium and were found to contain a significantly smaller quantity than that present in the sediment on which they dwell. However, no significant differences were noted between the concentration of barium in the two organisms and the concentrations in the water column.

In man, studies have been conducted to determine a correlation between barium in the environment, measured as house dust, and the concentration of barium found in scalp hair of the inhabitants. A significant positive correlation has been determined between the geometric mean concentrations of the element in house dust and hair. Other covariants of significant value measured in the studies were sex, hair length, and, in children less than 16 years old, age (U.S. EPA 1978b; U.S. EPA 1978c).

III. PHARMACOKINETICS

Soluble barium is retained by muscle tissue for about 30 hours, after which the amount of retained barium decreases slowly (NAPCA 1969). Small amounts of barium become irreversibly deposited in the skeleton. However, the acceptance level is limited, as quantitative analysis of human bone reveals no accumulation of barium from birth to death. Barium levels averaged 7 ug/g ashed bone. Very little barium is retained by the liver, kidneys, or spleen, and practically none by the brain, heart, or hair. Transient high concentrations are seen in the liver with lesser amounts in lung and spleen following acute experimental dosing.

Barium administered orally or intraperitoneally as $BaCl_2$ to weanling male rats at doses of 1, 5, 25, or 125 mg/kg was taken up rapidly by the soft tissues (30 mins), showed slow uptake by the skeleton (2 hrs) and was excreted primarily in the feces (Clary and Tardiff, 1974). No retention data were reported.

Pulmonary clearance rates of inhaled radioactive ^{133}Ba salts ranged from several hours for the soluble $BaCl_2$ to hundreds of days for Ba^{++} in fused clay . Large amounts of barium were excreted in the feces; a lesser amount was excreted in the urine. Although $BaSO_4$ is "insoluble" in water, 50% of $^{133}BaSO_4$ dissolved in a simulated biological fluid within 2-3 days, indicating that solubilization is relatively rapid.

IV. HEALTH EFFECTS

A. Carcinogenicity

Bronchogenic carcinoma developed in rats injected with radioactive ^{35}S (unspecified dose) labelled barium sulfate (Patty 1963). $BaSO_4$ powder (particle size undefined) injected intrapleurally in female and male mice produced a mesothelioma in only 1 out of 30 animals. No other pathological lesions were investigated or reported. Saline controls (32) resulted in no mesotheliomas. Barium sulfate had an oncogenic potency similar to that of glass powder and aluminum oxide. It therefore appears likely that the observed tumor was due to foreign-body-oncogenesis (Wagner).

B. Acute and Chronic Toxicity

The soluble salts of barium are highly toxic when ingested. Barium chloride and barium carbonate, two of the soluble compounds, have been reported to cause toxic symptoms of a severe but usually nonfatal degree. Seven grams of barium chloride (≈4.5 g Ba) taken orally produced severe abdominal pain and near-collapse, but not death (NAPCA 1969). However, Patty (1963) indicates 800 to 900 mg of barium chloride (550-600 mg Ba) to be a fatal human dose. Few cases of industrial poisoning from soluble barium salts have been reported. Most of these have been cases of accidental ingestion (NAPCA 1969).

Ingested soluble barium compounds produce a strong stimulating effect on all muscles of the body. The effect on the heart muscle is manifested by irregular contractions followed by arrest of systolic action. Gastrointestinal effects include vomiting and diarrhea. Central nervous system effects observed include violent tonic and clonic spasms followed in some cases by paralysis (NAPCA 1969).

Death resulting from barium exposure may occur in a few hours or a few days, depending on the dose and solubility of the barium compound. A death attributed to barium oxide poisoning has been reported. However, the usual effect of exposure to dusts and fumes of barium oxide, barium sulfide, and barium carbonate is irritation of eyes, nose, throat and the skin (NAPCA 1969).

Some of the $BaSO_4$ used in orthopedic bone cements has been shown to escape into surrounding tissues (Rae 1977). Mouse peritoneal macrophages exposed to barium sulfate (10 particles of unspecified size/macrophage) for periods up to 144 hours showed a marked cytoplasmic vacuolization. Following cessation of exposure only partial recovery occurred. No cell membrane damage was observed (Rae 1977). The use of barium sulfate in barium swallows and enemas resulted in severe toxic effects on rupture of the intestinal tract (Gardiner and Miller 1973, Bayer et al. 1974).

Inhalation of barium compounds is known to cause a benign respiratory affliction (pneumoconiosis) called baritosis, which has been reported in workers exposed to finely divided barium sulfate in Italy, in barite miners in the United States, Germany, and Czechoslovakia, and among workers exposed to barium oxide. Generally, baritosis produces no symptoms of emphysema or bronchitis, and lung function tests show no respiratory incapacity, although some afflicted workers complain of dyspnea upon exertion. In the majority of cases nodulation disappears if exposure to the barium compound is stopped (NAPCA 1969). Aspirated $BaSO_4$ can result in granulomas of the lung and other sites in man (Patty 1963).

Suicidal ingestion of a facial depilatory containing 15.8 g of BaS resulted in paralysis of head, neck, arms, and trunk as well as respiratory paralysis. Therapy with $MgSO_4$, saline and potassium resulted in recovery within 24 hours (Gould et al. 1973).

Acute oral toxicity values for barium carbonate were: mouse LD = 200 mg/kg; rat LD = 50-200 mg/kg, LD_{50} = 1480 $\pm$ 340 mg/kg; rabbit LD = 170-300 mg/kg. For barium chloride oral toxicity values were: mouse LD = 7-14 mg/kg; rat LD = 355-533 mg/kg; rabbit LD = 170 mg/kg; dog LD = 90 mg/kg. For barium flouride the acute oral LD for guinea pigs was 350 mg/kg (NAPCA 1969).

C. Other Relevant Information

Potassium acts as an in vitro antagonist of barium. Cardiac effects such as arrythmias exerted by barium are also reversed rapidly by potassium. Barium induces hypokalemia apparently by promoting a shift of potassium from plasma into cells. The prolongation of action-potentials and depolarization of smooth and skeletal muscle by barium are thought to be due to barium induced decreases in potassium conductance. In addition, barium can replace sodium to produce and/or prolong action potentials and can also substitute for calcium in neurosecretory processes as described below (Peach 1975).

Barium chloride has been shown to cause arterial contractions in in vitro preparations of human digital arteries at concentrations of 10^{-4} to 10^{-6} M (Jauernig and Moulds 1978). This activity was approximately 40 to 50 fold more than that of potassium chloride. At $BaCl_2$ concentrations above 10^{-2} M contractions developed very slowly. The action of $BaCl_2$ was inhibited by veraparmil, a calcium antagonist, at $BaCl_2$ contractions below 10^{-2} M.

V. AQUATIC TOXICITY

According to an EPA report, experimental data indicate that in fresh and marine waters, the soluble barium concentration would need to exceed 50 mg/L before toxicity to aquatic life would be expected (U.S. EPA 1976). Furthermore, in most natural waters, sufficient sulfate or carbonate is present to precipitate barium in the water to a virtually insoluble, non-toxic compound.

Soluble barium salts, however, are quite toxic. It has been reported that 10 to 15 mg/L of barium chloride (9.9 mg/L Ba) was lethal to an aquatic plant and two species of snails (species and origin unspecified). Bioassay with this same barium salt showed the LC_{90} for Coho Salmon to be 158 mg/L (104 mg/L Ba) (U.S. EPA 1973).

VI. GUIDELINES

A. Human Health

The OSHA Time Weighted Average for exposure to barium (soluble compound) is 0.5 mg/m^3 (29 CFR 1910:1000).

B. Aquatic

There is no established criterion for barium in the aquatic environment. The U.S. EPA (1973) suggests, however, that concentrations of barium equal to or exceeding 1.0 mg/L constitute a hazard in the marine environment, and levels less than 0.5 mg/L present minimal risk of deleterious effects.

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No. 14

Benzal Chloride

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

No. 14

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

BENZAL CHLORIDE

Summary

Benzal chloride has been reported to induce papillomas, carcinomas, and leukemia in mice. Details of this work were not available for assessment.

Mutagenic effects of benzal chloride exposure have been reported in Salmonella, Bacillus, and E. coli.

There is no available information on the teratogenic or adverse reproductive effects of the compound.

I. INTRODUCTION

Benzal chloride, CAS registry number 98-87-3, is a fuming, highly refractive, colorless liquid. It is made by free radical chlorination of toluene and has the following physical and chemical properties (Windholz, 1976; Verschueren, 1977):

Formula:	$C_7H_6Cl_2$
Molecular Weight:	161.03
Melting Point:	-16°C
Boiling Point:	207°C
Density:	1.256^{14}
Vapor Pressure:	0.3 torr @ 20°C
Solubility:	alcohol, ether insoluble in water

Benzal chloride is used almost exclusively for the manufacture of benzaldehyde. It can also be used to prepare cinnamic acid and benzoyl chloride (Sidi, 1971).

II. EXPOSURE

A. Water

Benzal chloride is converted to benzaldehyde and hydrochloric acid on contact with water (Sidi, 1971).

B. Food

Pertinent data could not be located in the available literature.

C. Inhalation

It is likely that the only source of benzal chloride in the air is production facilities. The compound will hydrolyze in moist air to give benzaldehyde and hydrochloric acid. Inhaled benzal chloride will probably produce effects similar to those of inhaled hydrogen chloride.

D. Dermal

Benzal chloride is irritating to the skin (Sidi, 1971).

III. PHARMACOKINETICS

Pertinent data on the pharmacokinetics of benzal chloride could not be located in the available literature.

IV. EFFECTS

A. Carcinogenicity

In a study of Matsushito, et al. (1975) benzal chloride, along with several other compounds, was found to induce carcinomas, leukemia, and papillomas in mice. The details of the study were not available, but benzal chloride was shown to possess a longer latency period than benzotrichloride before the onset of harmful effects.

B. Mutagenicity

Yasuo, et al. (1978) tested the mutagenicity of several compounds including benzal chloride in microbial assay systems which include the rec-assay using Bacillus subtilis, the reversion assay using E. coli, and the Ames assay using Salmonella typhimurium, with or without metabolic activation. Benzal chloride was positive in the rec-assay without activation and in the reversion assays using S. typhimurium and E. coli with metabolic activation.

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature.

D. Acute Toxicity

The oral LD_{50}'s for mice and rats exposed to benzal chloride are 2,462 mg/kg and 3,249 mg/kg, respectively (NIOSH, 1978).

V. AQUATIC TOXICITY

Pertinent aquatic toxicity data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

There are no existing guidelines or standards for exposure to benzal chloride.

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No. 15

Benzene

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated benzene and has found sufficient evidence to indicate that this compound is carcinogenic.

BENZENE

Summary

Benzene is a widely used chemical. Chronic exposure to it causes hematological abnormalities. Benzene is not mutagenic to bacteria, but recent evidence shows it to be carcinogenic in animals. Also, benzene has been shown to be leukemogenic in humans. There is suggestive evidence that benzene may be teratogenic and may cause reduced fertility.

Benzene has been shown to be acutely toxic to aquatic organisms over a concentration range of 5,800 to 495,000 µg/l. The marine fish striped bass was the most sensitive species tested.

BENZENE

I. INTRODUCTION

This profile is based on the draft Ambient Water Quality Criteria Document for Benzene (U.S. EPA, 1979).

Benzene (Benzol C_6H_6; molecular weight 78.1) is a volatile, colorless, liquid hydrocarbon produced principally from coal tar distillation, from petroleum by catalytic reforming of light naphthas, and in coal processing and coal coking operations (Weast, 1972; Ayers and Muder, 1964; U.S. EPA, 1976a). Benzene has a boiling point of 80.1°C, a melting point of 5.5°C, a water solubility of 1,780 mg/l at 25°C, and a density of 0.87865 g/ml at 20°C. The broad utility spectrum of benzene includes its use as: an intermediate for synthesis in the chemical and pharmaceutical industries, a thinner for lacquer, a degreasing and cleaning agent, a solvent in the rubber industry, an antiknock fuel additive, a general solvent in laboratories and in the preparation and use of inks in the graphic arts industries.

Current production of benzene in the U.S. is over 4 million metric tons annually, and its use is expected to increase when additional production facilities become available (Fick, 1976).

II. EXPOSURE

A. Water

A report by the National Cancer Institute (1977) noted benzene levels of 0.1 to 0.3 ppb in four U.S. city drinking water supplies. One measurement from a groundwater well in Jacksonville, Florida showed levels higher than 100 ppb. One possible source of benzene in the aquatic environment is from cyclings between the atmosphere and water (U.S. EPA, 1976b). Concentrations of benzene upstream and downstream from five benzene

production or consumption plants ranged from less than 1.0 to 13.0 ppb, with an average of 4.0 ppb (U.S. EPA, 1977a).

B. Food

Benzene has been detected in various food categories: fruits, nuts, vegetables, dairy products, meat, fish, poultry, eggs, and several beverages (Natl. Cancer Inst., 1977). NCI estimated that an individual might ingest as much as 250 µg/day from these foods. The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of benzene for the edible portion of fish and shellfish consumed by Americans to be 6.9. This estimate is based on the octanol/water partition coefficient of benzene.

C. Inhalation

The respiratory route is the major source of human exposure to benzene, and much of this exposure is by way of gasoline vapors and automotive emissions. American gasolines contain an average of 0.8 percent benzene (by weight) (Goldstein, 1977a), and automotive exhausts contain an average of 4 percent benzene (by weight) (Howard and Durkin, 1974). Concentrations of benzene in the ambient air of gas stations have been found to be 0.3 to 2.4 ppm (Natl. Acad. Sci/Natl. Res. Council, 1977). Lonneman and coworkers (1968) measured an average concentration of 0.015 ppm in Los Angeles air with a maximum of 0.057 ppm. The rural background level for benzene has been reported as 0.017 ppb (Cleland and Kingsbury, 1977).

III. PHARMACOKINETICS

A. Absorption

The respiratory absorption of benzene by humans has been measured several times and found to be 40 to 50 percent retained on exposures to 110 ppm or less (Srbova, et al. 1950; Teisinger, at al. 1952; Hunter and Blair, 1972; Nomiyama and Nomiyama, 1974). Absorption was slightly less efficient,

28 to 34 percent, on exposure to 6,000 ppm (Duvoir, et al. 1946). Deichmann, et al. (1963) demonstrated that rats exposed to benzene (44 to 47 ppm) for long periods of time maintained blood benzene levels of approximately 4.25 mg/l.

B. Distribution

Free benzene accumulates in lipid tissue such as fat and bone marrow, and benzene metabolites accumulate in liver tissue and bone marrow (U.S. EPA, 1977b).

C. Metabolism

Benzene is metabolized by the mixed-function oxidase system to produce the highly reactive arene oxide (Rusch, et al. 1977). Arene oxide can spontaneously rearrange to form phenol, undergo enzymatic hydration followed by dehydrogenation to form catechol or a glutathione derivative, or bind covalently with cellular macromolecules. Evidence has accumulated that a metabolite of benzene is responsible for benzene toxicity, in light of the fact that a protection from benzene toxicity is afforded by inhibitors of benzene metabolism (Nomiyama, 1964; Andrews, et al. 1977). The specific metabolite that produces benzene toxicity has not yet been identified, but likely candidates are benzene oxide, catechol, and hydroquinone, or the corresponding semiquinones (U.S. EPA, 1977b).

D. Excretion

Phenol measurement (free plus combined) of the urine of human volunteers indicated that 50 to 87 percent of the retained benzene was excreted as phenol (Hunter and Blair, 1972). The highest concentration of phenol was found in the urine within about 3 hours from termination of exposure. Elimination via the lungs was no more than 12 percent of the retained dose.

IV. EFFECTS

A. Carcinogenicity

On subcutaneous, dermal, oral, and inhalation exposure of rats and mice to benzene, animal experiments have failed to support the view that benzene is leukemogenic (U.S. EPA, 1979). Recent evidence suggests, however, that benzene is an animal carcinogen (Maltoni and Scarnato, 1979). The evidence that benzene is a leukemogen for man is convincing and has recently been reviewed by the Natl. Acad. Sci./Natl. Res. Coun. (1976), Natl. Inst. Occup. Safety and Health (1977), and U.S. EPA (1977b). Vigliani and Saita (1964) calculated a 20-fold higher risk of acute leukemia in workers in northern Italy exposed to benzene. In some studies of acute leukemia where benzene exposure levels have been reported, the concentrations have generally been above 100 ppm (Aksoy, et al. 1972, 1974a,b, 1976a,b; Vigliani and Fourni, 1976; Vigliani and Saita, 1964; Kinoshita, et al. 1965; Sellyei and Kelemen, 1971). However, other studies have shown an association of leukemic evidence to benzene levels less than 100 ppm (Infante et al., 1977; Ott et al., 1978).

B. Mutagenicity

Benzene has not shown mutagenic activity in the Salmonella/microsome in vitro bioassay (Lyon, 1975; Shahin, 1977; Simmon, et al. 1977).

C. Teratogenicity

With rats exposed to 100 to 2,200 ppm benzene during days 6 to 15 of gestation some skeletal deformities were observed in their offspring (Amer. Pet. Inst., 1978). Pregnant mice given single subcutaneous injections of benzene (3 ml/kg) on days 11 to 15 of gestation produced fetuses

with cleft palates, agnathia, and microagnathia, when delivered by caesarean section on day 19 (Watanabe and Yashida, 1970).

D. Other Reproductive Effects

Gofmekler (1968) found complete absence of pregnancy in female rats exposed continuously to 209.7 ppm benzene for 10 to 15 days prior to impregnation. One of ten rats exposed to 19.8 ppm exhibited resorption of embryos. The number of offspring per female exhibited an inverse relationship to benzene exposure levels from 0.3 to 209.7 ppm.

E. Chronic Toxicity

In humans, pancytopenia (reduction of blood erythrocytes, leukocytes, and platelets) has clearly been related to chronic benzene exposure (Browning, 1965; Goldstein, 1977b; Intl. Labour Off., 1968; Snyder and Kocsis, 1975). Also, impairment of the immunological system has been reported with chronic benzene exposure (Lange, et al. 1973a; Smolik, et al. 1973). Wolf, et al. (1956) reported that the no-effect level for blood changes in rats, guinea pigs, and rabbits was below 88 ppm in the air when the animals were exposed for 7 hours per day for up to 269 days.

F. Other Relevant Information

In rabbits and rats injected subcutaneously with 0.2 mg/kg/day benzene, the frequency of bone marrow mitosis with chromosomal aberrations increased from 5.9 percent to 57.8 percent after an average of 18 weeks (Kissling and Speck, 1971; Dobrokhotov, 1972). In patients with benzene induced aplastic anemia, lymphocyte chromosome damage, i.e., abnormal karyo-type and deletion of chromosomal material, has been found (Pollini and Colombi, 1964).

V. AQUATIC TOXICITY

A. Acute

Acute toxicity values for freshwater fish are represented by 96-hour static LC_{50} values of 20,000 to 22,490 µg/l for the bluegill, Lepomis macrochirus, to 386,000 µg/l for the mosquitofish, Gambusia affinis, with goldfish, Carassius auratus, fathead minnows, Pimephales promelas, and guppies, Poecilia reticulatius, being somewhat more resistant than the bluegill (U.S. EPA, 1979). Only one study was available for the acute effects of benzene to freshwater invertebrates. A 48-hour static LC_{50} value of 203,000 µg/l was obtained for the cladoceran Daphnia magna. LC_{50} values for marine fish were reported as 5,800 and 10,900 µg/l for striped bass, Morone saxatilis, and 20,000 to 25,000 µg/l for Pacific herring, Clupea pallasi, and anchovy, Engraulis mordax, larvae. Marine invertebrates were much more resistant with LC_{50} values of 27,000, 108,000, and 450,000 µg/l reported for grass shrimp, Palaemonetes pugio, dungeness crab, Cancer magister, and the copepod, Tigricopus californicus, respectively (U.S. EPA, 1979).

B. Chronic Toxicity

The only chronic toxicity test conducted on an aquatic species was performed on the freshwater cladoceran, Daphnia magna. There were no observed effects to these organisms at concentrations as high as 98,000 µg/l. Pertinent information of the chronic effects of benzene on marine fish and invertebrates could not be located in the available literature.

C. Plant Effects

A concentration of 525,000 µg/l was responsible for a 50 percent reduction in cell numbers at 48-hours for the freshwater algae, Chlorella vulgaris, while marine plants were reported as having growth inhibition at

concentrations ranging from 20,000 to 100,000 µg/l for the diatom, Skeletonema costatum, with the dinoflagellate, Amphidinium carterae, and the algae, Cricosphaera carterae, being intermediate in sensitivity with effective concentrations of 50,000 µg/l.

D. Residues

A bioconcentration factor of 24 was obtained for organisms with a lipid content of 8 percent.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979) which are summarized below have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Existing air standards for occupational exposure to benzene include 10 ppm, an emergency temporary level of 1 ppm by the U.S. Occupational Safety and Health Administration (Natl. Inst. Occup. Safety Health, 1974, 1977), and 25 ppm by the American Conference of Governmental Industrial Hygienists (ACGIH, 1971). Based on human epidemiology data, and using a modified "one-hit" model, the EPA (1979) has estimated levels of benzene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.15 µg/l	1.5 µg/l	15 µg/l
Consumption of fish and shellfish only.	0	2.5 µg/l	25 µg/l	250 µg/l

8. Aquatic

Criterion for the protection of freshwater organisms have been drafted at 3,100 µg/l as a 24-hour average concentration not to exceed 7,000 µg/l. For marine organisms criterion have been drafted as a 24-hour average concentration of 920 µg/l not to exceed 2,100 µg/l.

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No. 16

Benzidine

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated benzidine and has found sufficient evidence to indicate that this compound is carcinogenic.

BENZIDINE

Summary

Benzidine is a known carcinogen and has been linked to an increased incidence of bladder cancer in humans and to cancers and tumors in experimental animals. Benzidine is mutagenic in the Ames assay and gives positive results in a test measuring DNA synthesis inhibition in HeLa cells.

Pertinent data could not be located in the available literature concerning the toxic effects of benzidine to aquatic organisms.

BENZIDINE

I. INTRODUCTION

Benzidine (4,4'-diaminobiphenyl) is an aromatic amine with a molecular weight of 184.24. It exists at environmental temperature as a grayish-yellow, white, or reddish-gray crystalline powder. Its melting point is 128°C, and its boiling point is 400°C. Benzidine's amino groups have pKa values of 4.66 and 3.57 (Weast, 1972). Two and one-half liters of cold water will dissolve 1 g of benzidine, and its solubility increases as water temperatures rise. Dissolution into organic solvents greatly increases solubility. Benzidine is easily converted to and from its salt. Diazotization reactions involving benzidine will result in colored compounds which are used as dyes in industry (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Residential water supplies could be contaminated with benzidine and its derivatives if the industrial effluent containing these chemicals were discharged into water supplies, however, to date U.S. EPA (1979) finds no reports of such contamination.

B. Food

While food may become contaminated with benzidine due to poor industrial hygiene, U.S. EPA (1979) reports that the ingestion of contaminated food is not a real contribution to benzidine toxicity.

The U.S. EPA (1979) has estimated a weighted average bioconcentration factor (BCF) of 50 for benzidine, on octanol/water partition coefficients and other factors.

C. Inhalation

Due to poor industrial hygiene and the use of open systems in the early days of the chemical and dye industries, inhalation was formerly a principal route of entry for benzidine and its derivatives into the body. At present workers wear respirators and protective clothing to avoid exposure when cleaning equipment (Haley, 1975).

D. Dermal

Skin absorption is the most important route for entry of benzidine into the body. Intact skin is easily penetrated by the powdery benzidine base and is penetrated less readily by 3,3'-dimethoxybenzidine and 3,3'-dichlorobenzidine. High environmental air temperatures and humidity increase skin absorption of benzidine, 3,3'-dimethoxybenzidine, 3,3'-dichlorobenzidine, and 3,3'-dimethylbenzidine (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption and Distribution

Benzidine is rapidly absorbed into the bodies of intraveneously injected rats, with maximum concentrations of free and bound benzidine occurring at two and three hours, respectively. The highest concentration of benzidine was found in the blood followed by the liver, kidney, spleen, heart, and lung (Soloimskaya, 1968). Four hours after rats received intraperitoneal injections of 100 mg benzidine/kg, high concentrations of the compound were found in the stomach, stomach contents, and small intestine;

12 hours after administration, benzidine was found in the small intestine and its contents. Benzidine levels in the liver, the target organ for toxicity in the rat, remained relatively high and constant throughout the 12-hour period. The conjugated material, indicative of the presence of metabolites, was high in urine and tissues at 12 hours (Baker and Deighton, 1953). In rats given 20 mg of 3,3'-dimethylbenzidine subcutaneously once a week for eight weeks, amines were concentrated in the Zymbal's gland, followed by the kidney, omentum, spleen, and liver (Pliss and Zabezhinsky, 1970).

B. Metabolism and Excretion

The urine of humans exposed to benzidine contained a number of metabolites: N-hydroxyacetylamino benzidine, 3-hydroxybenzidine, 4-amino-4-oxybiphenyl, and mono- and diacetylbenzidine (Engelbertz and Babel, 1953; Troll, et al. 1963; Sciarini and Meigs, 1961; Vigliani and Barsotti, 1962). Benzidine metabolites in other species generally differ considerably from those in humans, although 3-hydroxybenzidine and its conjugation products are common to both animals and humans (Haley, 1975).

The half-life of benzidine in blood was 68 hours for the rat and 88 hours for the dog. Rats, dogs, and monkeys excreted 97, 96, and 83 percent, respectively, within one week of an 0.2 mg/kg dose of benzidine. The respective excretion rates for 3,3'-dichlorobenzidine were 98, 97, 88.5 percent. Dogs and monkeys excreted free benzidine in the urine and dichlorobenzidine in the bile while rats excreted both compounds via the bile (Kellner, et al. 1973).

Workers exposed to benzidine, who perspire freely and have wet skin, contain a higher concentration of benzidine in the urine (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

Benzidine is a proven human carcinogen. Its primary site of tumor induction is the urinary bladder (U.S. EPA, 1979).

Workers exposed to benzidine have a carcinogenicity risk 14 times higher than that of the unexposed population (Case, et al. 1954). The incidence of bladder tumors in humans resulting from occupational exposures to aromatic amines (benzidine) was first researched in Germany in 1895. In the United States, the first cases of this condition were diagnosed in 1931 and reported in 1934.

A number of studies document the high incidence of bladder tumors in workers exposed to benzidine and other aromatic amines (Gehrman, 1936; Case, et al. 1954; Scott, 1952; Deichmann and Gerarde, 1969; Hamblin, 1963; Rye, et al. 1970; Int. Agency Res. Cancer, 1972; Riches, 1972; Sax, 1975; Zavon, et al. 1973; Mancuso and El-Attar, 1966, 1967; Kuzelova, et al. 1969; Billiard-Duchesne, 1960; Vigliani and Barsotti, 1962; Forni, et al. 1972; Tsuchiya, et al. 1975; Goldwater, et al. 1965). Initial exposure concentration, exposure duration, and years of survival following exposure as well as work habits and personal hygiene are involved in the development of carcinomas where benzidine appears to be implicated (Rye, et al. 1970).

Benzidine has also produced carcinogenic effects or tumors in the mouse (hepatoma, lymphoma), the rat (hepatoma,

carcinoma of the Zymbal's gland, adenocarcinoma, sarcoma, mammary gland carcinoma), the hamster (hepatoma, liver carcinoma, cholangioma), the rabbit (bladder tumor, gall bladder tumor) and the dog (bladder tumor) (Haley, 1975).

At present, there is no evidence indicating that 3,3'-dimethylbenzidine, 3,3'-dimethoxybenzidine, or 3,3'-dichlorobenzidine are human bladder carcinogens (Rye, et al. 1970).

B. Mutagenicity

In the Ames test, benzidine is mutagenic to Salmonella typhimurium strains TA1537, TA1538, and TA98. Benzidine produces positive results in a DNA synthesis inhibition test using HeLa cells (Ames, et al. 1973; McCann, et al. 1975; Garner, et al. 1975; U.S. EPA, 1978; U.S. EPA, 1979).

C. Teratogenicity

No teratogenic effects of benzidine have been reported in humans. Mammary gland tumors and lung adenomas occurred in progeny of female mice that received 8 to 10 mg of 3,3'-dimethylbenzidine in the last week of pregnancy. The tumors may have resulted from transplacental transmission of the chemical or from its transfer to neonates in milk from dosed mothers (Golub, et al. 1974).

D. Other Reprodutive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

Glomerulonephritis and nephrotic syndrome were produced in Sprague-Dawley rats fed 0.043 percent N,N'-diacetylbenzidine, a metabolite of benzidine, for at least two months (Harman, et al. 1952; Harman, 1971). Glomerulonephritis also developed in rats fed

benzidine (Christopher and Jairam, 1970), and in rats receiving injections either 100 mg subcutaneously or 100 or 200 mg intraperitoneally of N,N'-diacetylbenzidine. The severity of the lesions in the later study was dose-related (Bremner and Tange, 1966).

Mice fed 0.01 and 0.08 percent benzidine dihydrochloride exhibited decreased carcass, liver, and kidney weights, increased spleen and thymus weights, cloudy swelling of the liver, vacuolar degeneration of the renal tubules, and hyperplasia of the myeloid elements in the bone marrow and of the lymphoid cells in the spleen and thymic cortex. There was a dose dependent weight loss of 20 percent in males and 7 percent in females (Rao, et al. 1971).

F. Other Relevant Information

Dermatitis, involving both benzidine and its dimethyl derivative, has been reported in workers in the benzidine dyestuff industry. Individual sensitivity played a large role in the development of this condition (Schwartz, et al. 1947).

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature concerning the toxic effects of benzidine to aquatic organisms.

VI. EXISTING GUIDELINES AND STANDARDS

Both the human health and aquatic criteria derived by U.S. EPA (1979), which are summarized below, have not yet gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

The ambient water concentration standard for benzidine is zero, due to potential carcinogenic effects of exposure to

benzidine by ingestion of water and contaminated aquatic organisms. U.S. EPA may set standards at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with respective corresponding criteria of 1.67×10^{-3} µg/l, 1.67×10^{-4}, and 1.67×10^{-5} µg/l.

B. Aquatic

Criteria for the protection of freshwater or marine aquatic organisms were not drafted, due to a lack of toxicological evidence (U.S. EPA, 1979).

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No. 17

Benz(a)anthracene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated benz(a)anthracene and has found sufficient evidence to indicate that this compound is carcinogenic.

BENZ(a)ANTHRACENE

SUMMARY

Benz(a)anthracene is a member of the polycyclic aromatic hydrocarbons (PAH) class. Although the PAH class contains several well-known potent carcinogens, benz(a)anthracene displays only weak carcinogenic activity. Benz(a)-anthracene apparently does not display remarkable acute or chronic toxicity other than the capability to induce tumors on the skin of mice. Although exposure to benz(a)-anthracene in the environment occurs in conjunction with exposure to other PAH, it is not known how these compounds may interact in human systems. Furthermore, the specific effects of benz(a)anthracene in humans are not known.

The only toxicity data for any of the polycyclic aromatic hydrocarbons is an 87 percent mortality of freshwater fish exposed to 1,000 µg/l benz(a)anthracene for six months.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multimedia Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Benz(a)anthracene ($C_{18}H_{12}$) is one of the family of polycyclic aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Benz(a)anthracene has the following physical/chemical properties (U.S. EPA, 1979b):

Melting point:	159.5-160.5°C
Boiling Point:	400°C
Vapor Pressue:	1.10×10^{-7} torr

PAH, including benz(a)anthracene, are ubiquitous in the environment, being found in ambient air, food, water, soils, and sediment (U.S. EPA, 1979b). The PAH class contains a number of potent carcinogens (e.g., benzo(a)pyrene), weak carcinogens (e.g., benz(a)anthracene), and cocarcinogens (e.g., fluoranthene), as well as numerous non-carcinogens (U.S. EPA, 1979b).

PAH which contain more than three rings (such as benz(a)-anthracene) are relatively stable in the environment, and may be transported in air and water by adsorption to particulate matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment.

The reader is referred to the PAH Hazard Profile for a more general discussion of PAH (U.S. EPA, 1979c).

II. EXPOSURE

A. Water

Benz(a)anthracene levels in surface waters or drinking water have not been reported. However, the concentration of six representative PAH (not including benz(a)-anthracene) in U.S. drinking water averaged 13.5 ng/l (Basu and Saxena, 1977, 1978).

B. Food

Benz(a)anthracene has been detected in a wide variety of foods including margarine (up to 29.5 ppb), smoked fish (up to 1.7 ppb), yeast (up to 203 ppb), and cooked or smoked meat (up to 33.0 ppb) (U.S. EPA, 1979a). The total intake of all types of PAH through the diet has been estimated at 1.6 to 16 µg/day (U.S. EPA, 1979b). The U.S. EPA (1979a) has estimated the bioconcentration factor for benz(a)anthracene to be 3,100 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of benz-(a)anthracene.

C. Inhalation

Benz(a)anthracene has been repeatedly detected in ambient air at concentrations ranging from 0.18 to 4.6 ng/m^3 (U.S. EPA, 1979a). Thus, the human daily intake of benz(a)anthracene by inhalation of ambient air may be in the range of 3.42 to 87.4 ng, assuming that a human breathes 19 m^3 of air per day.

III. PHARMACOKINETICS

There are no data available concerning the pharmacokinetics of benz(a)anthracene, or other PAH, in humans. Nevertheless, it is possible to make limited assumptions based on the results of animal research conducted with several PAH, particularly benzo(a)pyrene.

A. Absorption

The absorption of benz(a)anthracene in humans has not been studied. However, it is known (U.S. EPA, 1979a) that, as a class, PAH are well-absorbed across the respiratory and gastrointestinal epithelia. In particular, benz(a)-anthracene was reported to be readily transported across the gastrointestinal mucosa (Rees, et al., 1971). The high lipid solubility of compounds in the PAH class supports this observation.

B. Distribution

The distribution of benz(a)anthracene in mammals has not been studied. However, it is known (U.S. EPA, 1979a) that other PAH are widely distributed throughout the body following their absorption in experimental rodents. Relative to other tissues, PAH tend to localize in body fat and fatty tissues (e.g., breast).

C. Metabolism

Benz(a)anthracene, like other PAH, is metabolized by the microsomal mixed-function oxidase enzyme system in mammals (U.S. EPA, 1979b). Metabolic attack on one or more of the aromatic double bonds leads to the formation of phenols

and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed-function oxidases to yield diol epoxides, compounds which are known to be biologically reactive intermediates for certain PAH. Removal of activated intermediates by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

The excretion of benz(a)anthracene by mammals has not been studied. However, the excretion of closely related PAH is rapid and occurs mainly via the feces (U.S. EPA, 1979a). Elimination in the bile may account for a significant percentage of administered PAH. However, the rate of disappearance of various PAH from the body and the principal routes of excretion are influenced both by the structure of the parent compound and the route of administration (U.S. EPA, 1979a). It is unlikely that PAH will accumulate in the body with chronic low-level exposures.

IV. EFFECTS

A. Carcinogenicity

Benz(a)anthracene is recognized as a weak carcinogen in mammals (U.S. EPA, 1979a,b). It is a tumor initiator on the skin of mice, but failed to yield significant results in the strain A mouse pulmonary tumor bioassay system.

B. Mutagenicity

Benz(a)anthracene has shown weak mutagenic activity in several test system, including Ames Salmonella assay, somatic cells in culture, and sister chromatid exchange in Chinese hamster cells (U.S. EPA, 1979b).

C. Teratogenicity

Pertinent data could not be located in the available literature concerning the possible teratogenicity of benz(a)anthracene. Other related PAH are apparently not significantly teratogenic in mammals (U.S. EPA, 1979a).

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

The chronic toxicity of benz(a)anthracene has not been extensively studied. The repeated injection of benz(a)anthracene in mice for 40 weeks (total dose, 10 mg.) had little apparent effect on longevity or organ weights (U.S. EPA, 1979b).

V. AQUATIC TOXICITY

A. Acute

Pertinent data could not be located in the available information.

B. Chronic

No standard chronic toxicity data have been presented on freshwater or marine species. The only toxicity data available for benz(a)anthracene for fish is an 87 per-

cent mortality on the freshwater bluegill sunfish, Lepomis macrochirus, exposed to 1,000 µg/l for six months (Brown, et al., 1975).

C. Plant Effects

Pertinent data could not be located in the available information.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of review; therefore, there is a possibility that these criteria will be changed.

A. Human

There are no established exposure criteria for benz(a)anthracene. However, PAH as a class are regulated by several authorities. The World Health Organization (1970) has recommended that the concentration of PAH in drinking water (measured as the total of fluoranthene, benzo(g,h,i)-perylene, benzo(b)fluoranthene, benzo(k)fluoranthene, indeno-(1,2,3-cd)pyrene, and benzo(a)pyrene) not to exceed 0.2 µg/l. Occupational exposure criteria have been established for coke oven emissions, coal tar products, and coal tar pitch volatiles, all of which contain large amounts of PAH including benz(a)anthracene (U.S. EPA, 1979a)..

The U.S. EPA (1979a) draft recommended criteria for PAH in water are based upon the extrapolation of animal carcinogenicity data for benzo(a)pyrene and dibenz(a,h)anthracene.

B. Aquatic

Data were insufficient to propose criteria for freshwater or marine environments.

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No. 18

Benzo(b)fluoranthene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated benzo(b)fluoranthene and has found sufficient evidence to indicate that this compound is carcinogenic.

BENZO(b)FLUORANTHENE

SUMMARY

Benzo(b)fluoranthene is a member of the polycyclic aromatic hydrocarbon (PAH) class. Numerous compounds in the PAH class are well known for their carcinogenic effects in animals. Benzo(b)fluoranthene is carcinogenic to the skin of mice and produces sarcomas when injected in mice. Very little is known concerning the non-carcinogenic effects produced by chronic exposure to benzo(b)fluoranthene. Although exposure to benzo(b)fluoranthene in the environment occurs in conjunction with exposure to other PAH, it is not known how these compounds may interact in human systems. Furthermore, the specific effects of benzo(b)fluoranthene in humans are not known.

Standard acute or chronic toxicity testing for aquatic organisms has not been found in the available literature.

BENZO(b)FLUORANTHENE

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multimedia Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Benzo(b)fluoranthene ($C_{20}H_{12}$) is one of the family of polycyclic aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Its physical/chemical properties have not been well-characterized, other than a reported melting point of 167°C (U.S. EPA, 1979b).

PAH, including benzo(b)fluoranthene, are ubiquitous in the environment, being found in ambient air, food, water, soils, and sediment (U.S. EPA, 1979b). The PAH class contains a number of potent carcinogens (e.g., benzo(a)pyrene), moderately active carcinogens (e.g., benzo(b)fluoranthene), weak carcinogens (e.g., benz(a)anthracene), and cocarcinogens (e.g., fluoranthene), as well as numerous noncarcinogens (U.S. EPA, 1979b).

PAH which contain more than three rings (such as benzo-(b)fluoranthene) are relatively stable in the environment and may be transported in air and water by adsorption to particular matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment. Refer to the PAH Hazard Profile (U.S. EPA, 1979c) for a more general treatment of PAH.

II. EXPOSURE

A. Water

In a monitoring survey of U.S. drinking water, Basu and Saxena (1977, 1978) were unable to detect benzo(b)fluoranthene. However, the concentration of six representative PAH (fluoranthene, benzo(a)pyrene, benzo(g h i)perylene, benzo(j)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd) pyrene) averaged 13.5 ng/l.

B. Food

Levels of benzo(b)fluoranthene have not been reported for food. However, the total intake of all types of PAH through the diet has been estimated at 1.6 to 16 μg/day (U.S. EPA, 1979b). The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor of benzo(b)fluoranthene to be 6,800 for the edible portion of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of benzo(b)fluoranthene.

C. Inhalation

Benzo(b)fluoranthene has been detected in ambient air at concentrations ranging from 0.1 to 1.6 ng/m^3 (Gordon and Bryan, 1973). Thus, the human daily intake of benzo(b)-fluoranthene by inhalation of ambient air may be in the range of 1.9 to 30.4 ng, assuming that a human breathes 19 m^3 of air per day.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature concerning the pharmacokinetics of benzo(b)fluoranthene, or other PAH, in humans. Nevertheless, it is pos-

sible to make limited assumptions based on the results of animal research conducted with several PAH, particularly benzo(a)pyrene.

A. Absorption

The absorption of benzo(b)fluoranthene in humans or other animals has not been studied. However, it is known (U.S. EPA, 1979a) that, as a class, PAH are well-absorbed across the respiratory and gastrointestinal epithelia. The high lipid solubility of compounds in the PAH class supports this observation.

B. Distribution

The distribution of benzo(b)fluoranthene in mammals has not been studied. However, it is known (U.S. EPA, 1979a) that other PAH are widely distributed throughout the body following their absorption in experimental rodents. Relative to other tissues, PAH tend to localize in body fat and fatty tissues (e.g., breast).

C. Metabolism

The metabolism of benzo(b)fluoranthene in mammals has not been studied. Benzo(b)fluoranthene, like other PAH, is most likely metabolized by the microsomal mixed-function oxidase enzyme system in mammals (U.S. EPA, 1979b). Metabolic attack on one or more of the aromatic double bonds leads to the formation of phenols and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed-function oxidases to yield diol epoxides, compounds which are known to be biologically reactive intermediates for certain PAH. Removal of activated intermediates by conjugation with gluta-

thione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

The excretion of benzo(b)fluoranthene by mammals has not been studied. However, the excretion of closely related PAH is rapid and occurs mainly via the feces (U.S. EPA, 1979a). Elimination in the bile may account for a significant percentage of administered PAH. It is unlikely that PAH will accumulate in the body with chronic low-level exposures.

IV. EFFECTS

A. Carcinogenicity

Benzo(b)fluoranthene is regarded as a moderately active carcinogen (U.S. EPA, 1979b). It is carcinogenic by skin painting on mice, and by subcutaneous injection in mice (U.S. EPA, 1979b; LaVoie, et al. 1979). The sarcomagenic potency of benzo(b)fluoranthene is similar to that of benzo(a)pyrene (Buu-Hoi, 1964).

B. Mutagenicity

Benzo(b)fluoranthene is mutagenic in the Ames Salmonella assay in the presence of a microsomal activating system (LaVoie, et al. 1979). It is also positive in the induction of sister-chromatid exchanges by intraperitoneal injection in Chinese hamsters (U.S. EPA, 1979b).

C. Teratogenicity

Pertinent data could not be located in the literature available concerning the possible teratogenicity of

benzo(b)fluoranthene. Other related PAH are apparently not significantly teratogenic in mammals (U.S. EPA, 1979a).

D. Other Reproductive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

Published data are not available regarding the non-carcinogenic chronic effects of benzo(b)fluoranthene. It is known, however, that exposure to carcinogenic PAH may produce widespread tissue damage as well as selective destruction of proliferating tissues (e.g., hematopoietic and lymphoid systems) (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

There are no established exposure criteria for benzo(b)fluoranthene. However, PAH as a class are regulated by several authorities. The World Health Organization has recommended that the concentration of PAH in drinking water (measured as the total of fluoranthene, benzo(g,h,i)perylene, benzo(b)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd)pyrene, and benzo(a)pyrene) not exceed 0.2 µg/l. Occupational exposure criteria have been established for coke oven emissions, coal tar products, and coal tar pitch volatiles, all of which contain large amounts of PAH including benzo(b)-fluoranthene (U.S. EPA, 1979a).

The U.S. EPA (1979a) draft recommended criteria for PAH in water are based upon the extrapolation of animal carcinogenicity data for benzo(a)pyrene and dibenzo(a,h)anthracene.

B. Aquatic

The criteria for freshwater and marine life have not been drafted (U.S. EPA, 1979a).

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No. 19

Benzo(a)pyrene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

-216-

19-1

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated benzo(a)pyrene and has found sufficient evidence to indicate that this compound is carcinogenic.

BENZO(a)PYRENE

Summary

The first chemicals shown to be involved in the development of cancer belong to the polynuclear aromatic hydrocarbons (PAH) class. Benzo(a)pyrene is the most widely recognized and extensively studied of all carcinogenic PAH. It is among the most potent animal carcinogens known and produces tumors in virtually all species by all routes of administration.

Since humans are never exposed to only benzo(a)pyrene in the environment, it is not possible to attribute human cancers solely to exposure to benzo(a)pyrene. However, numerous epidemiologic studies support the belief that carcinogenic PAH, including benzo(a)pyrene, are also human carcinogens.

Measured steady-state bioconcentration factors are not available for freshwater or saltwater aquatic species exposed to benzo(a)pyrene. Standard toxicity data for freshwater and saltwater aquatic life have not been reported.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multimedia Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Benzo(a)pyrene ($C_{20}H_{12}$) is one of the family of polynuclear aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Its physical and chemical properties have not been well-characterized, other than a reported melting point of 178.8-179.3°C and a vapor pressure of 5.49×10^{-9} mm Hg (U.S. EPA, 1979b).

PAH, including benzo(a)pyrene, are ubiquitous in the environment, being found in ambient air, food, water, soils and sediment (U.S. EPA, 1979a). The PAH class contains a number of potent carcinogens (e.g., benzo(a)pyrene), moderately active carcinogens (e.g., benzo(b)fluoranthene), weak carcinogens (e.g., benz(a)anthracene), and cocarcinogens (e.g., fluoranthene), as well as numerous noncarcinogens (U.S. EPA, 1979a).

PAH which contain more than three rings (such as benzo(a)pyrene) are relatively stable in the environment and may be transported in air and water by adsorption to particulate matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment.

II. EXPOSURE

A. Water

Basu and Saxena (1977, 1978) have monitored various United States drinking water supplies for the presence of PAH, including benzo(a)pyrene. They reported that the average level of benzo(a)pyrene in drinking water was 0.55 nanograms/liter. This would result in a human daily intake of benzo(a)pyrene from water of about 0.0011 µg.

B. Food

Benzo(a)pyrene has been detected in a wide variety of foods by numerous investigators (U.S. EPA, 1979a). Benzo(a)pyrene levels are especially high in cooked or smoked meats, where in certain cases (i.e., charcoal-broiled steak) concentrations as high as 50 ppb have been reported (Lijinsky and Ross, 1967). It has been estimated (U.S. EPA, 1979b) that the daily dietary intake of benzo(a)pyrene is about 0.16 to 1.6 μg, and total PAH intake is about 1.6 to 16 μg. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for benzo(a)pyrene to be 6,800 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient for benzo(a)pyrene.

C. Inhalation

Benzo(a)pyrene levels have been routinely monitored in the ambient atmosphere for many years. The average urban-rural ambient benzo(a)pyrene concentration in the United States has been estimated at 0.5 nanograms/m^3 (U.S. EPA, 1979a). Thus, the human daily intake of benzo(a)pyrene by inhalation of ambient air is about 9.5 nanograms, assuming that a human breathes about 19 m^3 of air per day.

III. PHARMACOKINETICS

Pertinent data could not be found in available literature concerning the pharmacokinetics of benzo(a)pyrene, or other PAH, in humans. Nevertheless, it is possible to make limited assumptions based on the results of animal research conducted with several PAH, particularly benzo(a)pyrene.

A. Absorption

Toxicity data indicate that, as a class, PAH are capable of passage across epithelial membranes (Smyth, et al. 1962). In particular, benzo(a)-pyrene was reported to be readily transported across the intestinal mucosa

(Rees, et al. 1971) and the respiratory membranes (Kotin, et al. 1969; Vainiok, et al. 1976).

B. Distribution

Benzo(a)pyrene becomes localized in a wide variety of body tissues following its absorption (Kotin, et al. 1969). Due to its high lipid solubility, benzo(a)pyrene localizes primarily in body fat and fatty tissues (e.g., breast) (Schlede, et al. 1970a,b).

C. Metabolism

The metabolism of benzo(a)pyrene in mammals has been studied in great detail (U.S. EPA, 1979a). Benzo(a)pyrene, like other PAH, is metabolized by the microsomal mixed function oxidase enzyme system in mammals (U.S. EPA, 1979b). Metabolic attack on one or more of the aromatic rings leads to the formation of phenols and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed function oxidases to yield diol epoxides, compounds which are known to be ultimate carcinogens for certain PAH. Removal of activated intermediates by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

The excretion of benzo(a)pyrene by mammals has been studied by several groups of investigators. In general, the excretion of benzo(a)pyrene and related PAH is rapid, and occurs mainly via the feces (U.S. EPA, 1979a; Schlede, et al. 1970a,b). Elimination in the bile may account for a significant percentage of administered PAH. It is unlikely that PAH will accumulate in the body as a result of chronic low-level exposures.

IV. EFFECTS

A. Carcinogenicity

The carcinogenic activity of benzo(a)pyrene was first recognized decades ago, and since that time it has become a laboratory standard for the production of experimental tumors which resemble human carcinomas in animals. The carcinogenic activity of benzo(a)pyrene is distinguished by several remarkable features: (1) it is among the most potent animal carcinogens known, producing tumors by single exposures to microgram quantities; (2) it acts both at the site of application and at organs distant to the site of absorption; and (3) its carcinogenicity has been demonstrated in nearly every tissue and species tested, regardless of the route of administration (U.S. EPA, 1979a).

Oral administration of benzo(a)pyrene to rodents can result in tumors of the forestomach, mammary gland, ovary, lung, liver, and lymphoid and hematopoietic tissues (U.S. EPA, 1979a). Exposure to benzo(a)pyrene by intratracheal instillation in rodents can also be an effective means of producing respiratory tract tumors (Feron, et al. 1973). In addition, benzo(a)pyrene has remarkable potency for the induction of skin tumors in mice by direct dermal application (U.S. EPA, 1979a).

Numerous epidemiologic studies support the belief that carcinogenic PAH, including benzo(a)pyrene, are responsible for the production of human cancers both in occupational situations and among tobacco smokers (U.S. EPA, 1979b).

B. Mutagenicity

Benzo(a)pyrene gives positive results in nearly all mutagenicity test systems including the Ames Salmonella assay, cultured Chinese hamster cells, the sister-chromatid exchange test, and the induction of DNA repair synthesis (U.S. EPA, 1979a).

C. Teratogenicity and Other Reproductive Effects

Only limited data are available regarding the teratogenic effects of benzo(a)pyrene or other PAH in animals. Benzo(a)pyrene had little effect on fertility or the developing embryo in several mammalian and non-mammalian species (Rigdon and Rennels, 1964; Rigdon and Neal, 1965).

D. Chronic Toxicity

As long ago as 1937, investigators knew that carcinogenic PAH such as benzo(a)pyrene produced systemic toxicity as manifested by an inhibition of body growth in rats and mice (Haddow, et al., 1937). The target organs affected by chronic administration of carcinogenic PAH are diverse, due partly to extensive distribution in the body and also to the selective destruction of proliferating cells (e.g., hematopoietic and lymphoid system, intestinal epithelium, testis) (Philips, et al. 1973).

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

There are no established exposure standards specifically for benzo(a)pyrene. However, PAH as a class are regulated by several authorities. The World Health Organization (1970) has recommended that the concentration of PAH in drinking water (measured as the total of fluoranthene, benzo(g,h,i)perylene, benzo(b)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd)pyrene, and benzo(a)pyrene) not exceed 0.2 µg/l. Occupational exposure cri-

teria have been established for coke oven emissions, coal tar products, and coal tar pitch volatiles, all of which contain large amounts of PAH in water based upon the extrapolation of animal carcinogenicity data for benzo(a)pyrene and dibenz(a,h)anthracene. Levels for each compound are derived which will result in specified risk levels of human cancer as shown in the table below:

BaP

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams of fish and shellfish.	0	0.097	0.97	9.7
Consumption of fish and shellfish only.		0.44	4.45	44.46

DBA

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams of fish and shellfish.	0	0.43	4.3	43
Consumption of fish and shellfish only.		1.96	19.6	196

B Aquatic

Guidelines are not available for benzo(a)pyrene in aquatic environments.

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No. 20

Benzotrichloride

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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BENZOTRICHLORIDE

Summary

Benzotrichloride has been shown to be mutagenic in a number of microbial tests with and without metabolic activation. One study has described the carcinogenicity of benzotrichloride in mice. The lowest concentration producing a lethal effect (LC_{LO}) has been reported at 125 ppm for rats inhaling benzotrichloride for four hours. Pertinent data for the toxic effects to aquatic organisms were not found in the available literature.

I. INTRODUCTION

Benzotrichloride (CAS registry number 98-07-7), is a colorless, oily, fuming liquid. It is made by the free radical chlorination of boiling toluene (Sidi, 1964; Windholz, 1976). Benzotrichloride has the following physical and chemical properties (Windholz, 1976; Sidi, 1964):

Formula:	$C_6H_5Cl_3$
Molecular Weight:	195.48
Melting Point:	$-5^{o}C$
Boiling Point:	$220.8^{o}C$
Density:	1.3756^{20}_{4}
Solubility:	alcohol, ether, benzene, insoluble in water

Benzotrichloride is used extensively in the dye industry for the production of Malachite green, Rosamine, Quinoline red, and Alizarine yellow A. It can also be used to produce ethyl orthobenzoate (Sidi, 1964).

II. EXPOSURE

A. Water

Benzotrichloride decompose in the presence of water to benzoic and hydrochloric acids (Windholz, 1976).

B. Food

Pertinent data were not found in the available literature.

C. Inhalation

Pertinent data were not found in the available literature; however, significant exposure could occur in the workplace from accidental spills. Benzotrichloride decomposes in moist air to benzoic and hydrochloric acids (Windholz, 1976).

D. Dermal

Benzotrichloride is irritating to the skin (Windholz, 1976).

III. PHARMACOKINETICS

Pertinent pharmacokinetic data were not found in the available literature.

IV. EFFECTS

A. Carcinogenicity

In a study by Matsushito and coworkers (1975), benzotrichloride was found to induce carcinomas, leukemia, and papillomas in mice. The details of the study were not available for assessment.

B. Mutagenicity

Yasuo, et al. (1978) tested the mutagenicity of several compounds including benzotrichloride in microbial systems such as the rec-assay using Bacillus subtilis, reversion assays using E. coli, and the Ames assay using Salmonella typhimurium, with or without metabolic activation. Benzotrichloride was positive for mutagenicity in the rec-assay and was highly positive on certain strains of E. coli and S. typhimurium in the reversion assay with metabolic activation. Without metabolic activation, however, benzotrichloride was only weakly positive in the latter assay.

C. Teratogenicity, Reproductive Effects, and Chronic Toxicity

Pertinent data were not found in the available literature.

D. Acute Toxicity

The lowest lethal concentration (LC_{LO}) for rats inhaling benzotrichloride is 125 ppm for four hours (Smyth, et al. 1951).

Benzotrichloride was severely irritating to the skin of rabbits that received dermal applications of 10 mg for 24 hours and to the eyes of rabbits that received instillations of 50 µg to the eye (Smyth, et al. 1951).

V. AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Existing guidelines and standards were not found in the available literature.

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No. 21

Benzyl Chloride

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

DISCLAIMER

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BENZYL CHLORIDE

Summary

Benzyl chloride has been shown to produce carcinogenic effects in rats following subcutaneous administration and in mice following intraperitoneal administration.

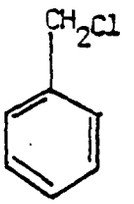
Weak mutagenic activity of the compound has been demonstrated in the Ames Salmonella assay and in E. coli.

There is no available information on the possible teratogenic or adverse reproductive effects of benzyl chloride.

Inhibition of cell multiplication in the alga, Microcystis aeruginosa, started at 30 mg/l. Concentrations of 10 mg/l and 17 mg/l caused paralysis in two species of fish.

I. INTRODUCTION

Benzyl chloride (alpha-chlorotoluene), CAS Registry number 100-44-7, is a colorless-to-light yellow, clear, lachrymatory liquid and is made by free-radical (photochemical) chlorination of tolene (Hawley, 1971; Austin, 1974). It has the following physical and chemical properties (Windholz, et al. 1976; Hawley, 1971; Weast, 1972):



Formula:	C_7H_7Cl
Molecular Weight:	126.59
Melting Point:	-43°C
Boiling Point:	179°C
Density:	1.100^{20}_{20}
Solubility:	Miscible in alcohol, chloroform, ether; insoluble in water
Production:	approximately 89 million lbs. 1977 (NIOSH, 1977)

Benzyl chloride is a moderately volatile compound with a vapor pressure of 1 mm Hg at 22°C (NIOSH, 1978). The compound decomposes relatively slowly in water with a 15-hour half-life of pH 7 (25°C) (NIOSH, 1978).

Benzyl chloride is used to make benzaldehyde through additional chlorination and hydrolysis, but modest amounts are also used as a benzylating agent for benzyl benzoate, n-butyl benzyl phthalate, benzyl ethyl aniline, benzyl cellulose, components of dyes and perfumes, and for production of phenylacetic acid by benzyl cyanide (Austin, 1974).

II. EXPOSURE

A. Water

Gruber (1975) reports that no benzyl chloride enters the water from production.

B. Food

Pertinent data could not be located in the available literature.

C. Inhalation

Pertinent data were not found in the available literature; however, benzyl chloride is used exclusively as a chemical intermediate in manufacturing and exposure and is most likely limited to the workplace. As such, the level of exposure is reported to be less than 1 ppm (NIOSH, 1978).

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data could not be located in the available literature.

B. Metabolism and Excretion

The major excretion product following ingestion of benzyl chloride is a cysteine conjugate, benzylmercapturic acid (Stekol, 1938, 1939; Witter, 1944; Barnes, et al. 1959; Knight and Young, 1958).

Bray, et al. (1958) administered benzyl chloride at 200 mg/kg body weight orally to rabbits. Urine collected for 24 hours showed 86.4 percent of the administered dose in the soluble fraction, with 49 percent as benzylmercapturic acid, 20 percent as a glycine conjugate, 0.4 percent as glucosiduronic acid, and 17 percent as unconjugated benzoic acid. Maitrya and Vyas (1970) found 30 percent of the total oral dose of benzyl chloride to be excreted by rats as hippuric acid.

Knight and Young (1958) found that benzyl chloride is converted directly to benzyl mercapturic acid, unlike related compounds such as chlorinated benzenes, which form acid-labile precursors.

Barnes, et al. (1959) found that 27 percent of the total oral dose of benzyl chloride administered to rats was excreted as benzyl mercapturic acid. This value compares with 49 percent excreted in rabbits (Bray, et al. 1958) and 4 percent in guinea pigs (Bray, et al. 1959).

Several studies have indicated that glutathione is the source of the thiol groups for mercapturic acid formation from benzyl chloride (Barnes, et al. 1959; Simkin and White, 1957; Anderson and Mosher, 1951; Waelsch and Rittenberg, 1942; Bray, et al. 1969; Beck, et al. 1964). The turnover rate of glutathione in the liver was found to be 49 mg/100 g of liver per hour (Simkin and White, 1957). An in vitro study by Suga, et al. (1966) revealed that conjugation with glutathione can occur both enzymatically and non-enzymatically in rat liver preparations. The enzymic conjugation has also been observed in human liver preparations (Boyland and Chasseaud, 1969).

IV. EFFECTS

A. Carcinogenicity

Benzyl chloride was reviewed by IARC (1976) and found to be carcinogenic in rats. Druckrey, et al. (1970) injected 14 rats subcutaneously with benzyl chloride at 2.1 g/kg body weight (total dose) and 8 rats with 3.9 g/kg body weight (total dose) during 51 weeks. Injection site sarcomas were noted in three of the rats receiving the lower dose and six receiving the higher dose; most of the tumors had metastasized to the lungs. The vehicle of administration, arachis oil, did not produce local tumors.

Poirier, et al. (1975) administered intraperitoneal injections of benzyl chloride in tricaprylin to three groups of 20 male and female A/Heston mice, three times per week for eight weeks, with total doses of 0.6, 1.5, and 2.0 g/kg body weight. After 24 weeks, all survivors were killed;

lung tumors occurred in 4/15, 7/16, and 2/8 surviving mice in the three groups, respectively. The average number of tumors per mouse was 0.26, 0.50, and 0.25, respectively. The incidence of tumors in mice receiving the benzyl chloride was not significantly different from the results recorded for untreated mice on the tricaprylin-vehicle treated mice.

B. Mutagenicity

McCann, et al. (1975a,b) found benzyl chloride to be weakly mutagenic (less than 0.10 revertants/nanomole) when tested using the Ames assay (Salmonella/microsomal activation).

Rosenkranz and Poirier (1978), in a National Cancer Institute report, found benzyl chloride to be marginally mutagenic in the Ames assay at doses of 5 µl and 10 µl/plate without activation. Microsomal activation had an inactivating effect on benzyl chloride. The investigators also evaluated the DNA-modifying activity in bacterial systems using Escherichia coli pol A mutants. A dose of 10 µl benzyl chloride produced a positive mutagenic effect.

Benzyl chloride was found to be non-mutagenic in the Ames Salmonella microsomal assay by Simmon (1979). The compound was mutagenic when exposure was by vapor phase in a dessicator.

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature.

D. Acute Toxicity

A number of studies have been conducted on the acute toxicity of benzyl chloride vapor to animals and were reviewed in a criteria document prepared by NIOSH (1978). Respiratory tract inflammation and secondary infections were observed in mice exposed to 390 mg/m^3 (LC_{50}) for two hours and rats exposed to 740 mg/m^3 (LC_{50}) for two hours (Mikhailova, 1965).

Rabbits exposed to 480 mg/m^3 of benzyl chloride for eight hours/day for six days suffered mild eye and nasal irritation by the sixth day, while cats exposed to the same regimen suffered a loss of appetite in addition to eye and respiratory tract irritation (Wolf, 1912). Death of a dog occurred within 24 hours of exposure to 1,900 mg/m^3 of benzyl chloride for eight hours. Corneal turbidity and irritation of the ocular, respiratory, and oral mucosa were observed before death (Schutte, 1915). Mikhailova (1965) observed hepatic changes and necrosis of the kidney in rats and mice exposed to benzyl chloride at 100 mg/m^3.

Landsteiner and Jacobs (1936) investigated the sensitizing properties of benzyl chloride to guinea pigs. Benzyl chloride, in a saline solution (0.01 mg/animal) was injected intracutaneously twice per week for 12 weeks. Two weeks later, re-exposure revealed that benzyl chloride had a sensitizing effect.

Occupational exposures to benzyl chloride have been reported by several investigators (Wolf, 1912; Schutte, 1915; Mikhailova, 1971; Katz and Talbert, 1930; Watrous, 1947). Lacrimination, conjunctivitis, and irritation of the respiratory tract and eyes have been reported following exposure to benzyl chloride vapor levels ranging from 6 to 8 mg/m^3 for five minutes to brief exposure at 23,600 mg/m^3. Although no cases were reported in the literature, liquid benzyl chloride has the potential for skin irritation based on its release of hydrochloric acid upon hydrolysis. The odor threshold and nasal irritation thresholds for benzyl chloride are 0.21 to 0.24 mg/m^3 and 180 mg/m^3, respectively (Katz and Talbert, 1930; Leonardos, et al. 1969).

V. AQUATIC TOXICITY

A. Acute and Chronic Toxicity

Pertinent data could not be located in the available literature.

B. Plant Effects

Inhibition of cell multiplication in Microcystis aeruginosa started at 30 mg/l (Bringmann and Kuhn, 1976).

C. Residues

Pertinent data could not be located in the available literature.

D. Other Relevant Information

Hiatt, et al. (1953) found that 1.0 mg/l of benzyl chloride produced no irritant response in marine fish, but 10 mg/l caused a slight irritant activity. This compound caused paralysis in the fish Trutta iridea and Cyprinus carpio at concentrations of 10 mg/l and 17 mg/l, respectively (Meinck, et al. 1970).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The American Conference of Governmental and Industrial Hygienists (ACGIH, 1977) recommends an occupational exposure limit of 1 ppm (5 mg/m^3) for benzyl chloride. The U.S. federal standard promulgated by OSHA is also 1 ppm (TWA) (29 CFR 1910.1000). NIOSH recommends an environmental exposure limit of 5 mg/m^3 as a ceiling value for a 15-minute exposure (NIOSH, 1978).

B. Aquatic

No guidelines to protect fish and saltwater organisms from benzyl chloride toxicity have been established because of the lack of available data.

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No. 22

Beryllium

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated beryllium and has found sufficient evidence to indicate that this compound is carcinogenic.

BERYLLIUM

SUMMARY

Beryllium was shown to be carcinogenic in three animal species, producing cancers of the lung and bone when administered by injection, inhalation, or intratracheal instillation. Ingestion of beryllium has failed to produce cancers in animals, possibly due to its poor gastrointestinal absorption. Several epidemiology studies support the hypothesis that beryllium is a human carcinogen.

Beryllium is toxic to freshwater organisms at concentrations as low as 5.3 µg/l. Pertintent data for marine organisms were not found in the available literature (U.S. EPA, 1979).

BERYLLIUM

I. INTRODUCTION

This profile is primarily based upon the Ambient Water Quality Criteria Document for Beryllium (U.S. EPA, 1979). Recent comprehensive reviews on the hazards of beryllium have also been prepared by the National Institute for Occupational Safety and Health (NIOSH, 1972) and the International Agency for Research on Cancer (IARC, 1972).

Beryllium (Be; atomic weight 9.01) is a dark gray metal of the alkaline earth family. Beryllium has the following physical-chemical properties (IARC, 1972):

Boiling point:	2970°C
Melting point:	1284 - 1300°C
Hardness:	60 - 125
Density:	1.84 - 1.85
Solubility:	Soluble in acids and alkalis

World production of beryllium was reported as approximately 250 tons annually, but much more reaches the environment as emissions from coal burning operations (Tepper, 1972). Most common beryllium compounds are readily soluble in water. The hydroxide is soluble only to the extent of 2 mg/l (Lange, 1956). Beryllium forms chemical compounds in which its valence is +2. At acid pH, it behaves as a cation but forms anionic complexes at pH greater than 8 (Krejci and Scheel, 1966). The major source of beryllium in the environment is the combustion of fossil fuels (Tepper, 1972). Beryllium enters the waterways through weathering of rocks and soils, through atmospheric fallout and through discharges from industrial and municipal operations.

II. EXPOSURE

A. Water

Kopp and Kroner (1967) reported the results of trace metal analyses of 1,577 drinking water samples obtained throughout the United States. Beryllium was detected in 5.4 percent of the samples. Concentrations ranged from 0.01 to 1.22 µg/l, with a mean value of 0.19 µg/l.

B. Food

Beryllium has been detected in a variety of vegetables, and in eggs, milk, nuts, bread, and baker's yeast (Meehan and Smythe, 1967; Petzow and Zorn, 1974). Measured levels of beryllium were generally in the range of 0.01 to 0.5 ppm. Using the data for consumption and bioconcentration for freshwater and saltwater fishes, mollusks, and decapods, and the measured steady-state bioconcentration factor (BCF) for beryllium in bluegills, the U.S. EPA (1979) has estimated a weighted average BCF for beryllium to be 19 for the edible portions of fish and shellfish consumed by Americans.

C. Inhalation

The detection of beryllium in air is infrequent and usually in trace amounts. In urban areas beryllium levels may reach 0.008 µg/m^3, while in rural areas beryllium concentrations have been measured at 0.00013 µg/m^3 (Tabor and Warren, 1958; National Air Sampling Network, 1968). At a beryllium extraction plant in Ohio, beryllium concentrations were generally around 2 µg/m^3 over a seven year period (Breslin and Harris, 1959).

III. PHARMACOKINETICS

Ingested beryllium is poorly absorbed within the gastrointestinal tract, presumably due to solubility problems in the alimentary canal (Hyslop, et al. 1943; Reeves, 1965). When inhaled, soluble beryllium compounds are rapidly removed from the lung, whereas insoluble beryllium compounds can remain in the lung indefinitely (Van Cleave and Kaylor, 1955; Wagner, et al. 1969; Sprince, et al. 1976). When parenterally administered, beryllium is distributed to all tissues, although it shows preferential accumulation in bone, followed by spleen, liver, kidney and muscle (Van Cleave and Kaylor, 1955; Crowley, et al. 1949; Klemperer, et al. 1952; Kaylor and Van Cleave, 1953; Spencer, et al. 1972). Absorbed beryllium tends to be either excreted in the urine or deposited in kidneys and bone (Scott, et al. 1950). Once deposited in the skeleton, beryllium is removed very slowly, with half-lives of elimination reported to be 1,210, 890, 1,770 and 1,270 days in mice, rats, monkeys, and dogs, respectively (Furchner, et al. 1973).

IV. EFFECTS

A. Carcinogenicity

Beryllium was shown to be carcinogenic in three animal species. Intravenous injection of beryllium, zinc beryllium silicate, and beryllium phosphate produced osteosarcomas in the rabbit (Gardner and Heslington, 1946; Dutra and Largent, 1950; Komitowski, 1969; Fodor, 1971; IARC, 1972). Inhalation and intratracheal instillation of beryl-

lium compounds have produced lung cancers in the rat and monkey (Vorwald and Reeves, 1959; Vorwald, et al. 1966; Reeves, et al. 1967). Ingestion of beryllium by rats and mice has failed to induce tumors, possibly due to the poor absorption of beryllium from the gastrointestinal tract.

Several epidemiological studies have failed to establish a clear association between beryllium exposure and cancer development (Stoeckle, et al. 1969; Mancuso, 1970; Niemoller, 1963). However, other recent studies support the hypothesis that beryllium is a human carcinogen (Berg and Burbank, 1972; Wagoner, et al. 1978; Discher, 1978).

B. Mutagenicity

Pertinent data were not found in the available literature.

C. Teratogenicity

Beryllium has been implicated as a teratogen in snails (Raven and Sprok, 1953) and has inhibited limb regeneration in the salamander, Amblystoma punctatum (Thorton, 1950).

D. Other Reproductive Effects

Pertinent data were not found in the available literature.

E. Chronic Toxicity

Chronic beryllium inhalation in humans produces a progressive, systemic disease which may follow the cessation of exposure by as long as five years (Tepper, et

al. 1961; Hardy and Stoeckle, 1959). Symptoms include pneumonitis with cough, chest pain, and general weakness. Systemic effects include right heart enlargement with cardiac failure, enlargement of liver and spleen, cyanosis, digital clubbing, and kidney stones (Hall, et al. 1959). Chronic beryllium disease can be produced in rats and monkeys by inhalation of beryllium sulfate at 35 $\mu g/m^3$ (Schepers, et al. 1957; Vorwald, et al. 1966).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity data for beryllium for freshwater fishes are taken from 22 static and 5 flow-through bioassays, all 96 hours in duration. U.S. EPA (1979) presents the most sensitive species, the guppy Poecilia reticulata, with LC_{50} values ranging from 71 to 17,500 µg/1. The data reflect that the toxicity of beryllium to freshwater fish is decreased in hard water. This has also been confirmed by U.S. EPA (1979) in the fathead minnow, Pimephales promelas, with LC_{50} values ranging from 82 to 11,000 µg/1. Acute toxicity for aquatic invertebrates provides two 48-hour LC_{50} values of 7,900 and 2,500 µg/1, with water hardness values of 180 and 200 µg/1 as $CaCo_3$. The source of these invertebrate studies is the same for chronic freshwater studies. No data for acute toxicity to marine species was found in the available literature.

B. Chronic Toxicity

No chronic tests for freshwater fish were found in the available literature. The cladoceran, Daphnia magna, was the only freshwater species tested for chronic effects; chronic values of less than 36 µg/l and 5.3 µg/l were obtained by the U.S. EPA (1979). No chronic data for marine species of fish or invertebrates was found in the available literature.

C. Plant Effects

The only plant study available reveals that the green algae, Chlorella vannieli, displayed growth inhibition at a concentration of 100,000 µg/l (U.S. EPA, 1979).

D. Residues

Exposure of the bluegill for 28 days produced a bioconcentration factor of 19 (U.S. EPA, 1978). No other data was found in the available literature.

E. Other Relevant Information

The only marine data presented showed reduced alkaline phosphatase activity in the mummichog, Fundulus heteroclitus, at concentrations as low as 9 µg/l. A teratogenic response was observed by Evola-Maltese (1957) in sea urchin embryos at concentrations of 9.010 µg/l.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The present standard for occupational exposure to beryllium prescribes an 8-hour time-weignted average

of 2.0 $\mu g/m^3$ with a ceiling concentration of 5.0 $\mu g/m^3$. This is the same value recommended by the American Conference of Governmental Industrial Hygienists (1977). The National Institute for Occupational Safety and Health (NIOSH, 1972) recommends that occupational exposure to beryllium and its compounds not exceed 1 $\mu g/m^3$ (8-hour time-weighted average) with a ceiling limit of 5 $\mu g/m^3$ (measured over a 15 minute sampling period).

National Emission Standards for Hazardous Air Pollutants set their criterion as not more than 10 g in 24 hours or emissions which result in maximum outplant concentrations of 0.01 $\mu g/m^3$, 30-day average (U.S. EPA, 1977).

Based on animal bioassay data for beryllium to which the linear model was applied, the U.S. EPA (1979) has estimated levels of beryllium in ambient water which will result in carcinogenic risk for humans. As a result of the public comments received, additional review and reevaluation of the data base is required before a final criterion level can be recommended.

B. Aquatic

The U.S. EPA proposed a water quality standard of 11 $\mu g/l$ for the protection of aquatic life in soft freshwater; 1,100 $\mu g/l$ for the protection of aquatic life in hard freshwater; and 100 $\mu g/l$ for continuous irrigation on all soils, except 500 mg/l for irrigation on neutral to alkaline lime-textured soils (U.S. EPA, 1977).

The National Academy of Science/National Academy of Engineering (1973) Water Quality Criteria recommendation for marine aquatic life is: hazard level - 1.5 µg/l; minimal risk of deleterious effects - 0.1 mg/l; and application factor - 0.01 (applied to 96-hour LC_{50}). Their recommendation for irrigation water is: 0.10 mg/l for continuous use on all soils.

The U.S. EPA (1979) has derived a draft criterion for beryllium to protect freshwater aquatic organisms. The 24-hour average concentration in µg/l is dependent on water hardness and is derived by the following equation:

$$CR = e^{(1.24 \ln (\text{hardness}) - 6.65)}$$

The concentration not to be exceeded at any time is:

$$CR = e^{(1.24 \ln (\text{hardness}) - 1.46)}$$

No draft criterion was derived for marine organisms (U.S. EPA, 1979).

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No. 23

Bis(2-chloroethoxy)methane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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BIS(2-CHLOROETHOXY)METHANE

Summary

Pertinent data could not be located in the available literature searches on the mutagenic, carcinogenic, teratogenic, or adverse reproductive effects of bis(2-chloroethoxy)methane (BCEXM) in mammals. A closely related compound, bis(2-chloroethoxy)ethane (BCEXE) has been shown to produce skin tumors and injection site sarcomas in animal studies.

Pertinent information could not be located in the available literature on bis(2-chloroethoxy)methane toxicity to aquatic organisms.

BIS(2-CHLOROETHOXY)METHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chloroalkyl Ethers (U.S. EPA, 1979a).

The chloroalkyl ethers are compounds in which a hydrogen atom in one or both of the aliphatic ether chains are substituted with chlorine. Bis(2-chloroethoxy)methane (BCEXM, dichloroethyl formal, $ClCH_2CH_2-O-CH_2-OCH_2-CH_2Cl$) is a colorless liquid at room temperature with a boiling point of 218.1°C and a specific gravity of 1.2339. The compound is slightly soluble in water but miscible with most organic solvents.

The chloroalkyl ethers have a wide variety of industrial uses in organic synthesis, treatment of textiles, the manufacture of polymers and insecticides, as degreasing agents and solvents, and in the preparation of ion exchange resins (U.S. EPA, 1979a).

The chloroalkyl ethers, like BCEXM, have a higher stability in water than the alpha chloroalkyl ethers, which decompose. BCEXM is decomposed by mineral acids.

II. EXPOSURE

No specific information on exposure to BCEXM is available. The reader is referred to a more general treatment of chloroalkyl ethers (U.S. EPA, 1979b). BCEXM has been monitored in rubber plant effluents at a maximum level of 140 mg/l (Webb, et al. 1973). Bis-1,2-(2-chloroethoxy)ethane (BCEXE), a closely related compound, has been reported in drinking water at a maximum level of 0.03 µg/l (U.S. EPA, 1975). Data on levels of BCEXM in foods was not found in the available literature.

No bioaccumulation factor for BCEXM has been derived.

III. PHARMACOKINETICS

Pertinent information could not be located in the available literature on BCEXM. The reader is referred to a more general treatment of chloroalkyl ethers (U.S. EPA, 1979b).

IV. EFFECTS

A. Carcinogenicity

Pertinent information could not be located in the available literature on carcinogenic effects of BCEXM. The reader is referred to a more general treatment of chloroalkyl ethers (U.S. EPA, 1979b). A closely related compound, BCEXE, has been shown to produce skin tumors in mice and injection site sarcomas (Van Duuren, et al. 1972).

B. Mutagenicity, Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature for BCEXM.

V. AQUATIC TOXICITY

Pertinent information could not be located in the available literature on the aquatic toxicity of BCEXM.

VI. EXISTING GUIDELINES AND STANDARDS

No standards or recommended criteria exist for the protection of human health or aquatic organisms to bis(2-chloroethoxy)methane.

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No. 24

Bis(2-chloroethyl)ether

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated bis(2-chloroethyl)ether and has found sufficient evidence to indicate that this compound is carcinogenic.

BIS(2-CHLOROETHYL)ETHER

Summary

Oral administration of bis(2-chloroethyl)ether (BCEE) did not produce an increase of tumors in rats. Male mice showed a significant increase in hepatomas after ingestion of BCEE. BCEE has also shown activity as a tumor initiator for mouse skin.

Testing of BCEE in the Ames' Salmonella assay, in E. coli, and in Saccharomyces cerevisiae has shown that this compound induces mutagenic effects.

There is no available evidence to indicate that BCEE produces adverse reproductive effects or teratogenic effects.

The data base for bis(2-chloroethyl)ether is limited to three studies. The 96-hr LC_{50} value for the bluegill is reported to be over 600,000 µg/l. Adverse chronic effects were not observed with the fathead minnow at test concentrations as high as 19,000 µg/l. A bioconcentration factor of 11 was observed during a 14-day exposure of bluegills. The half-life was 4-7 days.

BIS(2-CHLOROETHYL)ETHER

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chloralkyl Ethers (U.S. EPA, 1979a).

The chloroalkyl ethers are compounds in which a hydrogen atom in one or both of the aliphatic ether chains are substituted with chlorine. Bis(2-chloroethyl)ether (BCEE, molecular weight 143.01) is a colorless liquid at room temperature with a boiling point of 176-178°C at 760 mm Hg, and a density of 1.213. The compound is practically insoluble in water, but is miscible with most organic solvents (U.S. EPA, 1979a).

The chloroalkyl ethers have a wide variety of industrial and laboratory uses in organic synthesis, in textile treatment, the manufacture of polymers and insecticides, as degreasing agents, and in the preparation of ion exchange resins (U.S. EPA, 1979a).

The B-substituted chloroalkyl ethers, such as BCEE, are generally more stable and hence less reactive in aqueous systems than the a-substituted compounds (U.S. EPA, 1979a).

For additional information regarding chloroalkyl ethers in general, the reader is referred to the EPA/ECAO Hazard Profile on Chloroalkyl Ethers (U.S. EPA 1979b).

II. EXPOSURE

The B-chloroalkyl ethers have been monitored in water. Industrial discharges from chemical plants involved in the manufacture of glycol products, rubber, and insecticides may contain high levels of BCEE (U.S. EPA, 1979a). The highest concentration of BCEE in drinking water reported by the U.S. EPA

(1975) is 0.5 µg/l. There is no evidence of the occurrence of the chloroalkyl ethers in the atmosphere; human exposure appears to be confined to occupational settings.

Human exposure to chloroalkyl ethers via ingestion of food is unknown (U.S. EPA, 1979a). The B-chloroalkyl ethers, due to their stability and low water solubility, may have a high tendency to be bioaccumulated. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for BCEE to be 25 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on a measured steady-state bioconcentration factor using bluegills.

III. PHARMACOKINETICS

A. Absorption

Experiments with radiolabelled BCEE have indicated that the compound is readily absorbed following oral administration (Lingg, et al. 1978). Information on inhalation or dermal absorption of chloroalkyl ethers is not available (U.S. EPA, 1979a).

B. Distribution

Pertinent information on the distribution of BCEE could not be located in the literature.

C. Metabolism

The biotransformation of BCEE in rats following oral administration appears to involve cleavage of the ether linkage and subsequent conjugation with non-protein-free sulfhydryl groups, the major route, or with glucuronic acid (Lingg, et al. 1978). Thiodiglycolic acid and 2-chloroethanol-B-D-glucuronide were identified as urinary metabolites of BCEE in rats.

D. Excretion

BCEE administered to rats by intubation was eliminated rapidly in the urine, with more than 60 percent of the compound excreted within 24 hours (Lingg, et al. 1978).

IV. EFFECTS

A. Carcinogenicity

BCEE has shown activity as a tumor initiator in mouse skin (U.S. EPA, 1979a). Preliminary results of an NCI study indicate that oral administration of BCEE does not produce an increase in tumor incidence in rats (U.S. EPA, 1979a); however, mice administered BCEE by ingestion showed a significant increase in hepatomas (Innes, et al. 1969).

B. Mutagenicity

Testing of the chloroalkyl ethers in the Ames' Salmonella assay and in E. coli have indicated that BCEE induces mutagenic effects (U.S. EPA, 1979a). BCEE has also shown mutagenic effects in Saccharomyces cerevisiae (Simmon, et al. 1977), but none were found in the heritable translocation test for mice (Jorgenson, et al. 1977).

C. Teratogenicity, Chronic Toxicity and other Reproductive Effects

Pertinent information could not be located in the available literature.

D. Other Relevant Information

Acute physiological responses of the guinea pig to inhalation of high concentrations of BCEE were congestion, emphysema, edema and hemorrhage of the lungs (Shrenk, et al. 1933). Brief exposure of man to BCEE vapor, at levels 260 ppm, irritated the nasal passages and eyes with profuse lacrimation. Deep inhalation produced nausea. The highest concentration with no noticeable effect was 35 ppm (Shrenk, et al. 1933).

V. AQUATIC TOXICITY

A. Acute Toxicity

96-hr LC_{50} value for the bluegill, Lepomis macrochirus, could not be determined for bis(2-chloroethyl)ether with exposure concentrations as high as 600,000 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

An embryo-larval test has been reported with bis(2-chloroethyl) ether and the fathead minnow, Pimephales promelas. Adverse effects were not observed at test concentrations as high as 19,000 µg/l (U.S. EPA, 1978).

C. Plant Effects

Pertinent data could not be located in the available literature.

D. Residues

A bioconcentration factor of 11 was determined during a 14-day exposure of bluegills to bis(2-chloroethyl)ether. The half-life was 4-7 days.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a) which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on the results of an animal carcinogenesis bioassay, and using a linear, non-threshold model, the U.S. EPA (1979a) has estimated that an ambient water level of 0.42 µg/l will present an increased risk of 10^{-5} or less for BCEE, assuming water and the injection of contaminated aquatic organisms to be the only sources of exposure.

The 8-hour, time-weighted average threshold limit value (TLV-TWA) for BCEE determined by the American Conference of Governmental Industrial Hygienists (ACGIH, 1978) is 5 ppm for BCEE.

8. Aquatic

Freshwater or saltwater criteria cannot be derived for bis(2-chloroethyl)ether because of insufficient data (U.S. EPA, 1979a).

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No. 25

Bis(2-Chloroisopropyl)ether

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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BIS(2-CHLOROISOPROPYL)ETHER

Summary

Preliminary results from an NCI carcinogenesis bioassay do not show an increase in tumors following oral administration of bis(2-chloroisopropyl)-ether (BCIE).

BCIE has produced mutagenic effects in two bacterial test systems (Salmonella and E. coli) but has failed to show mutagenicity in one mammalian study.

No information is available on the teratogenic or adverse reproductive effects of BCIE.

Chronic exposure to BCIE has produced liver damage in animals.

Data on the toxicity of bis(2-chloroisopropyl)ether to aquatic organisms are not available.

BIS(2-CHLOROISOPROPYL)ETHER

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chloroalkyl Ethers (U.S. EPA, 1979a).

The chloroalkyl ethers are compounds in which a hydrogen atom in one or both of the aliphatic ether chains are substituted with chlorine. Bis(2-chloroisopropyl)ether (BCIE, molecular weight 171.07) is a colorless liquid at room temperature with a boiling point of 187-188°C at 760 mm Hg. The compound is practically insoluble in water but is miscible with organic solvents.

The chloroalkyl ethers have a wide variety of industrial and laboratory uses in organic synthesis, treatment of textiles, the manufacture of polymers and insecticides, as degreasing agents, and in the preparation of ion exchange resins (U.S. EPA, 1979a).

The beta-chloroalkyl ethers, like BCIE, are more stable in aqueous system than the alpha-chloroalkyl ethers, which decompose rapidly. For additional information regarding the chloroalkyl ethers as a class, the reader is referred to the Hazard Profile on Chloroalkyl Ethers (U.S. EPA, 1979b).

II. EXPOSURE

The beta-chloroalkyl ethers have been monitored in water. Industrial discharges from chemical plants involved in the manufacture of glycol products, rubber, and insecticides may present high effluent levels (U.S. EPA, 1979a). The highest concentration of BCIE monitored in drinking water by the U.S. EPA (1975) was reported as 1.58 µg/l.

The concentrations of chloroalkyl ethers in foods have not been monitored. The beta-chloroalkyl ethers, however, due to their relative stability and low water solubility, may have a high tendency to be bioaccumulated.

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for bis(2-chloroisopropyl)ether to be 106 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

III. PHARMACOKINETICS

A. Absorption

Experiments with radio-labeled BCIE have indicated that the compound is readily absorbed following oral administration (Smith, et al. 1977). No information on inhalation or dermal absorption of the chloroalkyl ethers is available (U.S. EPA, 1979a).

B. Distribution

Species differences in the distribution of radio-labeled BCIE have been reported by Smith, et al. (1977). Monkeys retained higher amounts of radioactivity in the liver, muscle, and brain than did rats. Urine and expired air from monkeys also contained higher levels of radioactivity than those determined in the rat. Blood levels of BCIE in monkeys reached a peak within 2 hours following oral administration and then declined in a biphasic manner (t 1/2 = 5 hours and 2 days, respectively).

C. Metabolism

Urinary metabolites of labeled BCIE identified in studies with rats included 1-chloro-2-propanol, propylene oxide, 2-(1-methyl-2-chloro-ethoxy) propionic acid, and carbon dioxide (Smith, et al. 1977).

D. Excretion

Smith, et al. (1977) found that in the rat, 63.36 percent, 5.87 percent, and 15.96 percent of a 30 mg orally-administered dose of BCIE were recovered after 7 days in the urine, feces, and expired air, respectively. In the monkey, the corresponding figures were 28.61 percent, 1.19 percent, and 0 percent, respectively.

IV. EFFECTS

A. Carcinogenicity

Preliminary results of an NCI carcinogenicity bioassay indicate that oral administration of BCIE does not produce an increase in tumor incidence (U.S. EPA, 1979a).

B. Mutagenicity

Testing of BCIE in the Ames Salmonella assay and in E. coli have indicated that the compound shows mutagenic activity (U.S. EPA, 1979a). BCIE did not show mutagenic effects in the murine heritable translocation test (Jorgenson, et al. 1977).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Chronic oral exposures of mice to BCIE produced centrilobular liver necrosis in mice. The major effects in rats were pulmonary congestion and pneumonia (U.S. EPA, 1979a).

E. Other Relevant Information

Several chloroalkyl ethers show initiating activity and therefore may interact with other agents to produce skin papillomas (Van Duuren, et al. 1969, 1972); however, data specific to BCIE is not available.

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

BCIE is an isomer of a group of chloroalkyl ethers which have been shown to have carcinogenic potential. BCIE has been shown to be mutagenic; however, definitive proof of carcinogenicity has not been demonstrated. The available data is presently under review and a definitive determination as to the carcinogenicity of this isomer cannot be made at this time.

B. Aquatic

No draft criteria to protect fish and saltwater aquatic organisms from bis(2-chloroisopropyl)ether toxicity have been derived (U.S. EPA, 1979).

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Jorgenson, T., et al. 1977. Study of the mutagenic potential of bis(2-chloroethyl) and bis(2-chloroisopropyl) ethers in mice by the heritable translocation test. Toxicol. Appl. Pharmacol. 41: 196.

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U.S. EPA. 1979b. Environmental Criteria and Assessment Office. Chloroalkyl Ethers: Hazard Profile. (Draft)

Van Duuren, B., et al. 1969. Carcinogenicity of haloethers. Jour. Natl. Cancer Inst. 43: 481.

Van Duuren, B., et al. 1972. Carcinogenicity of haloethers. II. Structure-activity relationships of analogs of bis(chloroethyl)ether. Jour. Natl. Cancer Inst. 48: 1431.

No. 26

Bis(Chloromethyl)ether

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated bis(chloromethyl)ether and has found sufficient evidence to indicate that this compound is carcinogenic.

BIS(CHLOROMETHYL)ETHER

Summary

Bis(chloromethyl)ether (BCME) has been shown to produce tumors in animals following administration by subcutaneous injection, inhalation, or dermal application. Epidemiological studies of workers in the United States, Germany, and Japan who were exposed to BCME and chloromethyl methyl ether (CMME) indicate that these compounds are human respiratory carcinogens.

BCME has produced mutagenic effects in the Ames' Salmonella assay and in E. coli. Increased cytogenetic abnormalities have been observed in the lymphocytes of workers exposed to BCME and CMME; this effect appeared to be reversible.

There is no available evidence to indicate that the chloroalkyl ethers produce adverse reproductive effects or teratogenic effects.

Information has not been found on the toxicity of bis(chloromethyl) ether to aquatic organisms. The hazard profiles on the haloethers and the chloroalkyl ethers should be consulted for the toxicity of related compounds.

BIS(CHLOROMETHYL)ETHER

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chloroalkyl Ethers (U.S. EPA, 1979a).

The chloroalkyl ethers are compounds in which hydrogen atoms in one or both of the aliphatic ether chains are substituted with chlorine. Bis-(chloromethyl)ether, (BCME; molecular weight 115.0), is a colorless liquid at room temperature with a boiling point of 104°C at 760 mm Hg, and a density of 1.328. The compound immediately hydrolyzes in water, but is miscible with ethanol, ether, and many organic solvents (U.S. EPA, 1979a).

The chloroalkyl ethers have a wide variety of industrial and laboratory uses in organic synthesis, textile treatment, the manufacture of polymers and insecticides, the preparation of ion exchange resins, and as degreasing agents (U.S. EPA, 1979a).

While BCME is very unstable in water, it appears to be relatively stable in the atmosphere (Tou and Kallos, 1974). Spontaneous formation of BCME occurs in the presence of both hydrogen chloride and formaldehyde (Frankel, et al. 1974). For additional information regarding the chloroalkyl ethers in general, the reader is referred to the EPA/ECAO Hazard Profile on Chloroalkyl Ethers (U.S. EPA, 1979b).

II. EXPOSURE

As might be expected from the reactivity of BCME in water, monitoring studies have not detected its presence in water. Human exposure by inhalation appears to be confined to occupational settings (U.S. EPA, 1979a).

Data for human exposure to chloroalkyl ethers by ingestion of food is not available, nor is data relevant to human dermal exposure to chloralkyl ethers (U.S. EPA, 1979a).

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for BCME to be 31 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

III. PHARMACOKINETICS

There is no specific information relating to the absorption, distribution, metabolism, or excretion of BCME (U.S. EPA, 1979a). Because of the high reactivity and instability of BCME in aqueous systems, it is difficult to generate pharmacokinetic parameters.

IV. EFFECTS

A. Carcinogenicity

BCME has been shown to produce tumors in several animal systems. Inhalation exposure of male rats to BCME produced malignant respiratory tract tumors (Kuschner, et al. 1975), while dermal application to mouse skin led to the appearance of skin tumors (Van Duuren, et al. 1968). Administration of BCME to newborn mice by ingestion has been shown to increase the incidence of hepatocellular carcinomas in males (Innes, et al. 1969).

Epidemiological studies of workers in the United States, Germany, and Japan who were occupationally exposed to BCME and CMME have indicated that these compounds are human respiratory carcinogens (U.S. EPA, 1979a).

BCME has been shown to accelerate the rate of lung tumor formation in strain A mice following inhalation exposure (Leong, et al. 1971). BCME has also shown activity as a tumor initiating agent for mouse skin (Slaga, et al. 1973).

B. Mutagenicity

Testing of the chloroalkyl ethers in the Ames Salmonella assay and in E. coli have indicated that BCME produced direct mutagenic effects (U.S. EPA, 1979a).

The results of a study on the incidence of cytogenetic aberrations in the lymphocytes of workers exposed to BCME and CCME indicate higher frequencies in this cohort. Follow-up indicates that removal of workers from exposure led to a decrease in the frequency of aberrations (Zudova and Landa, 1977).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature regarding teratogenicity and other reproductive effects.

D. Chronic Toxicity

Chronic occupational exposure to CMME contaminated with BCME has produced bronchitis in workers (U.S. EPA, 1979a). Cigarette smoking has been found to act synergistically with this type of exposure to produce bronchitis (Weiss, 1976, 1977).

E. Other Relevant Information

The initiating activity of several chloroalkyl ethers indicates that these compounds will interact with other agents to produce skin papillomas (Van Duuren, et al. 1969, 1972).

V. AQUATIC TOXICITY

Pertinent information could not be found in the available literature regarding aquatic toxicity for freshwater or marine species.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a) which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on animal carcinogenesis data, and using a linear, non-threshold model, the U.S. EPA (1979a) has recommended a maximum permissible

concentration of BCME for ingested water at .02 ng/l. Assuming water is the only source of exposure, compliance to this level should limit the risk carcinogenesis to not more than 10^{-5}.

Based on animal studies, the 8-hour, time-weighted threshold limit value (TLV-TWA) has been recommended for BCME as one ppb by the American Conference of Governmental and Industrial Hygienists (1978).

B. Aquatic

Criterion for the protection of freshwater or marine aquatic organisms were not drafted due to lack of toxicological evidence.

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American Conference of Governmental Industrial Hygienists. 1978. Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1978. Cincinnati, Ohio.

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No. 27

Bis(2-ethylexyl)phthalate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

BIS-(2-ETHYLHEXYL)PHTHALATE

SUMMARY

Bis-(2-ethylhexyl)phthalate has been shown to produce mutagenic effects in the Ames Salmonella assay and in the dominant lethal assay.

Teratogenic effects in rats were reported following interperitoneal (i.p.) administration and oral administration of bis-(2-ethylhexyl)phthalate. Additional reproductive effects produced by bis-(2-ethylhexyl)phthalate include impaired implantation and parturition, and decreased fertility in rats. Testicular damage and decreased spermatogenesis have been reported in rats, following i.p. or oral administration, and in mice, given bis-(2-ethylhexyl)phthalate by oral intubation.

Evidence has not been found indicating that bis-(2-ethylhexyl)phthalate has carcinogenic effects. Chronic animal feeding studies of bis-(2-ethylhexyl)phthalate have shown effects on the liver and kidneys.

Bis-(2-ethylhexyl)phthalate is acutely toxic to freshwater invertebrates at a concentration of 11,000 µg/l. The same species has been shown to display severe reproductive impairment when exposed to concentrations less than 3 µg/l.

BIS-(2-ETHYLHEXYL)PHTHALATE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Phthalate Esters (U.S. EPA, 1979).

Bis-(2-ethylhexyl)phthalate, most commonly referred to as di-(2-ethylhexyl)phthalate, (DEHP) is a diester of the ortho form of benzene dicarboxylic acid. The compound has a molecular weight of 391.0, specific gravity of 0.985, boiling point of 386.9°C at 5 mm Hg, and is insoluble in water (U.S. EPA, 1979).

DEHP is widely used as a plasticizer, primarily in the production of polyvinyl chloride (PVC) resins. As much as 60 percent by weight of PVC materials may be plasticizer (U.S. EPA, 1979). Through this usage, DEHP is incorporated into such products as wire and cable covering, floor tiles, swimming pool liners, upholstery, and seat covers, footwear, and food and medical packaging materials (U.S International Trade Commission, 1978).

In 1977, current production was 1.94×10^5 tons/year (U.S. EPA, 1979).

Phthalates have been detected in soil, air, and water samples; in animal and human tissues; and in certain vegetation. Evidence from in vitro studies indicates that certain bacterial flora may be capable of metabolizing phthalates to the monoester form (Englehardt, et al. 1975).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of the phthalates may occur through leaching of plasticizers from PVC materials, volatilization of phthalates from PVC materials, and the incineration of PVC items. Sources of human exposure to phthalates include contaminated foods and fish, and parenteral administration by use of PVC blood bags, tubings, and infusion devices (U.S. EPA, 1979).

Monitoring studies have indicated that phthalate concentrations in water are mostly in the ppm range, or 1-2 μg/liter (U.S. EPA, 1979). Air levels of phthalates in closed rooms that have PVC tiles have been reported to be 0.15 to 0.26 mg/m^3 (Peakall, 1975). Industrial monitoring has measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1973). Levels of DEHP have ranged from not detectable to 68 ppm in foodstuffs (Tomita, et al. 1977). Cheese, milk, fish and shellfish present potential sources of high phthalate intake (U.S. EPA, 1979). Estimates of parenteral exposure of patients to DEHP during use of PVC medical appliances have indicated approximately 150 mg DEHP exposure from a single hemodialysis course. An average of 33 mg DEHP exposure is possible during open heart surgery (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for DEHP to be 95 for the edible portions of fish and shellfish consumed by Americans. This

estimate is based on the measured steady-state bioconcentration studies in fathead minnow.

III. PHARMACOKINETICS

A. Absorption

The phthalates are readily absorbed from the intestinal tract, the peritoneal cavity, and the lungs (U.S. EPA, 1979). Daniel and Bratt (1974) found that seven days following oral administration of radiolabelled DEHP, 42 percent of the dose was recovered in the urine and 57 percent recovered in the feces of rats. Bilary excretion of orally administered DEHP has been noted by Wallin, et al. (1974). Limited human studies indicate that 2 to 4.5 percent of orally administered DEHP was recovered in the urine of volunteers within 24 hours (Shaffer, et al. 1945). Lake, et al. (1975) have suggested that orally administered phthalates are absorbed after metabolic conversion to the monoester form in the gut.

Dermal absorption of DEHP in rabbits has been reported at 16 to 20 percent of the initial dose within three days following administration (Autian, 1973).

B. Distribution

Studies in rats injected with radiolabelled DEHP have shown that 60 to 70 percent of the administered dose was detected in the liver and lungs within 2 hours after administration (Daniel and Bratt, 1974). Wadell, et al. (1977) have reported rapid accumulation of labelled DEHP in the kidney and liver of rats after i.v. injection, followed by rapid excretion into the urine, bile, and intes-

tine. Seven days after i.v. administration of labelled DEHP to mice, levels of compound were found preferentially in the lungs and to a lesser extent in the brain, fat, heart, and blood (Autian, 1973).

An examination of tissue samples, from two deceased patients who had received large volumes of transfused blood, detected DEHP in the spleen, liver, lungs, and abdominal fat (Jaeger and Rubin, 1970).

Injection of pregnant rats with labelled DEHP has shown that the compound may cross the placental barrier (Singh, et al. 1975).

C. Metabolism

Various metabolites of DEHP have been identified following oral feeding to rats (Albro, et al. 1973). These results indicate that DEHP is initially converted from the diester to the monoester, followed by the oxidation of the monoester side chain forming two different alcohols. The alcohols are oxidized to the corresponding carboxylic acid or ketone. Enzymatic cleavage of DEHP to the monoester may take place in the liver or the gut (Lake, et al. 1977). This enzymatic conversion has been observed in stored whole blood indicating widespread distribution of metabolic activity (Rock, et al. 1978).

D. Excretion

Excretion of orally administered DEHP is virtually complete in the rat within 4 days (Lake, et al. 1975). Major excretion is through the urine and feces, with biliary

excretion increasing the content of DEHP (or metabolites) in the intestine (U.S. EPA, 1979). Schulz and Rubin (1973) have noted an increase in total water soluble metabolites of labelled DEHP in the first 24 hours following injection into rats. Within one hour, eight percent of the DEHP was found in the liver, intestines and urine. After 24 hours, 54.6 percent was recovered in the intestinal tract, excreted feces and urine, and only 20.5 percent was recovered in organic extractable form. Blood loss of DEHP showed a biphasic pattern, with half-lives of 9 minutes and 22 minutes, respectively (Schulz and Rubin, 1973).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

Testing of DEHP in the Ames Salmonella assay has shown no mutagenic effects (Rubin, et al. 1979). Yagi, et al. (1978) have indicated that DEHP is not mutagenic in a recombinant strain of Bacillus, but the monoester metabolite of DEHP did show some mutagenic effects. Results of a dominant lethal assay in mice indicate that DEHP has a dose and time dependent mutagenic effect (Singh, et al. 1974).

C. Teratogenicity

DEHP has been shown to produce teratogenic effects in rats following i.p. administration (Singh, et al. 1972).

Following oral administration there was a significant reduction in fetus weight at 0.34 and 1.70 g/kg/day.

D. Other Reproductive Effects

Effects on implantation and parturition have been observed in pregnant rats injected intraperitoneally with DEHP (Peters and Cook, 1973). A three-generation reproduction study in rats has indicated decreased fertility in rats following maternal treatment with DEHP (Industrial Bio-Test, 1978).

Testicular damage has been reported in rats administered DEHP i.p. or orally. Seth, et al. (1976) found degeneration of the seminiferous tubules and changes in spermatagonia; testicular atrophy and morphological damage were noted in rats fed DEHP (Gray, et al. 1977; Yamada, et al, 1975). Otake, et al. (1977) noted decreased spermatogenesis in mice administered DEHP by intubation.

E. Chronic Toxicity

Oral feeding of DEHP produced increases in liver and kidney weight in several animal studies (U.S. EPA, 1979). Chronic exposure to transfused blood containing DEHP has produced liver damage in monkeys (Kevy, et al. 1978). Lake, et al. (1975) have produced liver damage in rats by administration of mono-2-ethylhexyl phthalate.

F. Other Relevant Information

Several animal studies have demonstrated that pre-treatment of rats with DEHP produced an increase in hexobarbital sleeping times (Daniel and Bratt, 1974; Rubin and Jaeger, 1973; Swinyard, et al. 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

Only one acute study on the freshwater cladoceran (Daphnia magna) has produced a 96-hour static LC_{50} value of 11,000 µg/l (U.S. EPA, 1978). Freshwater fish or marine data have not been found in the literature.

B. Chronic Toxicity

Chronic studies involving the rainbow trout (Salmo gairdneri) provided a chronic value of 4.2 µg/l in an embryo-larval assay (Mehrle and Mayer, 1976). Severe reproductive impairment was observed at less than 3 µg/l in a chronic Daphnia magna assay (Mayer and Sanders, 1973).

C. Plant Effects

Pertinent information could not be located in the available literature.

D. Residues

Bioconcentration factors have been obtained for several species of freshwater organisms: 54 to 2,680 for the scud (Gamarus pseudolimnaeus); 14 to 50 for the sowbug (Ascellus brevicaudus); 42 to 113 for the rainbow trout (Salmo gairdneri); and 91 to 886 for the fathead minnow (Pimephales promelas) (U.S. EPA, 1979).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on "no effect" levels observed in chronic feeding studies in rats or dogs, the U.S. EPA has calculated an acceptable daily intake (ADI) level for DEHP of 42 mg/day.

The recommended water quality criteria level for protection of human health is 10 mg/l for DEHP (U.S. EPA, 1979).

B. Aquatic

Criterion was not drafted for either freshwater or marine environments due to insufficient data.

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No. 28

Bromoform

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

BROMOFORM

SUMMARY

Bromoform has been detected in finished drinking water in the United States and Canada. It is believed to be formed by the haloform reaction that may occur during water chlorination. Bromoform can be removed from drinking water via treatment with activated carbon. Natural sources (especially red algae) produce significant quantities of bromoform. There is a potential for bromoform to accumulate in the aquatic environment because of its resistance to degradation. Volatilization is likely to be an important means of environmental transport.

Bromoform gave positive results in mutagenicity tests with Salmonella typhimurium TA100. In a short-term in vivo oncogenicity assay it caused a significant increase in tumor incidence at one dose level.

Inhalation of bromoform by humans can cause irritation of the respiratory tract and liver damage. Respiratory failure is the primary cause of death in bromoform-related fatalities.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria document for halomethanes (U.S. EPA 1979b).

Bromoform (tribromomethane; $CHBr_3$) is a colorless, heavy liquid similar in odor and taste to chloroform. Bromoform has the following physical/chemical properties (Weast, 1974):

Molecular Weight:	252.75
Melting Point:	8.3'C
Boiling Point:	149.5'C (at 760 mm Hg)
Vapor Pressure:	10 mm Hg al 34'C
Solubility:	slightly soluble in water; soluble in a variety of organic solvents.

A review of the production range (includes importation) statistics for bromoform (CAS No. 75-25-2) which is listed in the initial TSCA Inventory (1979a) has shown that between 100,000 and 900,000 pounds of this chemical were produced/imported in 1977.*/

Bromoform is used as a chemical intermediate; solvent for waxes, greases, and oils; ingredient in fire-resistant chemicals and gauge fluids (U.S. EPA 1978a; Hawley, 1977).

II. EXPOSURE

A. Environmental Fate

Bromoform gradually decomposes on standing; air and light accelerate decomposition (Windholz, 1976). The vapor pressure of bromoform, while lower than that for chloroform and other chloroalkanes, is, nonetheless, sufficient to ensure that volatilization will be an important means of environmental transport. The

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

half-life for hydrolysis of bromoform is estimated at 686 years. Bromoform should be much more reactive in the atmosphere. Oxidation by HO radical will result in a half-life of a few months in the troposphere (U.S. EPA, 1977).

B. Bioconcentration

The bioconcentration factor for bromoform in aquatic organisms that contain about 8% lipid is estimated to be 48. The weighted average bioconcentration factor for bromoform in the edible portion of all aquatic organisms consumed by Americans is estimated to be 14 (U.S. EPA, 1979b).

C. Environmental Occurence

The National Organics Reconnaissance Survey detected bromoform in the finished drinking water of 26 of 80 cities, with a maximum concentration of 92 ug/l. Over 90% of the samples contained 5 ug/l or less. No bromoform was found in raw water samples (Symons et al., 1975). Similarly, the EPA Region V Organics Survey found bromoform in 14% of the finished drinking water samples and none in raw water (U.S. EPA, 1975). Using a variety of sampling and analysis methods, the National Organic Monitoring Survey found bromoform in 3 of 111, 6 of 118, 38 of 113, 19 of 106, and 30 of 105 samples with mean concentrations ranging from 12-28 ug/l (U.S. EPA, 1978b). A Canadian survey of drinking water found 0-0.2 ug/l with a median concentration of 0.01 ug/l (Health and Welfare Can., 1977).

The National Academy of Sciences (1978) concluded that water chlorination, via the haloform reaction, results in the production of trihalomethanes (including bromoform) from the organic precursors present in raw water.

Significant quantities of bromoform are also produced from natural sources, especially red algae. For example, the essential oil of Asparagopsis taxiformis (a red marine algae eaten by Hawaiians) contains approximately 80% bromoform (Burreson et al., 1975).

III. PHARMACOKINETICS

Bromoform is absorbed through the lungs, gastrointestinal tract, and skin. Some of the absorbed bromoform is metabolized in the liver to inorganic bromide ion. Bromide is found in tissues and urine following inhalation or rectal administration of bromoform (Lucas, 1929). Metabolism of bromoform to carbon monoxide has also been reported (Ahmed, 1977). Recent studies show that phenobarbital-induced rats metabolize bromoform to carbonyl bromide ($COBr_2$), the brominated analog of phosgene (COCl) (Pohl et al., 1979).

IV. HEALTH EFFECTS

A. Carcinogenicity

Bromoform caused a significant increase in tumor incidence at one dose level in a short-term in vivo oncogenicity assay known as the strain A mouse lung adenoma test. The increase was observed at a dose of 48 mg/kg/injection with a total dose of 1100 mg/kg. The tumor incidence was not increased significantly at doses of 4 mg/kg (total dose of 72 mg/kg) or 100 mg/kg (total dose of 2400 mg/kg) (Theiss et al., 1977.

B. Mutagenicity

Bromoform was mutagenic in S. typhimurium strain TA 100 (without metabolic activation) (Simmon, 1977).

C. Other Toxicity

Rats inhaling 250 mg/m^3 bromoform for 4 hr/day for 2 months developed impaired liver and kidney function (Dykan, 1962).

In humans, inhalation of bromoform causes irritation to the respiratory tract. Mild cases of bromoform poisoning may cause only headache, listlessness, and vertigo. Unconsciousness, loss of reflexes, and convulsions occur in severe cases. The primary cause of death from a lethal dose of bromoform is respiratory failure. Pathology indicates that the chemical causes fatty degenerative and centrolobular necrotic changes in the liver (U.S. PHS, 1955).

Acute animal studies indicate impaired function and pathological changes in the liver and kidneys of animals exposed to bromoform (Kutob and Plaa, 1962; Dykan, 1962).

V. AQUATIC EFFECTS

A. Fresh Water Organisms

The 96-hr LC_{50} (static) in bluegill sunfish is 29.3 mg/l. The 48-hr LC_{50} (static) for Daphnia magna is 46.5 mg/l. The 96-hr EC_{50}s for chlorophyll A production and cell number in S. capricornutum are 112 mg/l and 116 mg/l, respectively (U.S. EPA, 1978a). (See also Section II.B.)

B. Marine Organisms

The 96-hr LC_{50} (static) in sheepshead minnow is 17.9 mg/l. The 96-hr LC_{50} (static) in mysid shrimp is 20.7 mg/l. The EC_{50}s for chlorophyll A production and cell number in S. costatum are, respectively, 12.3 mg/l and 11.5 mg/l (U.S. EPA, 1978a).

VI. EXISTING GUIDELINES

A. Human

The OSHA standard for bromoform in air is a time weighted average (TWA) of 0.5 ppm (39CFR23540).

The Maximum Contaminant Level (MCL) for total trihalomethanes (including bromoform) in drinking water has been set by the U.S. EPA at 100 ug/l (44FR68624). The concentration of bromoform produced by chlorination can be reduced by treatment of drinking water with powdered activated carbon (Rook, 1974). This is the technology that has been proposed by the EPA to meet this standard.

B. Aquatic

The proposed ambient water criterion for the protection of fresh water aquatic life from excessive bromoform exposure is 840 ug/l as a 24-hour average. Bromoform levels are not to exceed 1900 ug/l at any time. The criterion for the protection of marine life is 180 ug/l (24 hr avg), not to exceed 1900 ug/l (U.S. EPA, 1979b).

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No. 29

Bromomethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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BROMOMETHANE

Summary

On acute exposure to bromomethane, neurologic and psychiatric abnormalities may develop and persist for months or years. There is no information on the chronic toxicity, carcinogenicity, or teratogenicity of bromomethane. Bromomethane has been shown to be mutagenic in the Ames S. typhimurium test system.

Acute LC_{50} values have been reported in two tests as 12,000 and 11,000 µg/l for a marine and freshwater fish, respectively.

BROMOMETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Halomethanes (U.S. EPA, 1979a).

Bromomethane (CH_3Br, methyl bromide, monobromomethane, and embafume; molecular weight 94.94) is a colorless gas. Bromomethane has a melting point of -93.6°C, a boiling point of 3.56°C, a specific gravity of 1.676 g/ml at -20°C, and a water solubility of 17.5 g/l at 20°C (Natl. Acad. Sci., 1978). Bromomethane has been widely used as a fumigant, fire extinguisher, refrigerant, and insecticide (Kantarjian and Shaheen, 1963). Today the major use of bromomethane is as a fumigating agent. Bromomethane is believed to be formed in nature, with the oceans as a primary source (Lovelock, 1975). The other major environmental source of bromomethane is from its agricultural use as a soil, seed, feed and space fumigant. For additional information regarding Halomethanes as a class the reader is referred to the Hazard Profile on Halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

The U.S. EPA (1975) has identified bromomethane qualitatively in finished drinking waters in the U.S. There are, however, no data on its concentration in drinking water, raw water, or waste water (U.S. EPA, 1979a).

B. Food

There is no information on the concentration of bromomethane in food. Bromomethane residues from fumigation decrease rapidly through loss to the atmosphere and reaction with protein to form

inorganic bromide residues. With proper aeration and product processing, most residual bromomethane will rapidly disappear due to methylation reactions and volatilization (Natl. Acad. Sci., 1978; Davis, et al. 1977). There are no bioconcentration data for bromomethane (U.S. EPA, 1979a).

C. Inhalation

Saltwater atmospheric background concentrations of bromomethane averaging about 0.00036 mg/m^3 have been reported (Grimsrud and Rasmussen, 1975; Singh, et al. 1977). This is higher than reported average continental background and urban levels and suggests that the oceans are a major source of global bromomethane (Natl. Acad. Sci., 1978). Bromomethane concentrations of up to 0.00085 mg/m^3 may occur outdoors locally with light traffic, as a result of exhaust containing bromomethane as a breakdown product of ethylene dibromide, which is used in leaded gasoline (Natl. Acad. Sci., 1978).

III. PHARMACOKINETICS

A. Absorption

Absorption of bromomethane most commonly occurs via the lungs, although it can also occur through the gastrointestinal tract and the skin (Davis, et al. 1977; von Oettingen, 1964).

B. Distribution

Upon absorption, blood levels of residual non-volatile bromide increase, indicating rapid uptake of bromomethane or its metabolites (Miller and Haggard, 1943). Bromomethane is rapidly distributed to various tissues and is broken down to inorganic bromide. Storage, only as bromides, occurs mainly in lipid-rich tissues.

C. Metabolism

Evidently the toxicity of bromomethane is mediated by the bromomethane molecule itself. Its reaction with tissue (methylation of sulfhydryl groups in critical cellular proteins and enzymes) results in disturbance of intracellular metabolic functions, with irritative, irreversible, or paralytic consequences (Natl. Acad. Sci., 1978; Davis, et al. 1977; Miller and Haggard, 1943).

D. Excretion

Elimination of bromomethane is rapid initially, largely through the lungs. The kidneys eliminate much of the remainder as bromide in the urine (Natl. Acad. Sci., 1978).

IV. EFFECTS

Pertinent information relative to the carcinogenicity, teratogenicity or other reproductive effects, or chronic toxcity of bromomethane were not found in the available literature.

A. Mutagenicity

Simmon and coworkers (1977) reported that bromomethane was mutagenic to Salmonella typhimurium strain TA100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required, and the number of revertants per plate was directly dose-related.

B. Other Relevant Information

In several species, acute fatal poisoning has involved marked central nervous system disturbances with a variety of manifestations: ataxia, twitching, convulsions, coma, as well as changes in lung, liver,

heart, and kidney tissues (Sayer, et al. 1930; Irish, et al. 1940; Gorbachev, et al. 1962; von Oettingen, 1964). Also, residual bromide in fumigated food has produced some adverse effects in dogs (Rosenblum, et al. 1960).

V. AQUATIC TOXICITY

Two acute toxicity studies on one freshwater and one marine fish species were reported with LC_{50} values of 11,000 µg/l for freshwater bluegill (Lepomis macrochirus) and an LC_{50} value of 12,000 µg/l for the marine tidewater silversides (Menidia beryllina) (U.S. EPA, 1979a). Pertinent information relative to aquatic chronic toxicity or plant effects for bromomethane were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The current OSHA standard for occupational exposure to bromomethane (1976) is 80 mg/m^3; the American Conference of Governmental Industrial Hygienist's (ACGIH, 1971) threshold limit value is 78 mg/m^3. The U.S. EPA (1979a) draft water quality criteria for bromomethane is 2 µg/l. Refer to the Halomethane Hazard Profile for discussion of criteria derivation (U.S. EPA, 1979b).

B. Aquatic Toxicity

The draft criterion for protecting freshwater life is a 24-hour average concentration of 140 µg/l, not to exceed 320 µg/l. The marine criterion is 170 µg/l as a 24-hour average, not to exceed 380 µg/l.

BROMOMETHANE

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No. 30

4-Bromophenyl Phenyl Ether

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4-Bromophenyl phenyl ether

SUMMARY

Very little information on 4-bromophenyl phenyl ether exists. 4-Bromophenyl phenyl ether has been identified in raw water, in drinking water and in river water. 4-Bromophenyl phenyl ether has been tested in the pulmonary adenoma assay, a short-term carcinogenicity assay. Although the results were negative, several known carcinogens also gave negative results. No other health effects were available. 4-Bromophenyl phenyl ether appears to be relatively toxic to freshwater aquatic life: a 24-hour average criterion of 6.2 ug/L has been proposed.

I. INTRODUCTION

4-Bromophenyl phenyl ether ($BrC_6H_4OC_6H_5$; molecular weight 249.11) is a liquid at room temperature; it has the following physical/chemical properties (Weast 1972):

Melting point:	18.72°C
Boiling point:	310.14°C (760 mm Hg) 163°C (10 mm Hg)
Density:	1.4208^{20}
Solubility:	Insoluble in water; soluble in ether

No information could be found on the uses of this substance.

A review of the production range (includes importation) statistics for 4-bromophenyl phenyl ether (CAS No1 101-55-3) which is listed in the initial TSCA Inventory (1979) has shown that between 0 and 900 pounds of this chemical were produced/imported in 1977.*

*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise confidential business information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

II. EXPOSURE

No specific information relevant to the environmental fate of 4-bromophenyl phenyl ether was found in the literature. A U.S. EPA report (1975a) included this substance in a category with several other drinking water contaminants considered to be refractory to biodegradation (i.e., lifetime greater than two years in unadapted soil; point sources unable to be treated biologically). However, the authors did not present or reference experimental data to support the inclusion of 4-bromopheny phenyl ether in this category. U.S. EPA (1975a) estimated that three tons of 4-bromophenyl phenyl ether are discharged annually.

4-Bromophenyl phenyl ether has been identified as a contaminant in finished drinking water on three occasions, in raw water on one occasion and in river water on one occasion. No quantitative data were supplied (U.S. EPA, 1976). Friloux (1971) and U.S. EPA (1972) have also reported the presence of 4-bromophenyl phenyl ether in raw and finished water of the lower Mississippi River (New Orleans area). Again, no quantitative data were supplied. U.S. EPA (1975) suggest that 4-bromophenyl phenyl ether may be formed during the chlorination of treated sewage and drinking water.

III. PHARMACOKINETICS

No information was located.

IV. HEALTH EFFECTS

A. Carcinogenicity

Three groups of 20 male mice were administered intraperitoneal doses (23, 17 or 18 doses, respectively) of 4-bromophenyl phenyl ether in tricaprylin vehicle three times a week for 8 weeks (Theiss et al. 1977). The total doses were 920, 1700, or 3600 mg/kg, respectively. Animals were sacrificed at 24 weeks from the start of the experiment. Incidences of lung adenomas were not significantly increased, as compared with vehicle controls. However, this short-term assay should not be considered indicative of the nononcogenicity of 4-bromophenyl phenyl ether as several known oncogens tested negative in this assay.

V. AQUATIC TOXICITY

A. Acute

An unadjusted 96 hour LC_{50} of 4,940 ug/L was determined by exposing bluegills to 4-bromophenyl phenyl ether (Table 1). Adjusting this value for test conditions and species sensitivity, a Final Fish Acute Value of 690 ug/L is obtained (U.S. EPA, undated).

Exposure of Daphnia magna, yielded an unadjusted 48 hour LC_{50} of 360 ug/L (Table 2). The Final Invertebrate Acute Value (and the Final Acute Value) for 4-bromophenyl phenyl ether is 14 ug/L (U.S. EPA, undated).

B. Chronic

In an embryo-larval test using the fathead minnow (in which survival and growth were observed), a chronic value of 61 ug/L was obtained for 4-bromophenyl phenyl ether exposure (Table 3). Dividing by the species sensitivity factor (6.7), a Final Fish Chronic Value of 9.1 ug/L is derived. Since no other information is available, this value is also the Final Chronic Value (U.S. EPA, undated).

VI. EXISTING GUIDELINES

A. Aquatic

A 24 hour average concentration of 6.2 ug/L (6.2 ug/L = 0.44 x 14 ug/L (Final Acute Value)) is the recommended criterion to protect freshwater aquatic life. The maximum allowable concentration should not exceed 14 ug/L at any time (U.S. EPA, undated).

Table 1. Freshwater fish acute values

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC_{50} (ug/L.)	Adjusted LC50 (ug/L)
Bluegill, Lepomis macrochirus	S	U	4-Bromophenyl-phenyl ether	96	4,940	2,700

* S = static

** U = unmeasured

Geometric mean of adjusted values: 4-Bromophenylphenyl ether = 2,700 ug/L

$\frac{2,700}{3.9}$ = 690 ug/L

Table 2. Freshwater invertebrate acute values

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC_{50} (ug/L)	Adjusted LC_{50} (ug/L)
Cladoceran, Daphnia magna	S	U	4-Bromophenyl-phenyl ether	48	360	300

* S = static

** U = unmeasured

Geometric mean of adjusted values: 4-Bromophenyl phenyl ether = 300 ug/L

$\frac{300}{21}$ = 14 ug/L

Table 3. Freshwater fish chronic values, 4-Bromophenyl phenyl ether

Organism	Test*	Limits (ug/L)	Chronic Value (ug/L)
Fathead minnow, Pimephales promelas	E-L	89-167	61

* E-L = embryo-larva

Geometric mean of chronic values = 61 ug/L $\frac{61}{6.7}$ = 9.1 ug/L

Lowest chronic value = 61 ug/L

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No. 31

Cadmium

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated cadmium and has found sufficient evidence to indicate that this compound is carcinogenic.

CADMIUM

Summary

The major non-occupational routes of human cadmium exposure are through food and tobacco smoke. Drinking water also contributes relatively little to the average daily intake.

Epidemiological studies indicate that cadmium exposure may increase the mortality level for cancer of the prostate. Long-term feeding and inhalation studies in animals have not produced tumors, while intravenous administration of cadmium has produced only injection site tumors. Mutagenic effects of cadmium exposure have been seen in animal studies, bacterial systems, in vitro tests, and in the chromosomes of occupationally exposed workers.

Cadmium has produced teratogenic effects in several species of animals, possibly through interference with zinc metabolism. Testicular necrosis and neurobehavioral alterations in animals following exposure during pregnancy have been produced by cadmium in animals.

Chronic exposure to cadmium has produced emphysema and a characteristic syndrome (Itai-Itai disease) following renal damage and osteomalacia. A causal relationship between chronic cadmium exposure and hypertension in humans has been suggested but not confirmed.

Cadmium is acutely toxic to freshwater fish at levels as low as 0.55 µg/l. Freshwater fish embryo/larval stages tended to be the most sensitive to cadmium. Marine fish were generally more resistant than freshwater fish. The long half-life of cadmium in aquatic organisms has been postulated, and severe restrictions to gill-tissue respiration have been observed at concentrations as low as 0.5 µg/l.

CADMIUM

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Cadmium (U.S. EPA, 1979).

Cadmium is a soft, bluish-silver-white metal, harder than tin but softer than zinc. The metal melts at 321°C and shows a boiling point of 765°C (U.S. EPA, 1978b). Cadmium dissolves readily in mineral acids. Some of the physical/chemical properties of cadmium and its compounds are summarized in Table 1 (U.S. EPA, 1978b).

Cadmium is currently used in electroplating, paint and pigment manufacture, and as a stabilizer for plastics (Fulkerson and Goeller, 1973).

Current production: 6000 metric tons (1968) (U.S. EPA, 1978b)

Projected production: 12,000 metric tons (2000) (U.S. EPA, 1978b)

Since cadmium is an element, it will persist in some form in the environment. Cadmium is precipitated from solution by carbonate, hydroxide, and sulfide ions (Baes, 1973); this is dependent on pH and on cadmium concentration. Complexing of cadmium with other anions will produce soluble forms (Samuelson, 1963). Cadmium is strongly adsorbed to clays, muds, humic and organic materials and some hydrous oxides (Watson, 1973), all of which lead to precipitation from aqueous media. Cadmium corrodes slightly in air, but forms a protective surface film which prevents further corrosion (U.S. EPA, 1978b).

II. EXPOSURE

Cadmium is universally associated with zinc and appears with it in natural deposits (Hem, 1972). Major sources of cadmium release into the environment include emissions from metal refining and smelting plants, incineration of polyvinyl chloride plastics, emissions from use of fossil

Table 1. Some Properties of Cadmium and its Important Compounds

Compound	Primary use or occurrence	Formula	Molecular weight (g/mole)	Density (g/ml)	Physical state, 20°C	Melting point (°C)	Boiling point (°C)	Solubility in water 20°C (g/liter)	Solubility in other solvents	Acute lethal dose[a]
Cadmium metal	Cadmium nickel batteries	Cd	112.4	8.6	Silver metal	321	765	Insoluble	Soluble in acid and NH_4NO_3	9 mg/m^3 is the approximate lethal concentration in man, inhaled as fume
Cadmium oxide	Smelting plant or coal combustion emission	CdO	128.4	7.0	Brown powder	Decomposes at 900		0.00015[b]	Soluble in acid and NH_3 salts	50 mg/m^3 is the approximate lethal concentration in man, inhaled; 72 mg/kg, rat, LD_{50} (oral)
Cadmium sulfide	Pigment for plastics and enamels; phosphors	CdS	144.5	4.8	Yellow crystal	1750	Decomposes	0.0013	Soluble in acid, very slightly soluble in NH_4OH	
Cadmium sulfate	Fruit tree fungicide	$CdSO_4$	208.5	4.7	White crystalline	1000		755	Insoluble in acid and alcohol	27 mg/kg dog, LD_{50} (subcutaneous)
Cadmium carbonate	Turf treatment	$CdCO_3$	172.4	4.3	White powder or crystalline	Decomposes below 500		0.001	Soluble in acid and KCN, NH_4 salts	

Table 1. Some Properties of Cadmium and its Important Compounds (Cont'd)

Compound	Primary use or occurrence	Formula	Molecular weight (g/mole)	Density (g/ml)	Physical state, 20°C	Melting point (°C)	Boiling point (°C)	Solubility in water 20°C (g/liter)	Solubility in other solvents	Acute lethal dose[a]
Cadmium chloride	Turf grass fungicide	$CdCl_2$	183.3	4.0	Colorless crystal	568	960	1400	15.2 g/liter in alcohol	88 mg/kg rat, LD_{50} (oral)
Cadmium potassium cyanide	Electroplating	$K_2Cd(CN)_4$	294.7	1.85	Colorless, glass crystal			333	Insoluble in alcohol	
Cadmium cyanide	Electroplating	$Cd(CN)_2$	164.4		Colorless crystal	Decomposes at 200		17, soluble in hot water	Soluble in acid and KCN	

Sources:

[a] Fulkerson and Goeller, 1973
[b] Hulme and Kroontje, 1973
Other data compiled from Weast, 1971

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fuels, use of certain phosphate fertilizers, and leaching of galvanized iron pipes (U.S. EPA, 1978b). The major non-occupational routes of human exposure to cadmium are through foods and tobacco smoke (U.S. EPA, 1979).

Based on available monitoring data, the U.S. EPA (1979) has estimated the uptake of cadmium by adult humans from air, water, and food:

Source	Adult µg/day
	Maximum conditions
Air-ambient	.008 mg/day
Air-smoking	9.0
Foods	75.0
Drinking water	20.0
Total	304.008
	Minimum conditions
Air-ambient	0.00002
Air-smoking	0
Food	12.0
Drinking water	1.0
Total	13.00002

The variation of cadmium levels in air, food, and water is quite extensive as indicated above. Leafy vegetables, contaminated water, and air near smelting plants all present sources of high potential exposure. The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of cadmium to be 17 in the edible portions of fish and shellfish consumed by Americans.

III. PHARMACOKINETICS

A. Absorption

The main routes by which cadmium can enter the body are inhalation and ingestion. Particle size and solubility greatly influence the biological fate of inhaled cadmium. When a large proportion of particles are in

the respirable range, up to 25% of the inhaled amount may be absorbed (EPA, 1979). Cadmium fumes may have an absorption of up to 50%, and it is estimated that up to 50% of cadmium in cigarette smoke may be absorbed (WHO, 1977; Elinder, et al. 1976). Large particles are trapped by the mucous membranes and may eventually be swallowed, resulting in gastrointestinal absorption (EPA, 1979).

Only a small proportion of ingested cadmium is absorbed. Two human studies using radiolabelled cadmium have indicated mean cadmium absorption from the gastrointestinal tract of 6% and 4.6% (Rahola, et al. 1973; McLellan, et al. 1978). Various dietary factors interact with cadmium absorption; these include calcium levels (Washko and Cousins, 1976), vitamin D levels (Worker and Migicovsky, 1961), zinc, iron, and copper levels (Banis, et al. 1969). and ascorbic acid levels (Fox and Fry, 1970). Low protein diets enhance the uptake of cadmium from the gastrointestinal tract (Suzuki, et al. 1969).

Dermal absorption of cadmium appears to occur to a small extent; Wahlberg (1965) has determined that up to 1.8 percent of high levels of cadmium chloride were absorbed by guinea pig skin.

Cadmium levels have been determined in human embryos (Chaube, et al. 1973) and in the blood of newborns (Lauwerys, 1978), indicating passage of cadmium occurs across the placental membranes.

B. Distribution

Cadmium is principally stored in the liver, kidneys, and pancreas with higher levels initially found in the liver (WHO Task Group, 1977). continued exposure leads to accumulation in all of these organs; levels as

high as 200-300 mg/kg wet weight may be found in the renal cortex. This storage appears to be dependent on the association of cadmium with the cadmium binding protein, metallothionen (Nordberg et al., 1975).

Animal studies indicate that following intraperitoneal or intravenous administration of cadmium most of the compound is found in the blood plasma. After 12-24 hours the plasma is cleared and most of the compound is associated with red blood cells (U.S. EPA, 1978b).

The cadmium body burden of humans increases with age (Friberg, et al. 1974) from very minimal levels at birth to an average of up to 30-40 mg by the age of 50 in non-occupationally exposed individuals. Liver accumulation continues through the last decades of life, while kidney concentrations increase until the fourth decade and then decline (Gross, et al. 1976). The pancreas and salivary glands also contain considerable concentrations of cadmium (Nordberg, 1975). Smoking effects the body burden of cadmium; levels in the renal cortex of smokers may be double those found in non-smokers (Elinder, et al. 1976; Hammer, et al. 1971).

C. Metabolism.

Pertinent data were not found in the available literature.

D. Excretion

Since only about 6 percent of ingested cadmium is absorbed, a large proportion of the compound is eliminated by the feces (U.S. EPA, a or b). Some biliary excretion of cadmium has been demonstrated in rats (Stowe, 1976); this represented less than 0.1 percent of a subcutaneously administered dose.

Urinary excretion of cadmium is approximately 1-2 mg/day in the general population (Imbus, et al. 1963; Szadkowski, et al. 1969). Occupationally exposed individuals may show markedly higher urinary excretion

levels (Friberg, et al. 1974). A modest increase in human urinary excretion of cadmium has been noted with increasing age (Katagiri, et al. 1971).

Additional sources of cadmium loss are through salivary excretion and shedding of hair (U.S. EPA, 1979).

Biological half-life calculations for exposed workers have given values of up to 200 days (urine). Direct comparisons of urinary excretion levels and estimated body burden using Japanese, American, and German data, suggest a half-time of 13-47 years. Using more complex metabolic models, Frieberg, et al. 1974 concluded that the biologic half-time is probably 10-30 years. The most recent estimate of biologic half-time is 15.7 years by Ellis (1979).

IV. EFFECTS

A. Carcinogenicity

The results of several epidemiology studies of the relationship of cancer to occupational exposure to cadmium are summarized in Table 3 (U.S. EPA, 1978a). The only consistent trend seen in these studies is an increased incidence of prostate cancer in cadmium-exposed workers. A recent study by Kjellstrom, et al. (1979) of 269 cadmium-nickel battery factory workers found increased cancer mortality from nasopharyngeal cancer (significant) and increased mortality trends for prostate, lung, and colon-rectum cancers (not significant). After reviewing these studies, EPA (1979) has concluded that cadmium cannot be definitely implicated as a human carcinogen with the available data.

Animal experiments with the administration of cadmium by subcutaneous or intravenous injection have demonstrated that cadmium produces

injection site sarcomas and testicular tumors (Leydigiomas) (see Table 2; U.S. EPA, 1978a). A large number of metals and irritants produced comparable injection site sarcomas. Long term feeding and inhalation studies with cadmium have not produced tumors (Schroeder, et al. 1964, Levy, et al. 1973; Decker, et al. 1958; Anwar, et al. 1961; Paterson, 1947; Malcolm, 1972)

At the present time, the draft ambient water quality criterion for protection of human health is based on the toxicity of cadmium rather than on any carcinogenic effects. Though the studies summarized above qualitatively indicate a carcinogenic potential for cadmium, quantitatively, the issue has not been resolved.

B. Mutagenicity

An increased incidence of chromosomal aberrations has been noted in workers occupationally exposed to cadmium and in Japanese patients suffering cadmium toxicity (Itai-Itai disease) (Bauchinger, et al. 1976; Bui, et al. 1975; Deknudt and Leonard, 1976; Shiraishi and Yoshida, 1972).

Cadmium has been shown to produce mutagenic effects in vitro and in vivo in several systems (see Table 4; U.S. EPA, 1978 a or b). These effects include induction of point mutations in bacterial systems, chromosome aberrations in cultured cells and cytogenetic damage in vivo, and promotion of error prone base incorporation in DNA in vitro. Several investigators have been unable to show dominant lethal effects of cadmium in mice (Epstein, et al. 1972; Gillivod and Leonard, 1975; Suter, 1975). Point mutation studies with cadmium in Drosophila have also produced negative findings (Shabalina, 1968; Friberg et al., 1974; Sorsa and Pfeiffer, 1973).

C. Teratogenicity

Damage to the reproductive tract resulting from a single dose of parenterally administered cadmium chloride (2 mg/kg) have been observed in

TABLE 2

STUDIES ON CADMIUM CARCINOGENESIS IN EXPERIMENTAL ANIMALS[a]

Authors	Animals	Compounds and routes	Tumors
Heath et al., 1962; Heath and Daniel, 1964	Rats	Cd powder in fowl serum (im)[b]	Sarcomas
Kazantzis, 1963; Kazantzis and Hanbury, 1966	Rats	CdS, Cdo (sc)[b]	Sarcomas
Haddow et al., 1964; Roe et al., 1964	Rats	$CdSO_4$, $CdCl_2$ (sc)	Sarcoms and Leydigiomas
Guthrie, 1964	Chickens	$CdCl_2$ (intratesticular)	Teratoma
Gunn et al., 1963; 1964; 1965; 1967	Rats, Mice	$CdCl_2$ (im)	Sarcomas and Leydigiomas
Schroeder et al., 1965; Kanisawa and Schroeder, 1969	Rats, Mice	Cd-acetate (drinking water)	No Tumorigenic Effect
Nazari et al., 1967; Favion et al., 1968	Rats	$CdCl_2$ (sc)	Sarcomas and Leydigiomas
Knorre, 1970; 1971	Rats	$CdCl_2$ (sc)	Sarcomas and Leydigiomas
Lucis et al., 1972; 1973	Rats	$CdCl_2$ (sc, intrahepatic)	Sarcomas and Leydigiomas
Reddy et al., 1973	Rats	$CdCl_2$ (sc)	Leydigiomas
Levy et al., 1973	Rats	$CdSO_4$ (sc)	Sarcomas
Levy and Clark, 1975; Levy et al., 1975	Rats, Mice	$CdSO_4$ (gastric intubation)	No Tumorigenic Effect

[a]Adapted from Sunderman, 1977.

[b]Intramuscular: im; subcutaneous: sc.

TABLE 3

SUMMARY OF RESULTS OF HUMAN EPIDEMIOLOGY STUDIES OF CANCER EFFECTS ASSOCIATED WITH OCCUPATIONAL EXPOSURES TO CADMIUM

Population Group Studied	Cadmium Compound Exposed To	Incidences of All Cancers	Incidences of Lung Cancer	Incidences of Prostrate Cancer	Reference
Battery factory workers	Cadmium oxide	High	Normal	High	Potts (1965)
Battery factory workers	Cadmium oxide	Normal	Normal	High	Kipling and Waterhouse (1967)
Cadmium smelter workers	Cadmium oxide, others	High	High	High	Lemon et al. (1976)
Rubber industry workers	Cadmium oxide	High	Normal	High	McMichael et al. (1976)

rats, rabbits, guinea pigs, hamsters, and mice (Parizek and Zahor, 1956; Parizek, 1957; Meek, 1959). This susceptibility appears to be genetically regulated since different strains of mice show differential susceptibility (Wolkowski, 1975).

Teratogenic effects of cadmium compounds administered parenterally have been reported in mice (Eto, et al. 1975), hamsters (Ferm and Carpenter, 1968; Mulvihill, et al. 1970; Ferm, 1971; Gale and Ferm, 1973) and rats (Chernoff, 1973; Barr, 1973). Oral administration of cadmium (10 ppm) has demonstrated teratogenic effects in rats (Schroeder, and Mitchener, 1971), but no teratogenicity has been reported in rats and monkeys (Cuetkova, 1970; Pond and Walker, 1975; Willis, et al. 1976; Campbell and Mills, 1974).

D. Other Reproductive Effects

Rats in late pregnancy are apparently more sensitive to cadmium than non-gravid animals or those immediately post-partum. A single dose of 2-3 mg/kg of body weight given during the last 4 days of pregnancy resulted in high mortality (76 percent).

In addition to the embryotoxic effects of cadmium indicated in Section C, persisting effects of cadmium exposure during pregnancy on postulated development and growth of offspring have been observed. This includes neurobehavioral alteration in newborn rats (Chowdbury and Lauria, 1976) and growth deficiencies in lambs (U.S. EPA, 1978a).

E. Chronic Toxicity

Friberg (1948, 1950) observed emphysema in workmen exposed to cadmium dust in an alkaline battery factory. This finding has subsequently been well documented (U.S. EPA, 1979).

TABLE 4

SUMMARY OF MUTAGENICITY TEST RESULTS

Test System	Genetic Effect	Reported Mutagenicity	References
	Systems in vitro		
Human cells	Chromosomal damage	+	Shiraishi *et al.*, 1972
Chinese Hamster Cells	Point mutation	+	Costa *et al.*, 1976
S. cerevisiae	Point mutation	+	Takahoshi, 1972
B. subtilis recombinant assay	Gene mutation	+	Nishioka, 1975
Polynucleotides	Base mispairing	+	Sirover and Loeb, 1976
	Systems in vivo		
Human leukocytes	Chromosomal damage	+	Shirashi and Yoshida, 1972
Human leukocytes	Chromosomal damage	-	Bui *et al.*, 1975
Human leukocytes	Chromosomal damage	+	Deknudt and Leonard, 1975
Human leukocytes	Chromosomal damage	+	Bauchinger *et al.*, 1976
Rat spermatogonia	Altered spermatogenesis	+	Lee and Dixon, 1973
Mouse oocytes	Cytogenetic damage	+	Shimada *et al.*, 1976
Mouse breeding	Dominant lethal mutations	-	Epstein *et al.*, 1972
Mouse breeding	Dominant lethal mutations	-	Gilliavod and Leonard, 1975
Mouse breeding	Dominant lethal mutations	-	Suter, 1975
Mammals	Chromosomal abnormalities	-	Shimada *et al.*, 1976
D. melanogaster	Sex-linked recessive lethal	-	Sorsa and Pfeifer, 1973

31-16

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Rat spermatogonia	Altered spermatogenesis	+	Lee and Dixon, 1973
House oocytes	Cytogenetic damage	+	Shimada et al., 1976
House breeding	Dominant lethal mutations	-	Epstein et al., 1972
House breeding	Dominant lethal mutations	-	Gilliavod and Leonard, 1975
House breeding	Dominant lethal mutations	-	Suter, 1975
Mammals	Chromosomal abnormalities	-	Shimada et al., 1976
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31-16

Chronic cadmium exposure produces renal tabular damage that is characterized by the appearance of a characteristic protein (β_2-microglobulin) in the urine. Renal damage has been estimated to occur when cadmium levels in the renal cortex reach 200 mg/kg (Kjellstron, 1977). Itai-Itai disease is the result of cadmium induced renal damage plus osteomalacia (U.S. EPA, 1978a).

Exposure to high ambient cadmium levels may contribute to the etiology of hypertension (U.S. EPA, 1979). Several studies, however, have been unable to show a correlation between renal levels of cadmium and hypertension (Morgan 1972; Lewis, et al. 1972; Beevers, et al. 1976).

Friberg (1950) and Blejer (1971) have noted abnormal liver function tests in workers exposed to cadmium; however, these workers were occupationally exposed to a variety of agents.

The immunosuppressive effects of cadmium exposure, including an increased susceptibility to various infections, have been reported in several animal studies (Cook, et al. 1975; Koller, 1973; Exon, et al. 1975).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity in freshwater fish has been studied in a number of 96-hour bioassays consisting of one static renewal, 22 static, and 19 flow-through tests. LC_{50} values ranged from 1 µg/l for stripped bass larvae (Roccus saxatilus) (Hughes, 1973) to 73,500 for the fathead minnow (Pimephales promelas) (Pickering and Henderson, 1966). Increased resistance to the toxic action of cadmium in hard waters was observed. The LC_{50} values for freshwater invertebrates ranged from 3.5 for Cladoceran (Simoephalus serrulatus) to 28,000 µg/l for the mayfly (Eohemerella grandis grandis). Acute LC_{50} values for marine fish ranged from 1,600 µg/l for

larval Atlantic silversides (Menidia menida) (Middaugh and Dean, 1977) to 114,000 µg/l for juvenile mummichog (Fundulus heteroclitus) (Voyer, 1975). Intraspecific and life stage differences have shown that larval stages of the Atlantic silversides and mummichog are four times more sensitive than adults under the same test conditions (Middaugh and Dean, 1977). Marine invertebrates are more sensitive to cadmium than are marine fishes. LC_{50} values ranged from 15.5 µg/l for the mysid shrimp (Nimmo, et al. 1977a)- to 46,600 for the fiddler crab (Uca pugilator) (O'Hara, 1973).

B. Chronic Toxicity

Chronic values for freshwater fish ranged from 0.9 µg/l in a brook trout (Salvelinus fontinalis) embryo larval assay (Sauter, et al. 1976) to 50 µg/l in a life cycle (or partial life cycle) assay for the bluegill (Lepomis marcochirus) in hard water (Eaton, 1974). Salmonids were in general the most sensitive species examined. Data for freshwater invertebrates depend on a single µg/l obtained for Daphnia magna (Biesinger and Christensen, 1972). No chronic studies were available for cadmium effects in marine fishes. The only marine invertebrates data reported was the chronic value of 5.5 µg/l for the mysid shrimp, Mysidopsis bahia. In this animal no measurable effects on brood appearance in the pouch, release, average number per female, or survival were observed at concentrations of 4.8 µg/l.

C. Plant Effects

Effective concentrations for freshwater plants ranged from 2 µg/l, which causes a 10 fold growth rate decrease in the diatom, Asterionella formosa (Conway, 1978), to 7,400 µg/l, which causes a 50% root weight inhibition in Eurasian water-milfoil (Myriophyllum spicatum). In marine algae,

96-hour EC_{50} growth rate assays yielded values of 160 and 175 µg/l for Cyclotella nana and Skeletonema costatum respectively (Gentile and Johnson, 1974).

D. Residues

Bioconcentration factors ranged from 151 for brook trout to 1,988 for the flagfish (Jordanella floridae). One characteristic of cadmium toxicity in aquatic organisms was the possible long half-life of the chemical in certain tissues of exposed brook trout even after being placed in clean water for several weeks. Testicular damage to adult mallards was observed when fed 20 mg/kg cadmium in the diet for 90 days. In marine organisms bioconcentration values ranged from 37 for the shrimp Crangon crangon to 1,230 for the American oyster, Crassostrea virginica (Schuster and Pringle, 1969).

E. Miscellaneous

Several studies on marine organisms have demonstrated significant reduction in gill-tissues respiratory rates in the cunner, Tautogolabrus adspersus, the winter flounder, Pseudopleuronectes americanus, and the stripped bass, Morone saxatilis, at concentrations as low as 0.5 µg/l.

VI. EXISTING GUIDELINES

A. Human

It is not recommended that cadmium be considered a suspect human carcinogen for purposes of calculating a water quality criterion (U.S. EPA, 1979).

The EPA Primary Drinking Water Standard for protection of human health is 10 µg/l. This level was also adopted as the draft ambient water quality criterion (U.S. EPA, 1979).

The OSHA time-weighted average exposure criterion for cadmium is 100 $\mu g/m^3$.

B. Aquatic

The draft criterion proposed for freshwater organisms to cadmium has been prepared following the Guidelines, and is listed according to the following equation:

$$e^{(0.867\ \ln(\text{hardness}) - 4.38)}$$

for a 24-hour average and not to exceed the level described by the following equation:

$$e^{(1.30\ \ln(\text{hardness}) - 3.92)}$$

The proposed marine criterion derived following the Guidelines is 1.0 µg as a 24-hour average not to exceed 16 µg/l at any time (U.S. EPA, 1979).

CADMIUM

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LB:44-1

No. 32

Carbon Disulfide

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCTOBER 30, 1980

CARBON DISULFIDE

I. PHYSICAL AND CHEMICAL PROPERTIES

CS_2 (FW 76.14) is soluble in water at 0.294% (20°C), and chelates trace metals, especially Cu and Zn. It is a colorless, volatile, and extremely flammable liquid at RT. CS_2 has no odor when pure.

II. PRODUCTION AND USE

CS_2 is produced in petroleum and coal tar refining. Its principal uses are as a solvent in the manufacture of rayon, rubber, chemicals, solvents, and pesticides.[1] In 1974, 782 million pounds of CS_2 were produced in the United States.[2] In 1971, 53% was used in production of viscose rayon and cellphane and 25% for manufacture of CC_{14}.

III. EXPOSURE

CS_2 was detected in 5 of 10 water supplies surveyed by the EPA.[3] NIOSH[25] estimates that in the U.S. 20,000 employees are potentially exposed to CS_2.

III. PHARMACOKINETICS

A. Absorption: Absorption differs with species and route of administration[4]; inhalation and skin absorption are the most important routes for humans (31).

B. Distribution: Large concentrations of both free and bound CS_2 are found in brain (guinea pig) and peripheral nerves (rats) of exposed animals. The ratio of bound to

free CS_2 is brain 3:1. Blood and fatty tissues contain mainly bound CS_2, while liver contains CS_2 mainly in the free (unbound) form.

C. Metabolism: CS_2 is 90% metabolized by the P-450 system to inorganic sulfate.[5] A portion of the S released by CS_2 is thought to react with SH groups of cysteine residues in the microsomal proteins to form hydro-sulfide.[6]

D. Excretion: small amounts of CS_2 metabolites such as thiourea, 5-mercaptothioazolidone, and inorganic constituents are excreted in urine.[7] Inhalation studies have shown that 18% of the CS_2 inhaled is exhaled unchanged. Of the remaining inhaled dose, 70% is excreted as free or bound CS_2 and urinary sulfates, and 30% is stored in the body and slowly excreted as CS_2 and its metabolites.

V. EFFECTS ON MAMMALS

A. Carcinogenicity: No available data.[4]

B. Mutagenicity: No available data.[4]

C. Teratogenicity: Bariliah et al.[8] showed that inhalation of 10 mg/m^3 is lethal to embryos before and after implantation. CS_2 at 2.2 mg/m^3 inhaled for 4 hours/day was toxic to dams, and embryotoxic if administered during gestation, and had no effect on male rats.[9] Inhalation of lower concentrations (0.34 mg/l for 210 days) caused disturbances of estrus.[10] Topical application of CS_2 induced teratogenic effects in rats.[3] In a dominant lethal test, inhalation of 10 mg/m^3 by male rats before copulation proved lethal to embryos.[8]

D. Toxicity

1. Humans

CS_2 causes damage to the central and peripheral nervous systems and may accelerate the development of, or worsen, coronary heart disease.[31]

The lowest lethal concentration has been reported as 4,000 ppm in 30 minutes.[11] In the same study, a person subjected to a concentration of 50 mg/m^3 for 7 years had CNS effects. Moderate chronic exposure of humans at less than 65 mg/m^3 for several years has been reported by Cooper[12] to cause polyneuropathy. In a study by Baranowska et al.[13] humans have been shown to absorb 8.8-37.2 mg from an aqueous solution containing 0.33-1.67 gm/l. This was over a period of 1 hour of hand-soaking.

In poisoning due to continued exposure at fairly low levels (0.9-378 ppm)[31] neuritis and visual disturbances are the most common symptoms.[31,32] Sensory changes, sensations of heaviness and coldness, "veiling" of objects, pain in affected limbs, are often followed by gradually increasing loss of strength. Mental symptoms varying in severity (excitation, irritability, personality changes, insomnia, and even insanity) may occur.[32]

There are several studies on cardiovascular effects of CS_2 exposure.[26-29] Heinberg et al.[26,27] report significantly elevated rates of coronary heart disease mortality, angina, and high blood pressure in viscose rayon workers. A five year follow-up again reported increased

coronary heart disease mortality and higher than expected incidences of total infarctions, nonfatal infarctions and angina. In an 8-year followup in 1976, Heinberg[30] found no excess coronary heart disease mortality during the last 3 years of the study.

2. Other species.

IP injection of 400 mg/kg was the lowest lethal dose in guinea pigs.[14] An IV LD50 of 694 mg/kg in mice was reported by Hylen and Chin.[15]
Toxic effects have been observed at doses as low as 1.7 mg/kg in rabbits.[17] Rats showed toxic SC effects at 1 mg/kg.[17-19] Vinogradov[20] showed that 1 ppm in drinking water was nontoxic to rabbits; 70 ppm was fatal.

In a chronic study, Paterni et al.[21] found that 6 mg/kg/day produced toxic effects in rabbits. The lowest lethal chronic dose for rabbits was shown to be 0.1 ml 3 times a week for 7 months.[22] Applied topically, CS_2 produced higher incidence of
anemia in female than in male rats, and teratogenic effects (see above) were observed.[23] When rats inhaled CS_2 at 10 mg/m^3, abnormalities of genitourinary and skeletal systems were noted. In addition, disturbances of ossification and blood formation and dystrophic changes in liver and kidney were noted.[8]

VI. EXISTING GUIDELINES AND STANDARDS

The NAS[4] did not recommend limits for drinking water

because estimates of effects of chronic oral exposure cannot be made with any confidence.

The current OSHA PEL is 20 ppm (62 mg/m^3), with a ceiling concentration of 30 ppm (93 mg/m^3) for an 8-hour day, 5 day work week.[25] The NIOSH[24] recommended standard is 3 mg/m^3.[24]

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No. 33

Carbon Tetrachloride (Tetrachloromethane)

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated carbon tetrachloride and has found sufficient evidence to indicate that this compound is carcinogenic.

CARBON TETRACHLORIDE

Summary

Carbon tetrachloride (CCl_4) is a haloalkane with a wide range of industrial and chemical applications. Toxicological data for non-human mammals are extensive and show that CCl_4 causes liver and kidney damage, biochemical changes in liver function, and neurological damage. CCl_4 has been found to induce liver cancer in rats and mice. Mutagenic effects have not been observed and teratogenic effects have not been conclusively demonstrated.

The data base on aquatic toxicity is limited. LC_{50} (96-hour) values for bluegill range from 27,300 to 125,000 µg/l in static tests. For Daphnia magna, the reported 48-hour EC_{50} is 35,200 µg/l. The 96-hour LC_{50} for the tidewater silverside is 150,000 µg/l. An embryo-larval test with the fathead minnow showed no adverse effect from carbon tetrachloride concentrations up to 3,400 µg/l. No plant effect data are available. The bluegill bioconcentrated carbon tetrachloride to a factor of 30 times within 21 days expcsure. The biological half-life in the bluegill was less than 1 day.

CARBON TETRACHLORIDE

I. INTRODUCTION

Carbon tetrachloride (CCl_4) is a haloalkane with a wide range of industrial and chemical applications. Approximately 932.7 million pounds are produced at 11 plant sites in the U.S. (U.S. EPA, 1977b; Johns, 1976). The bulk of CCl_4 is used in the manufacture of fluorocarbons for aerosol propellants. Other uses include grain fumigation, a component in fire extinguisher solutions, chemical solvent, and a degreaser in the dry cleaning industry (Johns, 1976).

Carbon tetrachloride is a heavy, colorless liquid at room temperature. Its physical/chemical properties include: molecular weight, 153.82; melting point, -22.99°C; solubility in water, 800,000 µg/l at 25°C; and vapor pressure, 55.65 mm Hg at 10°C. CCl_4 is relatively non-polar and miscible with alcohol, acetone and most organic solvents.

Carbon tetrachloride may be quite stable under certain environmental conditions. The hydrolytic breakdown of CCl_4 in water is estimated to require 70,000 years for 50 percent decomposition (Johns, 1976). This decomposition is accelerated in the presence of metals such as iron (Pearson and McConnell, 1975). Hydrolytic decomposition as a means of removal from water is insignificant when compared with evaporation. In one experiment the evaporative half-life of CCl_4 in water at ambient temperatures was found to be 29 minutes (Dilling, et al. 1975), but this is highly dependent on experimental conditions, such as surface area to bulk volume ratios. For additional information regarding Halomethanes as a class, the reader is referred to the Hazard Profile on Halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

CCl_4 has been found in many water samples including rain, surface, potable, and sea, in the sub-part per billion range (McConnell, et al. 1975). The National Organics Monitoring Survey (NOMS) found CCl_4 in 10 percent of 113 public water systems sampled, with mean values ranging from 2.4-6.4 µg/l (U.S. EPA, 1977a).

Although CCl_4 is a chlorinated hydrocarbon, it is not produced in finished drinking water as a result of the chlorination process (Natl. Res. Coun., 1977,1978).

B. Food

Carbon tetrachloride has been detected in a variety of foodstuffs other than fish and shellfish in levels ranging from 1 to 20 µg/kg (McConnell, et al. 1975).

Results of various studies on CCl_4 fumigant residues in food indicate that the amount of residue is dependent upon fumigant dosage, storage conditions, length of aeration and the extent of processing (U.S. EPA, 1979a). Usually, proper storage and aeration reduce CCl_4 residues to trace amounts.

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for carbon tetrachloride to be 69 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

C. Inhalation

The occurrence of CCl_4 in the atmosphere is due largely to the volatile nature of the compound. Concentrations of CCl_4 in continental and marine air masses range from .00078 - .00091 mg/m^3. Although some

higher quantities (.0091 mg/m^3) have been measured in urban areas, concentrations of CCl_4 are universally widespread with little geographic variation (U.S. EPA, 1979a).

III. PHARMACOKINETICS

A. Absorption

CCl_4 is readily absorbed through the lungs, and more slowly through the gastrointestinal tract (Nielsen and Larsen, 1965). It can also be absorbed through the skin. The rate and amount of absorption are enhanced with the ingestion of fat and alcohol (Nielson and Larson, 1965; Moon, 1950). Robbins (1929) found that considerable amounts of CCl_4 are absorbed from the small intestine, less from the colon, and little from the stomach. Absorption from the gastorintestinal tract appears to vary by species, i.e., it occurs more rapidly in rabbits than dogs.

B. Distribution

The organ distribution of CCl_4 varies with the route of administration, its concentration, and the duration of exposure (U.S. EPA, 1979a).

After oral administration to dogs, Robbins (1929) found the highest concentrations of CCl_4 in the bone marrow. The liver, pancreas and spleen had one-fifth the amount found in the bone marrow. The highest concentrations of CCl_4 after inhalation, however, were found in the brain (Von Oettingen, et al. 1949,1950). After inhalation of CCl_4 by monkeys, the highest levels were detected in fat, followed by liver and bone marrow (McCollister, et al. 1950). McConnell, et al. (1975) found human tissue levels of CCl_4 to range as follows: kidney, 1-3 mg/l; liver, 1-5 mg/l and fat, 1-13 mg/l.

On the cellular level, McClean, et al. (1965) found CCl_4 in all cell fractions with higher concentrations in ribosomes.

C. Metabolism

When CCl_4 is administered to mammals, it is metabolized to a small extent, the majority being excreted through the lungs. The metabolites include chloroform, hexachloroethane, and carbon dioxide. These metabolites play an important role in the overall toxicity of CCl_4 (U.S. EPA, 1979a). Some of the CCl_4 metabolic products are also incorporated into fatty acids by the liver and into liver microsomal proteins and lipids (Gordis, 1969).

The chemical pathology of liver injury induced by CCl_4 is a result of the initial homolytic cleavage of the C-Cl bond which liberates trichloromethyl- and chlorine-free radicals (Fishbein, 1976). The next step may be one of two conflicting reactions: direct attack via alkylation on cellular constituents (especially sulfhydryl groups), or peroxidative decomposition of lipids of the endoplasmic reticulum as a key link between the initial bond cleavage and the pathological phenomena characteristic of CCl_4 (Butler, 1961; Tracey and Sherlock, 1968).

D. Excretion

The largest portion of absorbed CCl_4 is rapidly excreted. Approximately 50-79 percent of absorbed radioactive CCl_4 is eliminated through the lungs, and the remainder is excreted in the urine and feces. No CCl_4 was detected in the blood or in the expired air, 48 hours and 6 days, respectively, after CCl_4 inhalation (Beamer, et al. 1950). CCl_4 is excreted as 85 percent parent compound, 10 percent carbon dioxide, and smaller quantities of other products including chloroform (NRC, 1977).

IV. EFFECTS

A. Carcinogenicity

CCl_4 has been shown to be carcinogenic in rats, mice, and hamsters via subcutaneous injection, intubation, and rectal instillation (U.S.

EPA, 1979). Current knowledge lead to the conclusion that carcinogenesis is a non-threshold, non-reversible process. However, some scientists do argue that a threshold may occur.

Rueber and Glover (1970) administered injections of 1.3 ml/kg of body weight of a 50 percent solution of CCl_4 in corn oil to rats, two times per week until death. Carcinoma of the liver were present in 12/15 (80 percent) Japanese male rats, 4/12 (33 percent) Wistar rats, and 8/13 (62 percent) Osborne-Mendel rats, whereas Black Rats or Sprague-Dawley rats did not develop carcinomas. The incidence of cirrhosis of the liver also differed with the strain of the rat. Carcinoma of the liver tended to develop along with mild or moderate, rather than severe cirrhosis of the liver. When administered with CCl_4, methylcholanthrene (a potent enzyme inducer) was found to increase the incidence of hyperplastic hepatic nodules and early carcinomas in rats (Rueber, 1970). Females were found to be more susceptible to the development of hyperplastic nodules and carcinomas.

The National Cancer Institute (1976) studied the carcinogenic effect of CCl_4 in male and female mice (1,250 mg/kg or 2,500 mg/kg of body weight, oral gavage 5 times/week/78 weeks). Hepatocellular carcinomas were found in almost all of the mice receiving CCl_4. Andervant and Dunn (1955) transplanted 30 CCl_4-induced tumors into mice. They observed growth in 28 of the hepatomas, through 4 to 6 transplant generations.

8. Mutagenicity

Conclusive evidence on the mutageniciity of CCl_4 has not been reported. Kraemer, et al. (1976) found negative results using the Ames bacterial reversion tests. However, they explain that halogenated hydrocarbons are usually negative in the Ames test.

C. Teratogenicity

Very little data are available concerning the teratogenic effects of CCl_4. Schwetz, et al. (1974) found CCl_4 to be slightly embryotoxic, and to a certain degree retarded fetal development, when administered to rats at 300 or 1,000 mg/l for 7 hr/day on days 6 through 15 of gestation. Bhattacharyya (1965) found that subcutaneous injection occasionally gave rise to changes in fetal liver.

D. Other Reproductive Effects

Pertinent data concerning other reproductive effects of CCl_4 were not encountered in the available literature.

E. Chronic Toxicity

Cases of chronic poisoning have been reported by Butsch (1932), Wirtschafter (1933), Strauss (1954), Von Oettingen (1964), and others. The clinical picture of chronic CCl_4 poisoning is much less characteristic than that of acute poisoning. Von Oettingen (1964) has done an excellent job of reviewing the symptoms. Patients suffering from this condition may complain of fatigue, lassitude, giddiness, anxiety, and headache. They suffer from paresthesias and muscular twitchings, and show increased reflex excitability. They may be moderately jaundiced, have a tendency to hypoglycemia, and biopsy specimens of the liver may show fatty infiltration. Patients may complain of a lack of appetite, nausea, and occasionally of diarrhea. In some instances, the blood pressure is lowered and is accompanied by pain in the cardiac region and mild anemia. Other patients have developed pain in the kidney region, dysuria, and slight nocturia, and have had urine containing small amounts of albumin and a few red blood cells. Burning of the eyes and, in a few instances, blurred vision are frequent complaints of those exposed. If these symptoms are not pronounced, or of long

standing, recovery usually takes place upon discontinuation of the exposure if the proper treatment is received (Von Oettingen, 1964).

Reports on pathological changes in fatalities from CCl_4 poisonings are generally limited to findings in the liver and kidneys. The brain and lungs may be edematous. The intestines may be hyperemic and covered with numerous petechial hemorrhages and the spleen may be enlarged and hyperemic. Occasionally the adrenal glands may show degenerative changes of the cortex and the heart may undergo toxic myocarditis (Von Oettingen, 1964).

F. Other Relevant Information

The toxic effects of CCl_4 are potentiated by both the habitual and occasional ingestion of alcohol (U.S. EPA, 1979a). Pretreatment of laboratory animals with ethanol, methanol, or isopropanol increases the susceptibility of the liver to CCl_4 (Wei, et al. 1971; Traiger and Plaa, 1971).

Hafeman and Hoekstra (1977) reported that protective effects against CCl_4-induced lipid peroxidation are exhibited by vitamin E, selenium, and methionine.

According to Davis (1934), very obese or undernourished persons or those suffering from pulmonary diseases, gastric ulcers or a tendency to vomiting, liver or kidney diseases, diabetes or glandular disturbances, are especially sensitive to the toxic effect of CCl_4 (Von Oettingen, 1964).

V. AQUATIC TOXICITY

A. Acute Toxicity

Two studies have investigated the acute toxicity of carbon tetrachloride to bluegills (Lepomis macrochirus) in static tests. The determined LC_{50} varied from 27,300 µg/l to 125,000 µg/l (Dawson, et al. 1977; U.S. EPA, 1978). With Daphnia magna, the reported 48-hr. EC_{50} is 35,200 µg/l (U.S. EPA, 1978). The 96-hr. LC_{50} for the tidewater silversides (Menidia beryllina) is 150,000 µg/l (Dawson, et al. 1977).

B. Chronic Toxicity

An embryo-larval test with the fathead minnow (Pimephales promelas) showed no adverse effect from carbon tetrachloride concentrations up to 3,400 µg/l (U.S. EPA, 1978). Other chronic data are not available.

C. Plant Effects

There are no data in the available literature describing the effects of carbon tetrachloride on freshwater or saltwater plants.

D. Residues

The bluegill bioconcentrated carbon tetrachloride to a factor of 30 times within 21 days. The biological half-life in these tissues was less than 1 day.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have been reviewed; therefore, there is a possibility that these criteria will be changed.

A. Human

The American Conference of Governmental Industrial Hygienists (1971) recommends a threshold limit value (TLV) of 10 mg/m^3 for CCl_4, with peak values not to exceed 25 mg/m^3 even for short periods of time. The Occupational Safety and Health Administration adopted the American National Standards Institute (ANSI, 1967) standard Z37.17 - 1967 as the Federal standard for CCl_4 (29 CFR 1910.1000). This standard is 10 mg/m^3 for an 8-hour TWA, with an acceptable ceiling of 25 mg/m^3 and a maximum peak for 5 minutes in any 4-hour period of 200 mg/m^3.

The draft ambient water quality criteria for carbon tetrachloride has been set to reduce the human carcinogenic risk levels to 10^{-5}, 10^{-6} or 10^{-7} (U.S. EPA, 1979a). The corresponding criteria are 2.6 µg/l, 0.26

µg/l, and 0.026 µg/l, respectively. Refer to the Halomethane Hazard Profile for discussion of criteria derivation (U.S. EPA, 1979b).

8. Aquatic

For carbon tetrachloride, the drafted criteria to protect freshwater aquatic life is 620 µg/l as a 24-hour average and the concentration should never exceed 1,400 µg/l at any time. To protect saltwater aquatic life, the drafted criterion is 2,000 µg/l as 24-hour average and the concentration should not exceed 4,600 µg/l at any time (U.S. EPA, 1979a).

No. 34

Chloral

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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CHLORAL

Summary

Chloral (trichloroacetaldehyde) is used as an intermediate in the manufacture of DDT, methoxychlor, DDVP, naled, trichlorfon, and TCA. Chloral is readily soluble in water, forming chloral hydrate. Chloral hydrate decomposes to chloroform with a half-life of two days. Chloral hydrate has been used as a therapeutic agent due to its hypnotic and sedative properties.

Chloral (as chloral hydrate) has been identified in chlorinated water samples at concentrations as high as 5.0 µg/l. Chloral hydrate is formed through the chlorination of natural humic substances in the raw water. Atmospheric chloral concentrations up to 273.5 mg/m^3 have been reported from spraying and pouring of polyurethanes in Soviet factories. Similar data on exposure levels in U.S. plants were not found in the available literature.

Specific information on the pharmacokinetic behavior, carcinogenicity, mutagenicity, teratogenicity, and other reproductive effects of chloral was not found in the available literature. However, the pharmacokinetic behavior of chloral may be similar to chloral hydrate where metabolism to trichloroethanol and trichloroacetic acid and excretion via the urine (and possibly bile) have been observed. Chloral hydrate produced skin tumors in 4 of 20 mice dermally exposed. Information on the chronic or acute effects of chloral in humans was not found in the available literature. Chronic effects from respiratory exposure to chloral as indicated in laboratory animals include reduction of kidney function and serum transaminase activity, change in central nervous system function (unspecified), decrease in

antitoxic and enzyme-synthesizing function of the liver, and alteration of morphological characteristics of peripheral blood. Slowed growth rate, leukocytosis and changes in arterial blood pressure were also observed. Acute oral LD_{50} values in rats ranged from 0.05 to 1.34 g/kg.

U.S. standards and guidelines for chloral were not found in the available literature.

CHLORAL

ENVIRONMENTAL FATE

Chloral (trichloroacetaldehyde) is freely soluble in water, forming chloral hydrate (Windholz, et al. 1976). Chloral hydrate was identified in drinking water from 6 of 10 cities sampled (Keith, 1976). The author postulated that chloral hydrate was formed by the chlorination of other compounds during the addition of chlorine to the water supplies. Chloral hydrate was not identified prior to chlorination. Chloral hydrate may be formed by the chlorination of ethanol or acetaldehyde and may occur as an intermediate in the reaction involving the conversion of ethanol to chloroform as follows:

Ethanol - Acetaldehyde - Chloral - Chloral hydrate - Chloroform

Chloral hydrate decomposes to chloroform with a half-life of 2 days at pH 8 and 35°C (Luknitskii, 1975). Rook (1974) demonstrated the formation of haloforms from the chlorination of natural humic substances in raw water.

Chloral polymerizes under the influence of light and in the presence of sulfuric acid, forming a white solid trimer called metachloral (Windholz, 1976). Dilling, et al. (1976) studied the effects of chloral on the decomposition rates of trichloroethylene, NO, and NO_2 in the atmosphere and observed that chloral increases the photodecomposition rate of trichloroethylene to a greater extent than it does NO or NO_2.

CHLORAL

I. INTRODUCTION

This profile is based on literature searches in Biological Abstracts, Chemical Abstracts, MEDLINE, and TOXLINE.

Chloral [Cl_3CCHO], also referred to as trichloroacetaldehyde, anhydrous chloral, and trichloroethanol, is an oily liquid with a pungent, irritating odor. The physical properties of chloral are: molecular weight, 147.39; melting point, -57.5°C; boiling point, 97.75°C at 760 mm Hg; density, 1.5121 at 20/4°C (Weast, 1976). The compound is very soluble in water, forming chloral hydrate, and is soluble in alcohol and ether.

Industrial production of chloral involves direct chlorination of ethyl alcohol followed by treatment with concentrated sulfuric acid (Stanford Research Institute, 1976). Production may also occur by direct chlorination of either acetaldehyde or paraldehyde in the presence of antimony chloride. Prior to 1972, essentially all chloral produced was used in the manufacture of DDT. Production of chloral was greatest in 1963 at 79.8 million pounds, decreasing to 62.4 million pounds in 1969. Production data after 1969 were not reported. Consumption of chloral for DDT manufacture was estimated at 25 million pounds in 1975, with an additional 500,000 pounds used in the manufacture of other pesticides, including methoxychlor, DDVP, naled, trichlorfon, and TCA (trichloroacetic acid). Mel'nikov, et al. (1975) identified chloral as an impurity in chlorofos.

Chloral is also used in the production of chloral hydrate, a therapeutic agent with hypnotic and sedative effects used prior to the introduction of barbituates. Production of U.S.P. (pharmaceutical) grade chloral hydrate was estimated to be 300,000 pounds per year in 1975 (Stanford Research Institute, 1976).

II. EXPOSURE

Boitsov, et al. (1970) noted that chloral is evolved in spraying and pouring of polyurethane. The authors reported chloral concentrations as high as 273.5 mg/m^3 in Soviet factories. Similar information on atmospheric occupational exposure to chloral in Western countries was not found in the available literature.

Chloral exposure from water occurs as chloral hydrate. Keith (1976) reported chloral hydrate concentrations ranging from 0.01 µg/l to 5.0 µg/l in chlorinated drinking water supplies of six of ten U.S. cities studied. The mean concentration of chloral hydrate in drinking water for the six cities was 1.92 µg/l.

Chloral hydrate has been used as a hypnotic and sedative agent. Alcohol synergistically increases the depressant effect of the compound, creating a potent depressant commonly referred to as "Mickey Finn" or "knockout drops". Addiction to chloral hydrate through intentional abuse of the compound has been reported (Goodman and Gilman, 1970).

III. PHARMACOKINETICS

A. Absorption

Specific information on the absorption of chloral was not found in the available literature. Goodman and Gilman (1970) reported that chloral hydrate readily penetrates diffusion barriers in the body.

B. Distribution

Specific information on the distribution of chloral was not found in the available literature. Goodman and Gilman (1970), reporting on the distribution of chloral hydrate from oral administration, noted its presence in cerebrospinal fluid, milk, amniotic fluid, and fetal blood. The authors

noted that other investigators were unable to detect significant amounts of chloral hydrate in the blood after oral administration (owing probably to its rapid reduction).

C. Metabolism

Information on the metabolic reaction of chloral is obtained indirectly through a metabolic study of trichloroethylene (Henschler, 1977). The author reported that trichloroethylene oxidizes to a chlorinated epoxide which undergoes molecular rearrangement to chloral, which is further metabolized to either trichloroethanol or trichloroacetic acid. The rearrangement, detected by in vivo studies, is hypothesized to occur by a catalytic action of the trivalent iron of P-450.

Goodman and Gilman (1970) noted that chloral hydrate is reduced to trichloroethanol in the liver and other tissues, including whole blood, with the reaction catalyzed by alcohol dehydrogenase. Additional trichloroethanol is converted to trichloroacetic acid. Chloral hydrate may be directly oxidized to trichloroacetic acid in the liver and kidney.

D. Excretion

Both chloral and chloral hydrate are metabolized to trichloroethanol or trichloroacetic acid (Goodman and Gilman, 1970; Henschler, 1977). Trichloroethanol is then conjugated and excreted in the urine as a glucuronide (urochloralic acid) or is converted to trichloroacetic acid and slowly excreted in the urine. The glucuronide may also be concentrated and excreted in the bile. The fraction of the total dose excreted as trichloroethanol, glucuronide, and trichloroacetic acid is quite variable, indicating other possible routes of elimination.

IV. EFFECTS

A. Carcinogenicity

Specific information on the carcinogenicity of chloral was not found in the available literature. However, Keith (1976) reported skin tumors in 4 of 20 mice dermally exposed to chloral hydrate (4 to 5 percent solution in acetone). Further interpretation of the results and discussion of the study methodology were not given.

B. Mutagenicity, Teratogenicity, and Other Reproductive Effects

Specific information on the mutagenicity, teratogenicity, and reproductive effects of chloral was not found in the available literature.

C. Chronic Effects

Rats receiving 0.1 mg/kg chloral exhibited a reduction of kidney function and serum transaminase after seven months' exposure (Kryatov, 1970). No physiological effects were observed in rats receiving 0.01 mg/kg chloral for periods of seven months. The route of exposure was not reported.

Chronic respiratory exposure of rats and rabbits to chloral at 0.1 mg/l (100 mg/m^3) produced changes in central nervous system function, decreased antitoxic and enzyme synthesizing function of the liver, and altered morphological characteristics of peripheral blood (Pavlova, 1975). Boitsov, et al. (1970) reported slowed growth rate, leukocytosis, decreased albumin-globulin ratio, and changes in arterial blood pressure and central nervous system responses (unspecified) following prolonged respiratory exposure of mice to chloral at 60 mg/m^3.

Goodman and Gilman (1970) reported gastritis, skin eruptions, and parenchymatous renal injury in patients suffering from chronic chloral hydrate intoxication. Habitual use of chloral hydrate may result in the

development of tolerance, physical dependence, and addiction. Death may occur either as a result of an overdose or a failure of the detoxification mechanism due to hepatic damage.

F. Acute Toxicity

According to Hann and Jensen (1974), the human acute oral LD_{50} of chloral is between 50 and 500 mg/kg.

Kryatov (1970) reported the following LD_{50} values for chloral: mice, 0.850 g/kg; rats, 0.725 g/kg; and guinea pigs, 0.940 g/kg. The routes of exposure were not stated. Verschueren (1977) reported an oral LD_{50} for rats of 0.05 to 0.4 g/kg, while Pavlov (1975) reported an acute oral LD_{50} of 0.94 and 1.34 g/kg for mice and rats, respectively. Pavlov (1975) also reported inhalation LC_{50} values of 25.5 g/m^3 and 44.5 g/m^3 for mice and rats, respectively. Boitsov, et al. (1970) reported an LD_{50} of 0.710 g/kg in mice. The route of exposure was not stated. Hawley (1971) reported that chloral is a highly toxic, strong irritant and noted ingestion or inhalation may be fatal. Information on acute toxic effects from occupational exposure to chloral was not found in the available literature.

G. Other Relevant Information

Verschueren (1977) reported an odor threshold concentration of chloral in water of 0.047 ppm. The author also reported an inhibition of cell multiplication in Pseudomonas sp. at a chloral hydrate concentration of 1.6 mg/l.

V. AQUATIC TOXICITY

A. Acute Toxicity

Verschueren (1977) reported inhibition of cell multiplication in Microcystis sp. at 78 mg/l chloral hydrate. Hann and Jensen (1974) ranked the 96-hour TL_m aquatic toxicity of chloral in the range from 1 to 10 ppm.

B. Chronic Toxicity

Information on the chronic aquatic toxicity of chloral was not found in the available literature.

C. Plant Effects

Shimizu, et al. (1974) reported chloral inhibited the growth of rice stems by 63.4 percent relative to controls, but slightly stimulated root growth. The concentration of chloral in water culture was not reported.

D. Residue

Keith (1976) identified chloral hydrate in chlorinated drinking water in six of ten cities sampled. The sample locations and concentrations of chloral hydrate identified were: Philadelphia, PA, 5.0 µg/l; Seattle, WA, 3.5 µg/l; Cincinnati, OH, 2.0 µg/l; Terrebonne Parish, LA, 1.0 µg/l; New York City, NY, 0.02 µg/l; Grand Forks, ND, 0.01 µg/l.

E. Other Relevant Information

Hann and Jensen (1974) ranked the aesthetic effect of chloral on water as very low (zero), noting that the chemical neither pollutes waters nor causes aesthetic problems.

VI. EXISTING GUIDELINES AND STANDARDS

Boitsov, et al. (1970) reported a maximum recommended chloral concentration in workroom air of 0.22 mg/l (220 mg/m^3) (USSR). Kryatov (1970) reported a maximum recommended permissible concentration in bodies of water as 0.2 mg/l (USSR). Verschueren (1977) reported a maximum allowable chloral concentration of 0.2 mg/l in Class I waters used for drinking, but the nation applying this standard was not identified.

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No. 35

Chlordane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated chlordane and has found sufficient evidence to indicate that this compound is carcinogenic.

CHLORDANE

Summary

Chlordane is an organochlorinated cyclodiene insecticide commonly used as a formulation consisting of 24% trans-, 19% cis-chlordane, 10% heptachlor, 21.5% chlordenes, 7% nonachlor, and 18.5% of other organochlorinated material. Since heptachlor is also an insecticide and is more toxic than chlordane, technical chlordane is generally more toxic than pure chlordane.

Pure chlordane, which is a cis/trans mixture of isomers, induces liver cancer in mice and is mutagenic in some assays. Chlordane has not been shown to be teratogenic. Little information is available on chronic mammalian toxicity. Repeated doses of chlordane produced alterations in brain potentials and changes in some blood parameters. Chlordane is a convulsant. Chlordane and its toxic metabolite oxychlordane accumulate in adipose tissue.

Ten species of freshwater fish have reported 96-hr LC_{50} values ranging from 8 to 1160 µg/l. Freshwater invertebrates appear to be more resistant to chlordane, with observed 96-hr LC_{50} values ranging from 4 to 40 µg/l. Five species of saltwater fish have LC_{50} values of 5.5 to 160 µg/l, and marine invertebrate LC_{50} values range between 0.4 and 480 µg/l. Chronic studies involving the bluegill Daphnia magna gave an LC_{50} of 1.6 µg/l.

CHLORDANE

INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlordane (U.S. EPA, 1979).

Chlordane is a broad spectrum insecticide of the group of organochlorinated polycyclic hydrocarbons called cyclodiene insecticides. Chlordane has been used extensively over the past 30 years for termite control in homes and gardens, and as a control for soil insects.

Pure chlordane (1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene) is a pale yellow liquid having the empirical formula $C_{10}H_6Cl_8$ and a molecular weight of 409.8. It is composed of a mixture of stereoisomers, with the cis- and trans- forms predominating, commonly referred to as alpha- and gamma-isomers, respectively.) The solubility of pure chlordane in water is approximately 9 µg/l at 25°C (U.S. EPA, 1979).

Technical grade chlordane is a mixture of chlorinated hydrocarbons with a typical composition of approximately 24 percent trans(gamma)-chlordane, 19 percent cis(alpha)-chlordane, 10 percent heptachlor (another insecticidal ingredient), 21.5 percent chlordene isomers, 7 percent nonachlor, and 18.5 percent closely related chlorinated hydrocarbon compounds. Technical chlordane is a viscous, amber-colored liquid with a cedar-like odor. It has a vapor pressure of 1×10^{-5} mm Hg at 25°C. The solubility of technical chlordane in water is 150 to 220 µg/l at 22°C (U.S. EPA, 1979).

Production of chlordane was 10,000 metric tons in 1974 (41 FR 7559; February 19, 1976). Both uses and production volume have declined extensively since the issuance of a registration suspension notice by the U.S. EPA (40 FR34456; December 24, 1975) for all food, crop, home, and garden

uses of chlordane. However, use of chlordane for termite control and limited usage (through 1980) as an agricultural insecticide are still permitted (43 FR 12372; March, 1978).

Chlordane persists for prolonged periods in the environment (U.S. EPA, 1979). Photo-cis-chlordane can be produced in water and on plant surfaces by the action of sunlight (Benson, et al. 1971) and has been found to be twice as toxic as chlordane to fish and mammals (Ivie, et al. 1972; Podowski, et al. 1979). Photo-cis-chlordane (5 ng/l) is accumulated more (ca. 20%) by goldfish (Carassius auratus) than chlordane (5 ng/l) itself (Ducat and Khan, 1979).

Air transport of chlordane has been hypothesized to account for residues in Sweden (Jansson, et al. 1979). Residues in agricultural soils may be as high as 195 ng/g dry weight of soil (Requejo, et al. 1979).

II EXPOSURE

A. Water

Chlordane has been detected in finished waters at a maximum concentration of 8 µg/l (Schafer, et al. 1969) and in rainwater (Bevenue, et al. 1972; U.S. EPA, 1976). There have been reports of individual household wells becoming contaminated after a house is treated with chlordane for termite control (U.S. EPA, 1979). A recent contamination of a municipal water system has been discussed by Harrington, et al. (1978). Chlordane has also been detected in rainwater (U.S. EPA, 1976).

B. Food

Chlordane has been found infrequently in food supplies since 1965, when the FDA began systematic monitoring for chlordane (Nisbet, 1976). The only quantifiable sample collected was 0.059 mg chlordane/kg measured in a sample of grain in 1972 (Manske and Johnson, 1975). In the most recently

published results (for 1975), chlordane was not detected (Johnson and Manske, 1977). Fish are thought to represent the most significant dietary exposure. The average daily uptake from fish is estimated at 1 µg (Nisbet, 1976).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for chlordane to be 5,500 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on measured steady-state bioconcentration studies in the sheepshead minnow (Cyprinodon variegatus).

Eighty-seven percent of 200 samples of milk collected in Illinois from 1971 to 1973 were positive for chlordane. The average concentration was 50 µg/l (Moore, 1975 as reviewed by Nat. Acad. Sci., 1977). Cyclodienes, such as chlordane, apparently are ingested with forage and tend to concentrate in lipids. Oxychlordane, a metabolite of chlordane and heptachlor, was found in 46 percent of 57 human milk samples collected during 1973-74 in Arkansas and Mississippi. The mean value was 5 µg/l, and the maximum was 20 µg/l (Strassman and Kutz, 1977).

C. Inhalation

In a survey of the extent of atmospheric contamination by pesticides, air was sampled at nine localities representative of both urban and agricultural areas. Chlordane was not detected in any samples (Stanley, et al. 1971). In a larger survey, 2,479 samples were collected at 45 sites in 16 states. Chlordane was detected in only two samples, with concentrations of 84 and 204 ng/m^3 (Nisbet, 1976). The vapor concentrations to which spray operators are exposed have not been estimated.

D. Dermal Effects

Chlordane can be absorbed through the skin to produce toxic effects (Gosselin, et al. 1976). Spray operators, chlordane formulators and farmers may be exposed. Chlordane has been known to persist for as long as two years on the hands (Kazen, et al. 1974). Dermal LD_{50} values in rats range from 530 to 700 mg/kg (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Gastrointestinal absorption of chlordane in rats ranged from 6 percent with a single dose to 10-15 percent with smaller daily doses (Barnett and Dorough, 1974).

B. Distribution

In a study of the distribution of chlordane and its metabolites using radioactive carbon, the levels of residues in the tissues were low, except in the fat (Barnett and Dorough, 1974). Rats were fed 1, 5, and 25 mg chlordane/g in food for 56 days. Concentrations of chlordane residues in fat, liver, kidney, brain, and muscle were 300, 12, 10, 4, and 2 percent, respectively, of the concentration in the diet. All residues declined steadily for 4 weeks, at which time concentrations were reduced about 60 percent. During the next four weeks, residues declined only slightly.

C. Metabolism

Mammals metabolize chlordane to oxychlordane, via 1,2-dichloro-chlordene which is about twenty times more toxic than the parent compound and persists in adipose tissue (Polen, et al. 1971; Tashiro and Matsumura, 1978; Street and Blau, 1972). Oxychlordane can degrade to form 1-hydroxy-2-cyclochlordenes, and 1-hydroxy-2-chloro-2,3-epoxy-chlordenes (Tashiro and Matsumura, 1978). In general, the metabolism of chlordane takes place via a

series of oxidative enzyme reactions. None of the metabolic intermediates (except for oxychlordane) and end products are more toxic than chlordane (Barnett and Dorough, 1974; Tashiro and Matsumura, 1977; Mastri, et al. 1969). Trans-nonachlor, a major impurity in technical chlordene, is converted to trans-chlordane in rats, but this is not important in humans. This explains the fact that trans-nonachlor accumulates in humans but not in rats (Tashiro and Matsumura, 1978). A very small amount of cis- or trans-chlordane can be converted to heptachlor in rat liver (Tashiro and Matsumura, 1977).

D. Excretion

Chlordane is primarily excreted in the feces of rats, only about six percent of the total intake being eliminated in the urine. Urinary excretion of chlordane in rabbits is greater than excretion in the feces (Nye and Dorough, 1976).

The half-life of chlordane in a young boy was reported to be approximately 21 days (Curley and Garrettson, 1969), while for rats it was 23 days (Barnett and Dorough, 1974). The half-life of chlordane in the serum of a young girl was 88 days (Aldrich and Holmes, 1969).

IV. EFFECTS

A. Carcinogenicity

Hepatocellular carcinomas were induced in both sexes of two strains of mice fed pure (95%) chlordane (56.2 mg/kg) in the diet for 80 weeks (National Cancer Institute, 1977; Epstein, 1976). In contrast to findings with mice, a significantly increased incidence of hepatocellular carcinomas did not appear in rats administered chlordane. Dosages were near the maximum permissible (National Cancer Institute, 1977).

B. Mutagenicity

Pure or technical chlordane induced unscheduled DNA synthesis in the SV-40 transformed human fibroblast cell line VA-4. Metabolic activation eliminated this effect (Ahmed, et al. 1977). Chlordane did not induce mutations in the dominant lethal assay in mice (Arnold, et al. 1977).

While neither pure cis-chlordane nor pure trans-chlordane was mutagenic in the Ames Salmonella microsome assay, technical grade chlordane was mutagenic. Microsomal activation did not enhance the mutagenic activity (Simmon, et al. 1977).

C. Teratogenicity

Chlordane was found not to be teratogenic in rats when fed at concentrations of 150 to 300 mg/kg during gestation (Ingle, 1952).

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

There appears to be little information on chronic mammalian toxicity. Daily injections of 0.15 to 25 mg chlordane/kg in adult rats resulted in dose-dependent alterations of brain potentials (Hyde and Falkenberg, 1976). As changes were directly related to length of exposure, it was concluded that chlordane may be a cumulative neurotoxin. Length of exposure was not specified. Repeated doses of chlordane given to gerbils produced changes in serum proteins, blood glucose, and alkaline and acid phosphatase activities (Karel and Saxena, 1976). Again, duration of treatment was not specified.

F. Other Relevant Information

Carbon tetrachloride produced more extensive hepatocellular necrosis in chlordane-pretreated rats than in rats which were not pretreated (Stenger, et al. 1975). Rats suffered greater cirrhosis when chlordane (50

µg/kg/day) exposure for ten weeks followed prior exposures of ten weeks for carbon tetrachloride above (110 mg/l) or with chlordane (Mahon and Oloffs, 1979). Quail treated with chlordane followed by endrin had considerably more chlordane residues in their brains than did quail treated with chlordane alone (Ludke, 1976). Quail pretreated with 10 mg/kg chlordane exhibited decreased susceptibility to parathion (Ludke, 1977). Chlordane is a convulsant and emetic. It induces twitching, seizures and electroencephalographic dysrhythmia in humans. Acute symptoms can be alleviated with phenobarbital. Acute oral LD_{50} values for the rat range from 100 to 112 mg/kg (U.S. EPA, 1979). The no observable effect level was found to be 2.5 mg/kg/day over 15 days (Natl. Acad. Sci., 1977).

Chlordane inhibits growth of human viridans streptococci of the buccal cavity. Complete inhibition of growth occurred at 3 ppm, and about 20 percent inhibition was seen at 1 ppm (Goes, et al. 1978).

V. AQUATIC TOXICITY

A. Acute Toxicity

Ten species of freshwater fish have reported 96-hr LC_{50} values ranging from 8 to 1160 µg/l resulting from technical and pure chlordane exposure with a geometric mean of 16 µg/l. Rainbow trout, Salmo gairdneri (Mehrle, et al. 1974) was the most sensitive species tested, the channel catfish (Ictalurus punctatus) the least sensitive. The freshwater invertebrates were more sensitive to chlordane, with a reported LC_{50} value ranging from 4.0 for freshwater shrimp Palaemonetes kadiakensis (Sanders, 1972) to 40 µg/l (Gammarus fasciatus), with a geometric mean of 0.36 µg/l. In goldfish (Carassius auratus), only 0.13 percent of cis-chlordane is metabolized in 24 hours. Only 0.61 percent is converted after 25 days. Some metabolites were chlordene chlorohydrin and monohydroxy derivatives (Feroz and Khan, 1979).

The LC_{50}'s for four species of saltwater fish, sheepshead minnows (Cyprinodon veriegatus), striped bass (Morone saxatilis), pinfish (Lagodon rhomboides), and white mullet (Mugil curema), ranged from 5.5 to 24.5 µg/l. The three-spine stickleback (Gasterosteus aculeatus) yielded 96-hr LC_{50} values which ranged from 90-160 µg/l (Katz, 1961). Invertebrate LC_{50} values ranged from 0.4 for the pink shrimp, Penaeus duorarum (Parrish, et al. 1976) to 480 µg/l. The geometric mean of the adjusted LC_{50} values for invertebrates was 0.18 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

In a life cycle bioassay involving freshwater organisms, the chronic values for the bluegill Lepomis macrochirus (Cardwell, et al. 1977) was 1.6 µg/l. In two tests involving the sheepshead minnow, Cyprinodon variegatus, the chronic values were 0.63 µg/l for the life cycle test (Parrish, et al. 1978) and 5.49 µg/l for an embryo-level test (Parrish, et al. 1976).

Many blood parameters (clotting time, mean corpuscular hemoglobin and cholesterol level) are lowered after the teleost, Sacco-branchus fossilus, is exposed to 120 µg/l of chlordane for 15 to 60 days (Verna, et al. 1979). Similar results were obtained in Labeo rohita at doses $\geq$ 23 µg/l after 30 to 60 day exposures (Bansal, et al. 1979).

C. Plant Effects

A natural saltwater phytoplankton community suffered a 94 percent decrease in productivity during a 4-hour exposure at 1,000 µg/l (Butler, 1963).

D. Residues

In Daphnia magna, chlordane was bioconcentrated 6,000-fold after seven days' exposure and 7,400-fold by scuds (Hyallela azteca) after 65 days of exposure (Cardwell, et al. 1977). After 33 days' exposure, the fresh-

water alga (Oedegonium sp.) bioconcentrated chlordane 98,000-fold; Physa sp., a snail, concentrated it 133,000-fold (Sanborn, et al. 1976). Equilibrium bioconcentration factors for the sheepshead minnow ranged from 6,580 to 16,035 (Goodman, et al. 1978; Parrish, et al. 1976).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The issue of the carcinogenicity of chlordane in humans is being reconsidered; thus, there is a possibility that the criterion for human health will be changed. Based on the data for carcinogenicity in mice (Epstein, 1976), and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of chlordane in ambient water which will result in risk levels of human cancer as specified in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.012 ng/l	0.12 ng/l	1.2 ng/l
Consumption of fish and shellfish only.	0	0.013 ng/l	0.13 ng/l	1.3 ng/l

The ACGIH (1977) adopted a time-weighted average value of 0.5 mg/m^3 for chlordane, with a short-term exposure limit (15 minutes) of 2 mg/m^3.

A limit of 3 µg/l for chlordane in drinking water is suggested under the proposed Interim Primary Drinking Water Standards (40 FR 11990, March 14, 1975).

Canadian Drinking Water Standards (Dept. Natl. Health Welfare, 1968) limit chlordane to 3 µg/l in raw water supplies.

B. Aquatic

For chlordane, the proposed criterion to protect freshwater aquatic life is 0.024 µg/l for a 24-hour average, not to exceed 0.36 µg/l at any time (U.S. EPA, 1979). For saltwater aquatic species, the draft criterion is 0.0091 µg/l for a 24-hour average, not to exceed 0.18 µg/l at any time (U.S. EPA, 1979).

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No.36

Chlorinated Benzenes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OCTOBER 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CHLORINATED BENZENES

Summary

The chlorinated benzenes are a group of compounds with a wide variety of physical and chemical characteristics depending on the degree of chlorination. As chlorination increases, the persistence of the compound in the environment increases. On chronic exposure liver and kidney changes are noted, and the degree of toxicity increases with the degree of chlorination. The chlorinated benzenes have not been shown to be teratogens or mutagens. Only hexachlorobenzene has been demonstrated to be carcinogenic in laboratory animals.

Aquatic toxicity data indicate a trend to increasing toxicity with increasing chlorination for all species tested. For the bluegill, for example, the following 96-hour LC_{50} values; have been noted: chlorobenzene, 15,900 ug/l; 1,2,4-trichlorobenzene, 200 ug/l. Other freshwater and saltwater fish, invertebrates and plants are generally less sensitive to chlorobenzenes than the bluegill. The sheephead minnow yielded a chronic value of 14.5 ug/l for 1,2,4,5tetrachlorobenzene in an embryo-level test. After 28 days of exposure, the bioconcentration factors for the bluegill for pentachlorobenzene and 1,2,4,5-tetrachlorobenzene were 3,400 and 1,800, respectively.

CHLORINATED BENZENES

I. INTRODUCTION

This profile is based inpart on the Ambient Water Quality Criteria Document for Chlorinated Benzenes (U.S. EPA, 1980). This document summarizes the general properties of the chlorinated benzenes. For further information on monochlorobenzene, 1,2,4-trichlorobenzene, or hexachlorobenzene, refer to the specific EPA/ECAO Hazard Profiles for these compounds. For detailed information on the other chlorinated benzenes refer to the Ambient Water Quality Document (U.S. EPA, 1980).

The chlorinated benzenes, excluding dichlorobenzenes*, are monochlorobenzene (C_6H_3Cl), 1,2,4-trichlorobenzene ($C_6H_3Cl_3$), 1,3,5-trichlorobenzene ($C_6H_3Cl_3$), 1,2,3,4-tetrachlorobenzene ($C_6H_2Cl_4$), 1,2,3,5-tetrachlorobenzene ($C_6H_2Cl_4$), 1,2,4,5-tetrachlorobenzene ($C_6H_2Cl_4$), pentachlorobenzene (C_6Cl_5) and hexachlorobenzene (C_6Cl_6). All chlorinated benzenes are colorless liquids or solids with a pleasant aroma. The most important properties imparted by chlorine to these compounds are solvent power, viscosity and moderate chemical reactivity. Viscosity and nonflammability tend to increase with degree of chlorination. Vapor pressures and water solubility decrease progressively with the degree of chlorination (U.S. EPA, 1980).

*the health and environmental effects of dichlorobenzenes are discussed in HEBD's Nos. 64-67.

The current production, based on annual production in the U.S., was 139,105 kkg of monochlorobenzene in 1975, 12,849 kkg of 1,2,4-trichlorobenzene, 8,182 kkg of 1,2,4,5-tetrachlorobenzene and 318 kkg of hexachlorobenzene in 1973 (West and Ware, 1977; EPA, 1975a). The remaining chlorinated benzenes are produced mainly as by-products from the production processes for the above four chemicals. Chlorinated benzenes have many and diverse uses in industry depending upon the individual properties of the specific compound. Some uses are as solvents, chemical intermediates, flame retardants, and plasticizers.

II. EXPOSURE

A. Water

Mono-, tri-, and hexachlorobenzene have been detected in ambient water. Because of its high volatility, monochlorobenzene has a short half-life of only 5.8 hours (Mackay and Leinonen, 1975). However, hexachlorobenzene has an extremely long residue time in water, appearing to be ubiquitous in the aqueous environment. Monochlorobenzene has been detected in "uncontaminated" water at levels of 4.7 ug/l. Both trichlorobenzene and hexachlorobenzene have been detected in drinking waters at concentrations of 1.0 ug/l and 4 to 6 ng/l respectively (U.S. EPA, 1980). There is no information available on the concentration of the other chlorinated benzenes in water.

B. Food

There is little data on the consumption of chlorinated benzenes in food. All the chlorinated benzenes appear to

concentrate in fat, and can be absorbed by plants from contaminated soil. Both pentachlorobenzene and hexachlorobenzene have been detected in meat fat (e.g. Stijve, 1971; Ushio and Doguchi, 1977). Hexachlorobenzene, the most extensively studied compound, has been found in a wide variety of foods from cereals to milk (including human breast milk), eggs, and meat. The U.S. EPA (1980) has estimated the weighted bioconcentration factors for freshwater species:

Chemical	Weighted bioconcentration factor
monochlorobenzene	13
1,2,4-trichlorobenzene	182
1,2,3,5-tetrachlorobenzene	1,800
pentachlorobenzene	3,400
hexachlorobenzene	22,000

These estimates were based on the octanol/water partition coefficients of the chlorinated benzenes.

C. Inhalation

There is no available data on the concentration of chlorinated benzenes in ambient air with the exception of measurements of aerial fallout of particulate bound 1,2,4-trichlorobenzene in southern California. Five sampling sites showed median levels of 1,2,4-trichlorobenzene of less than 11 ng/m^2/day (U.S. EPA, 1980). The primary site of inhalation exposure to chlorinated benzenes is the workplace in industries utilizing and/or producing these compounds.

III. PHARMACOKINETICS

A. Absorption

There is little data on the absorption of orally administered chlorinated benzenes. It is apparent from the

toxicity of orally administered compounds that absorption does take place, and tetrachlorobenzene has been shown to be absorbed relatively efficiently by rabbits (Jondorf, et al. 1958). Pentachlorobenzene was absorbed poorly after subcutaneous injection (Parke and Williams, 1960). Hexachlorobenzene was absorbed poorly from an orally administered aqueous solution (Koss and Kornasky, 1975), but with high efficiency when administered in oil (Albro and Thomas, 1974). The more highly chlorinated compounds in food products selectively partition into the lipid portion and are absorbed far better than those in the aqueous portion (U.S. EPA, 1980).

B. Distribution

The chlorinated benzenes are lipophilic compounds, with greater lipophilic tendencies in the more highly chlorinated compounds. The predominant uptake site is either suspected or known to be the lipid tissues of the body (Lee and Metcalf, 1975; U.S. EPA, 1980).

C. Metabolism

The chlorinated benzenes are metabolized in the liver by the NADPH-cytochrome P-448 dependent microsomal enzyme system (Ariyoshi, et al. 1975; Koss, et al. 1976). At least for monochlorobenzene, there is evidence that toxic intermediates are formed during metabolism (Kohli, et al. 1976). Various conjugates and phenolic derivatives are the primary excretory end products of chlorinated benzene metabolism. Conjugates of the more highly chlorinated compounds, such as hexachlorobenzene, are only formed to a limited extent, and their metabolism is relatively slow.

D. Excretion

The less-chlorinated benzenes are excreted as polar metabolites or conjugates in the urine. An exception occurs with monochlorobenzene is an exception: in the rabbit, 27 percent of an administered dose appeared as unchanged compounds in expired air (Williams, 1959). The two highly chlorinated compounds, pentachlorobenzene and hexachlorobenzene, are predominately eliminated in unchanged form by fecal excretion (Koss and Koransky, 1975; Rozman, et al. 1979). The biological half-lives of these two compounds are extremely long in comparison to those of the less-chlorinated compounds (U.S. EPA, 1980).

IV. EFFECTS

A. Carcinogencity

The carcinogenic potential of mono- and tetrachlorobenzene have not been investigated (U.S. EPA, 1980). In one study, trichlorobenzene was not shown to produce any significant increase in liver tumors (Gotto, et al. 1972). There is one report, not critically evaluated by EPA (1980), which alludes to the carcinogencity of pentachlorobenzene in mice and the absence of this activity in rats and dogs (Preussman, 1975). Life-time feeding studies in hamsters (Cabral, et al. 1977) and mice (Cabral, et al. 1978) have demonstrated the carcinogenic activity of hexachlorobenezene. However, shorter term studies failed to demonstrate an increased tumor incidence in strain A mice or ICR mice (Theiss, et al. 1977; Shirai, et al. 1978). Chlorobenzene has been tentatively selected for long-term bioassay testing by NCI (U.S. EPA, 1978b).

B. Mutagenicity

There are no reports of studies conducted to evaluate the mutagenic potential of tri-,tetra- and pentachlorobenzene. Chlorobenzene causes mutations in S.antibioticus, and chromosomal damage and mitotic inhibition in root tips of higher plants, and is not mutagenic in the fungus A.nidulans (U.S. EPA, 1978b). Hexachlorobenzene was assayed for mutagenic activity in the dominant lethal assay, and shown to be inactive (Khera, 1974).

C. Teratogenicity

There are no available reports on the teratogenic potential of mono-, tri-, and tetra-, chlorobenzene (U.S. EPA, 1980). Khera (1974) concluded that hexachlorobenzene is not a teratogen when given to CD-1 mice at 50 mg/kg/day on gestation days from 7 to 11. Pentachlorobenzene, however, induces a dose-related incidence of sternebral defects in rats (Khera, 1975).

D. Other Reproductive Effects

Both penta- and hexachlorobenzene pass through the placenta and cause fetal toxicity in rats (Grant, et al. 1977). The distribution of hexachlorobenzene in the fetus appears to be the same as in the adult, with the highest concentration in fatty tissue.

E. Chronic Toxicity

There are no available data on the chronic effects of pentachlorobenzene (U.S. EPA, 1979). Mono- and trichlorobenzene product histological changes in the liver and kidney (Irish, 1963; Coate, et al. 1977). Chlorobenzene (orally administered at 250 mg/kg for 3 days) caused liver dysfunction and porphyria

(U.S. EPA, 1978b). There is also evidence for liver damage occurring with prolonged exposure of rats and dogs to tetrachlorobenzene (Fomenko, 1965; Braun, et al. 1978). Hexachlorobenzene has caused histological changes in the livers of rats (Koss, et al. 1978). In humans exposed to undefined amounts of hexachlorobenzene for an undetermined time, porphyrinuria has been shown to occur (Cam and Nigogosyan, 1963).

F. Other Relevant Information

Chlorinated benzenes appear to increase the activity of microsomal NADPH-cytochrome P-450 dependent enzyme systems.

V. ACUATIC TOXICITY (U.S. EPA, 1980)

A. Acute Toxicity

The dichlorobenzenes are covered in a separate EPA/ECAO hazard profile and will not be covered in this disucssion on chlorobenzenes.

All data reported for freshwater fish are from 96-hour static toxicity tests. Pickering and Henderson (1966) reported 96-hour LC_{50} values for goldfish, guppies and bluegills to be 51,620, 45,530, and 24,000 ug/l, respectively, for chlorobenzene. Two 96 hour LC_{50} values for chlorobenzene and fathead minnows are 33,930 ug/l in saltwater and 29,120 ug/l in hard water. Reported 96-hour values for the bluegill exposed to chlorobenzene, 1,2,4-trichlorobenzene, 1,2,3,5- and 1,2,4,5-tetrachlorobenzenes and pentachlorobenzene are 15,900, 3,360, 6,420, 1,550, and 250 ug/l, respectively (U.S. EPA, 1978). These data indicate increasing toxicity with chlorination, except for monochlorobenzene. EC_{50} (48 hour) values reported for Daphnia magna are: chlorcbenzene

86,000 ug/l, 1,2,4-trichlorobenzene 50,200 ug/l, 1,2,3,5-tetrachlorobenzene 9,710 ug/l, and pentachlorobenzene 5,280 ug/l.

Toxicity tests with the sheepshead minnow, Cyprinodon variegatus, performed with five chlorinated benzenes under static conditions and yielded the following 96-hour LC_{50} values: chlorobenzene 10,500 ug/l, 1,2,4-trichlorobenzene 21,400 ug/l, 1,2,3,5-tetrachlorobenzene 3,670 ug/l, 1,2,4,5 tetrachlorobenzene 840 ug/l, and pentrachlorobenzene 835 ug/l. As with sheepshead minnows, sensitivity of the mysid shrimp, Mysidopsis bahia, to chlorinated benzenes generally increases with increasing chlorination. The reported 96-hour LC_{50} values are as follows: chlorobenzene 16,400 ug/l, 1,2,4-trichlorobenzene 450 ug/l, 1,2,3,5-tetrachlorobenzene 340 ug/l, 1,2,4,5-tetrachlorobenzene 1,480 ug/l, and 160 ug/l for pentachlorobenzene.

B. Chronic Toxicity

Chronic toxicity data are not available for freshwater fish or invertebrate species. Only one saltwater species, Cyprinodon variegatus, has been chronically exposed to any of the chlorinated benzenes. In an embryo-level test, the limits for 1,2,4,5-tetrachlorobenzene are 92 to 180 ug/l, with a final chronic value of 64.5 ug/l.

C. Plant Effects

The green freshwater algae Selenastrum capricornutum has been exposed to five chlorinated benzenes. Based on cell number, the 96-hour EC_{50} values are as follows: chlorobenzene 220,000 ug/l, 1,2,4-trichlorobenzene 36,700 ug/l, 1,2,3,5-tetrachlorobenzene 17,700 ug/l, 1,2,4,5-tetrachlorobenzene 46,800

ug/l, and pentachlorobenzene 6,780 ug/l.

D. Residues

No measured bioconcentration factor (BCF) is available for chlorobenzenes. However, the average weighted BCF of 13 was calculated from octanol-water partition coefficient and other factors (See above) (U.S. EPA, 1980).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Monochlorobenzene: The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) threshold limit value for monochlorobenzene is 75 ppm. The U.S. EPA ambient water quality criterion for monochlorobenzene is 20 ug/l based on the threshold concentration for odor and taste, and 488 ug/l based on its toxic effects (U.S. EPA, 1980).

Trichlorobenzene: The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value for 1,2,4-trichlorobenzene is (5 ppm). Because of the insufficiency of available information for trichlorobenzene U.S. EPA (1980) determined that a criterion could not be derived using the guidelines in effect in 1980.

Tetrachlorobenzene: The U.S. EPA (1980) ambient water quality criterion for 1,2,4,5-tetrachlorobenzene based on its toxic effects, is 38 ug/l.

Pentachlorobenzene: The U.S. EPA (1979) ambient water quality criterion for pentachlorobenzene based on its toxic effects is 74 ug/l.

Hexachlorobenzene: The value of 0.6 ug/kg/day was suggested by FAO/WHO as a reasonable upper limit for residues in food for human consumption (FAO/WHO, 1974). The Louisiana State Department of Agriculture has set the tolerated level of hexachlorobenzene in meat fat at 0.3 mg/kg (U.S. EPA, 1976). The FAO/WHO recommendations for residues in foodstuffs were 0.5 mg/kg in fat for milk and eggs, and 1 mg/kg in fat for meat and poultry (FAO/WHO, 1974). For maximum protection of human health from the potential carcinogenic effects of hexachlorobenzene through ingestion of contaminated water and contaminated aquatic organisms, the ambient water criterion is 0.72 ug/l (10^{-7} incremental lifetime risk)(U.S. EPA, 1980).

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No. 37

Chlorinated Ethanes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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37-1

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated chlorinated ethanes and has found sufficient evidence to indicate that this compound is carcinogenic.

CHLORINATED ETHANES

SUMMARY

Four of the chlorinated ethanes have been shown to produce tumors in experimental animal studies conducted by the National Cancer Institute (NCI). These four are 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane, and hexachloroethane. Animal tumors were also produced by administration of 1,1,1-trichloroethane, but this bioassay is being repeated due to premature deaths in one initial study.

Two of the chlorinated ethanes, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, have shown mutagenic activity in the Ames Salmonella assay and in E. coli. 1,2-Dichloroethane has also shown mutagenic action in pea plants and in Drosophila.

No evidence is available indicating that the chloroethanes produce teratogenic effects. Some toxic effects on fetal development have been shown following administration of 1,2-dichloroethane and hexachloroethane.

Symptoms produced by toxic exposure to the chloroethanes include central nervous system disorders, liver and kidney damage, and cardiac effects.

Aquatic toxicity data for the effects of chlorinated ethanes to freshwater and marine life are few. Acute studies have indicated that hexachloroethane is the most toxic of the chlorinated ethanes reviewed. Marine organisms tend to be more sensitive than freshwater organisms with acute toxicity values as low as 540 µg/l being reported.

CHLORINATED ETHANES

I. INTRODUCTION

This profile is based on the draft Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979).

The chloroethanes (see table 1) are hydrocarbons in which one or more of the hydrogen atoms have been replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. Monochloroethane is a gas at room temperature, hexachloroethane is a solid, and the remaining compounds are liquids. All chloroethanes show some solubility in water, and all, except monochloroethane, are more dense than water.

The chloroethanes are used as solvents, cleaning and degreasing agents, in the manufacture of plastics and textiles, and in the chemical synthesis of a number of compounds.

Current production:

monochloroethane	335 x 10^3_3	tons/yr in 1976
1,2-dichloroethane	4,000 x 10^3_3	tons/yr in 1976
1,1,1-trichloroethane	215 x 10^3	tons/yr in 1976

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979).

II. EXPOSURE

The chloroethanes are present in raw and finished waters due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water or treatment of sewage. Water monitoring studies

have shown the following levels of various chloroethanes: 1,2-dichloroethane, 0.2-8 µg/l; 1,1,2-trichloroethane, 0.1-8.5 µg/l; 1,1,1,2-tetrachloroethane, 0.11 µg/l (U.S. EPA, 1979). In general, air levels of chloroethanes are produced by evaporation of volatile chloroethanes widely used as degreasing agents and in dry cleaning operations (U.S. EPA, 1979). Industrial monitoring studies have shown air levels of 1,1,1-trichloroethane ranging from 1.5 to 396 ppm (U.S. EPA, 1979).

TABLE 1

Chloroethanes and Synonyms

Compound Name	Synonyms	
Monochloroethane	Chloroethane	Ethyl chloride
1,1,-Dichloroethane	Ethylidene Dichloride	Ethylidene Chloride
1,2-Dichloroethane	Ethylene Dichloride	Ethylene Chloride
1,1,1-Trichloroethane	Methyl Chloroform	Chlorothene
1,1,2-Trichloroethane	Ethane Trichloride	Vinyl Trichloride
1,1,1,2-Tetrachloroethane	Tetrachloroethane	
1,1,2,2-Tetrachloroethane	Acetylene Tetrachloride	Sym-Tetrachloroethane
Pentachloroethane	Pentalin	Ethane Pentachloride
Hexachloroethane	Perchloroethane	

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. The two most widely used solvents, 1,2-dichloroethane and 1,1,1-trichloroethane, are the compounds most often detected in foods. Analysis of several foods indicated 1,1,1-trichloro-

ethane levels of 1-10 µg/kg (Walter, et al. 1976), while levels of 1,2-dichloroethane found in 11 of 17 species have been reported to be 2-23 µg/g (Page and Kennedy, 1975). Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976).

The U.S. EPA (1979) has derived the following weighted average bioconcentration factors for the edible portions of fish and shellfish consumed by Americans: 1,2-dichloroethane, 4.6; 1,1,1-trichloroethane, 21; 1,1,2,2-tetrachloroethane, 18; pentachloroethane, 150; hexachloroethane, 320. These estimates were based on the measured steady-state bioconcentration studies in bluegill. Bioconcentration factors for 1,1,2-trichloroethane (6.3) and 1,1,1,2-tetrachloroethane (18) were derived by EPA (1979) using octanol-water partition coefficients.

III. PHARMACOKINETICS

A. Absorption

The chloroethanes are absorbed rapidly following ingestion or inhalation (U.S. EPA, 1979). Dermal absorption is thought to be slower in rabbits based on studies by Smyth, et al. (1969). However, rapid dermal absorption has been seen in guinea pigs with the same trichloroethane (Jakobson, et al. 1977).

Human studies on the absorption of inhaled 1,1,2,2-tetrachloroethane indicate that the compound is completely absorbed after exposure to trace levels of radiolabeled vapor (Morgan, et al., 1970, 1972). At higher exposure levels absorption is rapid in man and animals, but obviously not complete.

B. Distribution

Studies on the distribution of 1,1,1-trichloroethane in mice following inhalation exposure have shown levels in the liver to be twice that found in the kidney and brain (Holmberg, et al. 1977). Postmortem examination of human tissues showed 1,1,1-trichloroethane in body fat (highest concentration) kidneys, liver, and brain (Walter, et al. 1976). Due to the lipid solubility of chloroethanes, body distribution may be expected to be widespread. Stahl, et al. (1969) have noted that human tissue samples of liver, brain, kidney, muscle, lung, and blood contained 1,1,1-trichloroethane following acute exposure, with the liver containing the highest concentration.

Passage of 1,1,1,2-tetrachloroethane across the placenta has been reported by Truhaut, et al. (1974) in rabbits and rats.

C. Metabolism

The metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation to corresponding alcohols (Monster, 1979; Truhaut, 1972). Oxidation reactions may produce unsaturated metabolites which are then transformed to the alcohol and ester (Yllner, 1971 a,b,c,d).

Metabolism appears to involve the activity of the mixed function oxidase enzyme system (Van Dyke and Wineman, 1971). Animal experiments by Yllner (1971 a,b,c,d,e) indicated that the percentage of administered compound metabolized decreased with increasing dose, suggesting saturation of metabolic pathways.

D. Excretion

The chloroethanes are excreted primarily in the urine and in expired air (U.S. EPA, 1979). As much as 60 to 80 percent of an inhaled dose of 1,1,1-trichloroethane (70 or 140 ppm for 4 hours) was expired unchanged by human volunteers (Monster, et al. 1979). Animal studies conducted by Yllner (1971 a,b,c,d) indicate that largest amount of chloroethanes, administered by intraperitoneal (i.p.) injection is excreted in the urine; this is followed by expiration (in the changed or unchanged form), with very little excretion in the feces. Excretion appears to be rapid, since 90 percent of i.p. administered doses of 1,2-dichloroethane or 1,1,2-trichloroethane were eliminated in the first 24 hours (U.S. EPA, 1979). However, the detection of chloroethanes in postmortem tissue samples indicates that some portion of these compounds persists in the body (Walter, et al. 1976).

IV. EFFECTS

A. Carcinogenicity

Several chlorinated ethanes have been shown to produce a variety of tumors in rats and mice in experiments utilizing oral administration. Tumor types observed after compound administration include squamous cell carcinoma of the stomach, hemangiosarcoma, adenocarcinoma of the mammary gland, and hepatocellular carcinoma (NCI, 1978a,b,c,d). The four chlorinated ethanes which have been classified as carcinogens based on animal studies are: 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane,

and hexachloroethane. Increased tumor production was also noted in animals treated with 1,1,1-trichloroethane, but high mortality during this study (NCI, 1977) caused retesting of the compound to be initiated. In vitro transformation of rat embryo cells and subsequent fibrosarcoma production by these cells when injected in vivo, indicate that 1,1,1-trichloroethane does have carcinogenic potential (Price, et al. 1978).

B. Mutagenicity

Two of the chlorinated ethanes, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, have shown mutagenic activity in the Ames Salmonella assay and for DNA polymerase deficient strain of E. coli (Brem, et al. 1974). In these two systems, 1,1,2,2-tetrachloroethane showed higher mutagenic activity than 1,2-dichloroethane (Rosenkranz, 1977).

Mutagenic effects have been produced by 1,2-dichloroethane in pea plants (Kirichek, 1974) and in Drosophila (Nylander, et al. 1978). Several metabolites of dichloroethane (chloroacetaldehyde, chloroethanol, and S-chloroethyl cysteine have also been shown to produce mutations in the Ames assay (U.S. EPA, 1979).

Testing of hexachloroethane in the Ames Salmonella assay or in a yeast assay system failed to show any mutagenic activity (Weeks, et al. 1979).

C. Teratogenicity

Inhalation exposure of pregnant rats and mice to 1,1,1-trichloroethane was shown to produce some soft

tissue and skeletal deformities; this incidence was not judged statistically significant by the Fisher Exact probability test (Schwetz, et al. 1975).

Testing of hexachloroethane administered to rats by intubation or inhalation exposure did not show an increase in teratogenic effects (Weeks, et al. 1979). Inhalation exposure of pregnant rats to 1,2-dichloroethane also failed to demonstrate teratogenic effects (Schwetz, et al. 1974; Vozovaya, 1974).

D. Other Reproductive Effects

Decreased litter size, reduced fetal weights and a reduction in live births have been reported in rats exposed to 1,2-dichloroethane (57 mg/m^{3}m four hours/day, six days/week) by inhalation (Vozovaya, 1974). 1,1-Dichloroethane retarded fetal development at exposures of 6,000 ppm. (Schwetz, et al. 1974). Higher fetal resorption rates and a decreased number of live fetuses per litter were observed in rats following administration of hexachloroethane by intubation (15, 48 or 260 ppm, 6 hours/day) or inhalation (50, 100 or 500 mg/kg/day) (Weeks, et al. 1979).

E. Chronic Toxicity

Neurologic changes and liver and kidney damage have been noted following long term human exposure to 1,2-dichloroethane (NIOSH, 1978). Cardiac effects (overstimulation) have been noted following human exposure to 1,1-dichloroethane (U.S. EPA, 1979).

Central nervous system disorders have been reported in humans exposed to 1,1,1-trichloroethane. Symptoms noted

were altered reaction time, perceptual speed, manual dexterity, and equilibrium (U.S. EPA, 1979).

Animal studies indicate that the general symptoms of toxicity resulting from exposure to the chloroethanes involve effects in the central nervous system, cardiovascular system, pulmonary system, and the liver and kidney (U.S. EPA, 1979). Laboratory animals and humans exposed to chloroethanes show similar symptoms of toxicity (U.S. EPA, 1979).

Based on data derived from animal studies, the U.S. EPA (1979) has concluded that the relative toxicity of the chloroethanes is as follows: 1,2-dichloroethane > 1,1,2,2-tetrachloroethane > 1,1,2-trichloroethane > hexachloroethane 1,1-dichloroethane > 1,1,1-trichloroethane > monochloroethane.

F. Other Relevant Information

The hepatotoxicity of 1,1,2-trichloroethane was increased in mice following acetone or isopropyl alcohol pretreatment (Traiger and Plaa, 1974). Similarly, ethanol pretreatment of mice increased the hepatic effects of 1,1,1-trichloroethane (Klassen and Plaa, 1966).

Hexobarbital sleeping times in rats were reported to be decreased following inhalation exposure to 1,1,1-trichloroethane (3,000 ppm), indicating an effect of the compound on stimulation of hepatic microsomal enzymes (Fuller, et al. 1970).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity studies were conducted on three species of freshwater organisms and two marine species.

For freshwater fish, 96-hour static LC_{50} values for the bluegill sunfish, Lepomis macrochirus, ranged from 980 µg/l hexachloroethane to 431,000 µg/l 1,2-dichloroethane, while the range of 48-hour LC_{50} values for the freshwater invertebrate Daphnia magna was 8,070 µg/l to 218,000 µg/l for hexachloroethane and 1,2-dichloroethane respectively. Among marine organisms, the sheepshead minnow (Cyprinodon vagiegatus) produced LC_{50} values ranging from 2,400 µg/l for hexachloroethane to 116,000 µg/l for pentachloroethane. The marine mysid shrimp (Mysidopsis bahia) produced LC_{50} values ranging from 940 µg/l for hexachloroethane to 113,000 µg/l for 1,2-dichloroethane. The general order of acute toxicities for the chlorinated ethanes reviewed for freshwater fish is: hexachloroethane (highest toxicity), 1,1,2,2-tetrachloroethane, 1,1,2-trichloroethane, pentachloroethane, and 1,2-dichloroethane (U.S. EPA, 1979).

B. Chronic Toxicity

The only chronic study available for the chlorinated ethanes is for pentachloroethane's chronic effects on the marine shrimp (Mysidopsis bahia), which produced a chronic value of 580 µg/l (U.S EPA, 1978).

C. Plant Effects

Effective EC_{50} concentrations, based on chlorophyll a and cell numbers for the freshwater algae Selenastrum capriconutum ranges from 87,000 µg/l for hexachloroethane to 146,000 µg/l for 1,1,2,2-tetrachloroethane, with pentachloroethane being intermediate in its phytotoxicity. For the marine algae Skeletonema costatum, a greater sensi-

tivity was indicated by effective EC_{50}- concentrations based on cell numbers and chlorophyll a ranging from 6,230 µg/l for 1,1,2,2-tetrachloroethane and 7,750 µg/l for hexachloroethane to 58,200 µg/l for pentachloroethane.

D. Residues

The bioconcentration value was greatest for hexachloroethane with a value of 139 µg/l being reported for bluegill. Bioconcentration values of 2, 8, and 9 were obtained for 1,2-dichloro, 1,1,2,2-tetrachloro, and 1,1,1-trichloroethane for bluegills. 1,1,2-Trichloroethane and 1,1,1,2-tetrachloroethane used the octanol/water coefficients to derive BCF's of 22 and 62, respectively.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on the NCI carcinogenesis bioassay data, and using a linear, non-threshold model, the U.S. EPA (1979) has estimated levels of four chloroethanes in ambient water that will result in an additional cancer risk of 10^{-5}: 1,2-dichloroethane, 7.0 µg/l; 1,1,2-trichloroethane, 2.7 µg/l; 1,1,2,2-tetrachloroethane, 1.8 µg/l; hexachloroethane, 5.9 µg/l. A draft ambient water quality criterion to protect human health has been derived by EPA for 1,1,1-trichloroethane based on mammalian toxicity data at the level of 15.7 mg/l.

Insufficient mammalian toxicological data prevented derivation of a water criterion for monochloroethane, 1,1-dichloroethane, 1,1,1,2-tetrachloroethane, or pentachloroethane (U.S. EPA, 1979).

The following compounds have had eight hour, TWA exposure standards established by OSHA: monochloroethane, 1,000 ppm; 1,1-dichloroethane, 100 ppm; 1,2-dichloroethane, 50 ppm; 1,1,1-trichloroethane, 350 ppm; 1,1,2-trichloroethane, 10 ppm; 1,1,2,2-tetrachloroethane, 5 ppm; hexachloroethane, 1 ppm.

B. Aquatic

Criteria for protecting freshwater organisms have been drafted for five of the chlorinated hydrocarbons: 62 µg/l (average concentation) not to exceed 140 µg/l for hexachloroethane; 170 µg/l not to exceed 380 µg/l for 1,1,2,2-tetrachloroethane; 440 µg/l not to exceed 1,000 µg/l for pentachloroethane; 3,900 µg/l not to exceed 8,800 µg/l for 1,2-dichloroethane; and 5,300 µg/l not to exceed 12,000 µg/l for 1,1,1-trichloroethane. For marine organisms, criteria have been drafted as: 7 µg/l (average concentration) not to exceed 16 µg/l for hexachloroethane; 38 µg/l not to exceed 87 µg/l for pentachloroethane; 70 µg/l not to exceed 160 µg/l for 1,1,2,2-tetrachloroethane; 240 µg/l not to exceed 540 µg/l for 1,1,1-trichloroethane; and 880 µg/l not to exceed 2,000 µg/l for 1,2-dichloroethane.

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No. 38

Chlorinated Naphthalenes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CHLORINATED NAPTHALENES

Summary

Chlorinated naphthalenes have been used in a variety of industries, usually as mixtures. Chronic toxicity varies with the degree of chlorination, with the more highly chlorinated species being more toxic. The clinical signs of toxicity in humans are damage to liver, heart, pancreas, gall bladder, lungs, adrenal glands, and kidney. No animal or human studies have been presented on the carcinogenicity, mutagenicity, or teratogenicity of polychlorinated naphthalenes.

Very little data on aquatic toxicity are available for individual chlorinated naphthalenes. 48-Hour and 96-hour LC_{50} values of octachloronaphthalene over 500,000 µg/l have been reported for Daphnia magna and the bluegill, respectively. A freshwater alga also resulted in a 96-hour LC_{50} value for octachloronaphthalene of over 500,000 µg/l.

Toxicity studies with aquatic organisms are confined to tests with 1-chloronaphthalene on one freshwater fish and two algal species (one fresh and one saltwater). All tests have reported 96-hour LC_{50} values of between 320 and 2,270 µg/l. Exposure of sheepshead minnow to 1-chloronaphthalene in an embryo-larval study resulted in a chronic value of 328 µg/l.

CHLORINATED NAPTHALENES

I. INTRODUCTION

This profile is based on the draft Ambient Water Quality Criteria Document for Chlorinated Naphthalenes (U.S. EPA, 1979).

Chlorinated naphthalenes consist of two fused six carbon-membered aromatic rings where any or all of the eight hydrogen atoms can be replaced with chlorine. The physical properties of the chlorinated naphthalenes are generally dependent on the degree of chlorination. Melting points range from 17°C for 1-chloronaphthalene to 198°C for 1,2,3,4-tetrachloronaphthalene. As the degree of chlorination increases, the specific gravity, boiling point, fire and flash points all increase, while the vapor pressure and water solubility decrease. Chlorinated naphthalenes have been used as the paper impregnant in automobile capacitors (mixtures of tri- and tetrachloronaphthalenes), and as oil additives for engine cleaning, and in fabric dyeing (mixtures of mono- and dichloronaphthalenes). In 1956, the total U.S. production of chlorinated naphthalenes was approximately 3,175 metric tons (Hardie, 1964).

II. EXPOSURE

A. Water

To date, polychlorinated naphthalenes have not been identified in drinking waters (U.S. EPA, 1979). However, these compounds have been found in waters or sediments adjacent to point sources or areas of heavy polychlorinated biphenyl contamination.

B. Food

Polychlorinated naphthalenes appear to be biomagnified in the aquatic ecosystem, with the degree of biomagnification being greater for the more highly chlorinated polychlorinated compounds (Walsh, et al. 1977).

Erickson, et al. (1978) also noted a higher relative biomagnification of the lowest chlorinated naphthalenes by the fruit of apple trees grown on contaminated soil. The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for Halowax 1014 (a mixture of chlorinated naphthalenes) to be 4,800 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured non-steady-state bioconcentration studies in brown shrimp.

C. Inhalation

Erickson, et al. (1978) found ambient air concentrations of polychlorinated naphthalenes ranging from 0.025 to 2.90 $\mu g/m^3$ near a polychlorinated naphthalene plant. Concentrations of trichloronaphthalene were as high as 0.95 $\mu g/m^3$, while hexachloronaphthalene concentrations never exceeded 0.007 $\mu g/m^3$.

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature.

B. Distribution

In the rat fed 1,2-dichloronaphthalene, the chemical and its metabolites were found primarily in the intestine, kidney, and adipose tissue (Chu, et al. 1977).

C. Metabolism

There appears to be appreciable metabolism in mammals of polychlorinated naphthalenes containing four chlorine atoms or less (U.S. EPA, 1979). Cornish and Block (1958) investigated the excretion of polychlorinated naphthalenes in rabbits and found 79 percent of 1-chloronaphthalene, 93 percent of dichloronaphthalene, and 45 percent of tetrachloronaphthalene

were excreted in the urine as metabolites of the parent compounds. Metabolism may involve hydroxylation alone or hydroxylation in combination with dechlorination. In some cases, an arene oxide intermediate may be formed (Ruzo, et al. 1976).

D. Excretion

In rats fed 1,2-dichloronaphthalene, initially more of the chemical and its metabolites were found in the urine; however, by the end of seven days a greater proportion had been excreted in the feces (Chu, et al. 1977). In the first 24 hours, 62 percent of the dose was excreted in the bile, as compared to 18.9 percent lost in the feces. This suggests that there is an appreciable reabsorption and enterohepatic recirculation of this particular chlorinated naphthalene.

IV. EFFECTS

No animal or human studies have been reported on the carcinogenicity, mutagenicity, or teratogenicity of chlorinated naphthalenes. No other reproductive effects were found in the available literature.

A. Chronic Toxicity

Chronic dermal exposure to penta- and hexachlorinated naphthalenes causes a form of chloracne which, if persistent, can progress to form a cyst or sterile abcess (Jones, 1941; Shelley and Kligman, 1957; Kleinfeld, et al. 1972). Workers exposed to these two isomers complained of eye irritation, headaches, fatigue, vertigo, nausea, loss of appetite, and weight loss (Kleinfeld, et al. 1972). More severe exposure to the fumes of polychlorinated naphthalenes has produced severe liver damage, together with damage to the heart, pancreas, gall bladder, lungs, adrenal glands, and kidney tubules (Greenburg, et al. 1939). Chronic toxicity in animals appears to be qualitatively the same (U.S. EPA, 1979). Polychlorinated naphthalenes containing

three or fewer chlorine atoms were found to be nontoxic, while tetrachloronaphthalene resulted in mild liver disease at levels as high as 0.7 mg/kg/-day; the higher chlorinated naphthalenes produce more severe disease at lower doses (Bell, 1953). Because of their insolubility, hepta- and octachloronaphthalene were less toxic when given in suspension than when given in solution.

B. Other Relevant Information

Drinker, et al. (1937) showed enhancement of hepatoxicity of a mixture of ethanol/carbon tetrachloride in rats pretreated with 1.16 mg/m^3 of a penta-/hexachloronaphthalene mixture in air for six weeks. In a similar study trichloronaphthalene was inactive.

V. AQUATIC TOXICITY

A. Acute Toxicity

The 96-hour LC_{50} value reported for the bluegill, Lepomis macrochirus, exposed to 1-chloronaphthalene is 2,270 µg/l (U.S. EPA, 1978). With saltwater species, exposure of the sheepshead minnow, Cyprinodon varigatus, and mysid shrimp, Mysidopsis bahia, to 1-chloronaphthalene provided 96-hour LC_{50} values of 1,290 and 370 µg/l, respectively. Daphnia magna and the bluegill, Lepomis macrochirus, have a slight sensitivity to octachloronaphthalene, with respective 48-hour and 96-hour LC_{50} values greater than 530,000 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

In the only chronic study reported (embryo-larval), exposure of 1-chloronaphthalene to the sheepshead minnow resulted in a chronic value of 329 µg/l (U.S. EPA, 1978).

C. Plant Effects

A freshwater alga, Selenastrum capricornutum, and a saltwater alga, Skeletonema costatum, when exposed to 1-chloronaphthalene, both produced 96-hour EC_{50} values ranging from 1,000 to 1,300 µg/l based on cell numbers.

Octachloronaphthalene exposure to Selenastrum capricornutum resulted in a 96-hour EC_{50} value of over 500,000 µg/l based on cell numbers (U.S. EPA, 1978).

D. Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The only standards for polychlorinated naphthalenes are the ACGIH Threshold Limit Values (TLV) adopted by the Occupational Safety and Health Administration and are as follow:

	ACGIH (1977) Threshold Limit Values	
Trichloronaphthalene	5	mg/m^3
Tetrachloronaphthalene	2	mg/m^3
Pentachloronaphthalene	0.5	mg/m^3
Hexachloronaphthalene	0.2	mg/m^3
Octachloronaphthalene	0.1	mg/m^3

There are no state or federal water quality or ambient air quality standards for chlorinated naphthalenes.

The U.S. EPA is presently evaluating the available data and has recommended that a single acceptable daily intake (ADI) of 70 µg/man/day be used for the tri-, tetra-, penta-, hexa-, and octa-chlorinated naphthalenes. This ADI will be used to derive the human health criteria for the chlorinated naphthalenes.

B. Aquatic

For 1-chloronaphthalene, the draft criterion to protect freshwater aquatic life is 29 µg/l as a 24-hour average, not to exceed 67 µg/l at any time. For saltwater aquatic species, the draft criteron is 2.8 µg/l as a 24-hour average, not to exceed 6.4 µg/l at any time (U.S. EPA, 1979).

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Chlorinated Phenols

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D. C. 20460

October 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

This document discusses the health and environmental effects of some of the di, tri, and tetra-substituted chlorinated phenols. The health effects of p-chloro-m-cresol, 2-chlorophenol, 2,4- and 2,6-dichlorophenol, 2,4,6-trichlorophenol, and pentachlorophenol are discussed in HEBD's nos. 43, 50, 75, 76, 143, and 168, respectively. The National Cancer Institute (1979) recently published the results of a bioassay indicating that 2,4,6-trichlorophenol induces cancer in rats and mice.

CHLORINATED PHENOLS

SUMMARY

Mammalian data supporting chronic effects for most of these compounds is limited. Except for trichlorophenol, there are not sufficient data to indicate whether any of the other chlorinated phenols are carcinogens. In skin painting studies, 3-chlorophenol and 2,4,5-trichlorophenol promoted papillomas. Tetrachlorophenol was not teratogenic or embryolethal in animals, but showed questionable fetotoxic effects. Chronic exposure to 4-chlorophenol produced myoneural disorders in humans and animals. Adverse health effects have been noted in workers exposed to 2,4,5-trichlorophenol. Workers chronically exposed to tetrachlorophenol and pentachlorophenol, perhaps contaminated with small amounts of chlorodibenzodioxins, developed severe skin irritations, respiratory difficulties, and headaches.

Chlorophenols are uncouplers of oxidative phosphorylation, and affect carbohydrate metabolism. Several affect the nervous system, causing convulsions.

The tainting of rainbow trout flesh has been demonstrated at exposures of 15 to 84 ug/l for several of the chlorinated phenols.

I. INTRODUCTION

This profile is based in part on the Ambient Water Quality Criteria Document for Chlorinated Phenols (U.S. EPA, 1980).

The chlorinated phenols represent a group of commercially produced substituted phenols and cresols also referred to as chlorophenols or chlorocresols. The compounds p-chloro-m-cresol, 2,4- and 2,6-dichlorophenols, 2,4,6-trichlorophenol, and pentachlorophenol are discussed in separate hazard profiles.

Purified chlorinated phenols are colorless, crystalline solids (with the exception of 2-chlorophenol which is a liquid), while the technical grades may be light tan or slightly pink due to impurities. Chlorophenols have pungent odors. In general, the volatility of chlorinated phenols decreases and the melting and boiling points increase as the number of substituted chlorine atoms increases. Although the solubility of chlorinated phenols in aqueous solutions is relatively low, it increases markedly when the pH of the solution exceeds their specific pKa. The solubilities of chlorinated phenols and chlorocresols (with the exception of 2,4,6-trichloro-m-cresol) range from soluble to very soluble in relatively non-polar solvents such as benzene and petroleum ether (U.S. EPA, 1980).

The chlorinated phenols that are most important commercially are 4-chlorophenol, 2,4,-dichlorophenol, 2,4,5-trichlorophenol, 2,3,4-tetrachlorophenol, pentachlorophenol, and 4-chloro-o-cresol. Many of the chlorophenols have no commercial application but are

produced to some extent as byproducts of the commercially important compounds. The highly toxic polychlorinated dibenzo-p-dioxins may be formed during the chemical synthesis of some chlorophenols. During the chlorination of drinking waters and wastewater effluents, chlorophenols may be inadvertently produced (U.S. EPA, 1980).

Chlorinated phenols are used as intermediates in the synthesis of dyes, pigments, phenolic resins, pesticides, and herbicides. Certain chlorophenols are used directly as flea repellants, fungicides, wood preservatives, mold inhibitors, antiseptics, disinfectants, and antigumming agents for gasoline.

Chlorinated phenols undergo photolysis in aqueous solutions as a result of ultraviolet irradiation; photodegration leads to the substitution of hydroxyl groups in place of the chlorine atoms with subsequent polymerization (U.S. EPA, 1980). Microbial degradation of chlorophenols has been reported by numerous investigators (U.S. EPA, 1980).

3-CHLOROPHENOL and 4-CHLOROPHENOL

II. EXPOSURE

Monochlorophenols have been found in surface waters in the Netherlands at concentrations of 2 to 20 ug/l (Piet and DeGrunt, 1975). Ingestion of chlorobenzene can give rise to internal exposure to 2-, 3-, and 4-chlorophenols, as chlorobenzene is metabolized to monochlorophenols (Lindsay-Smith, et al. 1972). No data were found demonstrating the presence of monochlorophenol in food.

For 4-chlorophenol the U.S. EPA has estimated the weighted average bioconcentration factor for the edible portions of all aquatic organisms consumed by Americans to be 12. This estimate is base don the octanol/water partition coefficient.

Data were not found in the available literature regarding inhalation exposure.

III. PHARMACOKINETICS

Systematic studies of the pharmacokinetics of 3- or 4-chlorophenol are not available. Dogs excreted 87 percent of administered 4-chlorophenol in the urine as sulfuric and glucuronic conjugates (Karpow, 1893, as cited in U.S. EPA, 1980).

IV. EFFECTS

A. Carcinogenicity

Information is not adequate to determine whether 3- or 4-chlorophenol posses carcinogenic properties. A 20 percent solution of 3-chlorophenol promoted papillomas when repeatedly applied to the backs of mice after initiation with dimethylbenzanthrene (Boutwell and Bosch, 1959).

B. Mutagenicity, Teratogenicity and Other Reproductive Effects

Pertinent data cannot be located in the available literature regarding mutagenicity, teratogenicity and other reproductive effects.

C. Chronic Toxicity

Rats exposed 6 hrs/day for four months to 2 mg 4-chlorophenol/m^3 showed a temporary weight loss and increased myoneural

excitability. Body temperature and hematological parameters were not altered (Gurova, 1964). Workers exposed to 4-chlorophenol had a significantly higher incidence of neurological disorders when compared with unexposed workers in the same plant. Peripheral nerve stimulation studies showed increased myoneural excitability in exposed workers. The minimum detection distance in a two-point touch discrimination test was also increased (Gurova, 1964).

D. Other Relevant Information

3- and 4-Chlorophenol are weak uncouplers of oxidative phosphorylation (U.S. EPA, 1980).

2,5-DICHLOROPHENOL, 3,4-DICHLOROPHENOL, and 3,5-DICHLOROPHENOL

II. EXPOSURE

Unspecified dichlorophenol (DCP) isomers have been detected in concentrations of 0.01 to 1.5 ug/l in Dutch surface waters (Piet and DeGrunt, 1975). Dichlorophenols have been found in flue gas condensates from municipal incinerators (Olie, et al., 1977). No data on exposure from foods or the dermal route were found. Exposure to other chemicals can result in exposure to dichlorophenols (i.e., dichlorobenzenes, lindane, and the alpha and delta isomers of 1,2,3,4,5,6-hexachlorocyclohexane are metabolized by mammals to dichlorophenols) (Kohle, et al., 1976; Foster and Saha, 1978).

III. PHARMACOKINETICS

Pharmacokinetic data specific to these dichlorophenol isomers

could not be located in the available literature. It is reasonable to assume that the dichlorophenol isomers are absorbed through the skin and from the gut, and rapidly eliminated as are other chlorophenols (U.S. EPA, 1980).

IV EFFECTS

A. Carcinogenicity

Pertinent data cannot be located in the available literature; 2,4-DCP has been selected for bioassay.

B. Mutagenicity

None of the dichlorophenols were found to be mutagenic in the Ames test with or without microsomal activation (Rasanen and Hattula, 1977). Mutagenicity in mammalian test systems has not been studied (U.S. EPA, 1980).

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data cannot be located in the available literature regarding teratogenicity, other reproductive effects and chronic toxicity.

D. Other Relevant Information

Phenol, and the lower chlorinated phenols, including 2,6-dichlorophenol are convulsants (Farquharson, et al, 1958); the latter readily penetrates the bovine lens capsule (Ismail et al., 1976), and inhibits oxidative phosphorylation in that tissue (Korte et al., 1976). The significance of these results is as yet unknown.

TRICHLOROPHENOLS*

I. EXPOSURE

Trichlorophenols have been detected in surface waters in Holland at concentrations ranging from 0.003 to 0.1 ug/l (Piet and DeGrunt, 1975). 2,4,5-Trichlorophenol can be formed from the chlorination of phenol in water (Burttschell et al., 1959).

One possible source of trichlorophenol exposure for humans is through the food chain, as a result of the metabolism by grazing animals of ingested chlorophenoxy acid herbicides 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and Silvex (2-(2,4,5-trichlorophenoxy)-propionic acid). Residues of these herbicides on sprayed forage are estimated to be 100-300 ppm. Studies in which cattle and sheep were fed these herbicides at 300, 1000, and 2000 ppm (Clark et al., 1976) showed the presence of 2,4,5-trichlorophenol in various tissues. In lactating cows fed 2,4,5-T at 100 ppm, an occasional residue of 0.06 ppm or less of trichlorophenol was detected in milk (Bjerke et al., 1972).

Exposure to other chemicals such as trichlorobenzenes, lindane, the alpha and delta isomers of 1,2,3,4,5,6- hexachlorocyclohexane, isomers of benzene hexachloride, and the insecticide Ronnel can result in exposure to trichlorophenols via metabolic degradation of the parent compound (U.S. EPA, 1980).

*The health and environmental effects of 2,4,6-trichlorophenol are more extensively discussed in HEBD No. 168.

The U.S. EPA (1980) has estimated the weighted average bioconcentration factors for the edible portions of all aquatic organisms consumed by Americans to be 130 to 2,4,5-trichlorophenol and 110 for 2,4,6-trichlorophenol. These estimates are based on the octanol/water partition coefficients for these chemicals.

Trichlorophenols are found in flue gas condensates from municipal incinerators (Olie et al., 1977).

Most commercial trichlorophenols and their derivatives contain appreciable amounts of the contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and/or its homologues (U.S. EPA, 1980). The presence of this highly toxic contaminant caused the U.S. EPA to publish a Rebuttable Presumption Against Registration (RPAR) and Continued Registration of Pesticide Products Containing 2,4,5-T (43 FR 17116). The published RPAR indicated that 2,4,5-trichlorophenol is also the subject of a separate potential RPAR.

III. PHARMACOKINETICS

A. Absorption and Distribution

The oral LD_{50} in the rat has been variously reported as 820 and 2960 mg/kg (U.S. EPA 1980). Information dealing with tissue distribution after administration of trichlorophenols could not be located in the available literature. Feeding of 2,4,5-T and Silvex to sheep and cattle produced high levels of 2,4,5-trichlorophenol in liver and kidney and low levels in muscle and fat (Clark et al., 1976).

B. Metabolism

Pertinent data could not be located in the available literature.

C. Excretion

In rats, 82 percent of an administered dose (1 ppm in the diet for 3 days) of 2,4,6-trichlorophenol was eliminated in the urine and 22 percent in the feces. Radiolabeled feces was not detected in liver, lung or fat obtained 5 days after the last dose (Korte, et al., 1976). The approximate blood half-life for 2,4,5-trichlorophenol is 20 hours, after dosing of sheep with Erbon (an herbicide which is metabolized to 2,4,5-trichlorophenol) (Wright et al., 1970).

2,4,5-Trichlorophenol was detected in 1.7 percent of urine samples collected from the general population (Kutz et al., 1978).

IV. EFFECTS

A. Carcinogenicity

A 21 percent solution of 2,4,5-trichlorophenol in acetone promoted papillomas but not carcinomas in mice after initiation with dimethylbenzanthrene (Boutwell and Bosch, 1959). 2,3,5-, 2,3,6-, 2,4,5-, and 2,4,6-Trichlorophenol were not found to be mutagenic in the Ames test with and without microsomal activation (Rasanen and Hattula, 1977). 2,4,6-Trichlorophenol induces cancer in rats and mice (NCI, 1979).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature regarding teratogenicity and other reproductive effects.

D. Chronic Toxicity

When rats were fed 2,4,5-trichlorophenol (99 percent pure) for 98 days (McCollister et al., 1961), levels of 1000 mg trichlorophenol/kg feed (assumed to be equivalent to 100 mg/kg body weight) or less produced no adverse effects as judged by behavior, mortality, food consumption, growth, terminal hematology, body and organ weights, and gross or microscopic pathology. At 10,000 mg/kg diet (1000 mg/kg body weight), growth was slowed in females. Histopathologic changes were noted in liver and kidney. There were no hematologic changes. At 3000 mg/kg feed (300 mg/kg body weight), milder histopathologic changes in liver and kidney were observed. The histopathologic changes were considered to be reversible.

Adverse health effects including chloracne, porphyria cutanea-tarda with hyperpigmentation, hirsutism and urinary excretion of porphyrins were described in workers involved in the manufacture of 2,4,5-D and 2,4,5-T (Bleiberg, et al., 1964). It is possible that some of these symptoms represent 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicosis (U.S. EPA, 1980).

E. Other Relevant Information

Studies on the subcellular effects of trichlorophenols shows them to be powerful uncouplers of oxidative phosphorylation. 2,4,5-Trichlorophenol readily penetrates the bovine eye lens (Ismael, 1975), and affects the carbohydrate metabolizing system of that tissue (Korte et al., 1976).

II. EXPOSURE

There are three isomers of tetrachlorophenol: 2,3,4,5-, 2,3,5,6, and, most importantly, 2,3,4,6-tetrachlorophenol. Commercial pentachlorophenol contains 3 to 10 percent tetrachlorophenol (Goldstein et al., 1977; Schwetz et al., 1974). Commercial tetrachlorophenol contains pentachlorophenol (27 percent) and toxic nonphenolic impurities such as chlorodibenzofurans and chlorodioxin isomers (Schwetz et al., 1974). The presence of tetrachlorophenol in drinking water has not been documented (U.S. EPA, 1980). Exposure to other chemicals such as tetrachlorobenzenes can result in exposure to tetrachlorophenols via degradation of the parent compound (Kohli et al., 1976).

Data could not be located in the available literature on ingestion from foods. The U.S. EPA (1980) has estimated a weighted average bioconcentration factor for 2,3,4,6-tetrachlorophenol of 320 for the edible portion of aquatic organisms consumed by Americans. This estimate is based on the octanol/water partition coefficient of 2,3,4,5-tetrachlorophenol.

Tetrachlorophenols have been found in flue gas condensates from municipal incinerators (Olie et al., 1977).

II. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data could not be located in the available literature regarding absorption and distribution.

B. Metabolism and Excretion

In rats, over 98 percent of an intraperitoneally administered dose of 2,3,4,6-tetrachlorophenol was recovered in the urine in 24 hours. About 66 percent was excreted as the unchanged compound and 35 percent as tetrachloro-p-hydroquinone. About 94 percent of the intraperitoneal dose of 2,3,4,6-tetrachlorophenol was recovered in the urine in 24 hours, primarily as the unchanged compound with trace amounts of trichloro-p-hydroquinone. Fifty-one percent of the intraperitoneal dose of 2,3,4,5-tetrachlorophenol was recovered in the urine in 24 hours, followed by an additional 7 percent in the second 24 hours, primarily as the unchanged compound with trace amounts of trichloro-p-hydroquinone. In these experiments, the urine was boiled to split any conjugates (Alhborg and Larsson, 1978).

Fungi methylate pentachlorophenols to the corresponding anisoles, (U.S. EPA, 1980). The chronic health effects consequences of these compounds are not known, and the possibility of methylation in mammalian liver or intestine has not been documented.

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

2,3,4,6-Tetrachlorophenol was reported to be nonmutagenic in the Ames test, both with and without microsomal activation (Rasanen et al., 1977).

C. Teratogenicity

Tetrachlorophenol did not induce teratogenic effects in rats at doses of 10 or 30 mg/kg administered on days six through 15 of gestation (Schwetz et al., 1974).

D. Other Reproductive Effects

Tetrachlorophenol produced fetotoxic effects (subcutaneous edema and delayed ossification of skull bones) in rats at doses of 10 and 30 mg/kg administered on days six through 15 of gestation (Schwetz, et al., 1974).

E. Chronic Toxicity

Sawmill workers exposed to wood dust containing 100-800 ppm 2,3,4,6-tetrachlorophenol, 30-40 ppm pentachlorophenol, 10-50 ppm chlorophenoxyphenols, 1-10 ppm chlorodibenzofurans and less than 0.5 ppm chlorodibenzo-p-dioxins developed severe skin irritations, respiratory difficulties and headaches (Levin et al., 1976).

No toxicity studies of 90 days or longer were found in the available literature.

F. Other Relevant Information

2,3,4,6-Tetrachlorophenol is a strong uncoupler of oxidative phosphorylation, and affects mixed function oxidases (U.S. EPA, 1980).

CHLORINATED PHENOLS

I. AQUATIC TOXICITY

A. Acute Toxicity (U.S. EPA, 1980)

The acute toxicity of eight chlorophenols was determined

in nine bioassays. Acute 96-hour LC_{50} values for freshwater fish ranged from 30 ug/l for the fathead minnow, Pimephales promelas, for 4-chloro-3-methylphenol to 9,040 ug/l for the fathead minnow for 2,4,6-trichlorophenol. Among the freshwater invertebrates, toxicity for Daphnia magna was tested with seven chlorophenols in eight 48-hour static bioassays. Acute LD_{50} values ranged from 290 ug/l for 2,3,4,6-tetrachlorophenol and 4-chloro-2-methylphenol to 6,040 ug/l for 2,4,6-trichlorophenol. Acute 96-hour static LC_{50} values in the sheepshead minnow ranged from 1,660 ug/l for 2,4,5-trichlorophenol to 5,350 ug/l for 4-chlorophenol. The only marine invertebrate species acutely tested has been the mysid shrimp, Mysidopsis bahia, with acute 96-hour static LC_{50} values reported as: 3,830 ug/l for 2,4,5-trichlorophenol; 21,900 ug/l for 2,3,5,6-tetrachlorophenol, and 29,700 ug/l for 4-chlorophenol.

B. Chronic Toxicity (U.S. EPA, 1980)

No data other than that presented in the specific hazard profile for 2-chlorophenol, 2,4-dichlorophenol, and pentachlorophenol were available for freshwater organisms. An embryo-larval study provided a chronic value of 180 ug/l for sheepshead minnows, Cyprinodon variegatus, exposed to 2,4-dichloro-6-methylphenol.

C. Effects on Plants (U.S. EPA, 1980)

Effective concentrations for 15 tests on four species of

freshwater plants ranged from chlorosis LC_{50} of 603 ug/l for 2,3,4,6-tetrachlorophenol to 598,584 ug/l for 2-chloro-6-methylphenol in the duckweed, Lemna minor. The marine algae, Skeletonema costatum, has been used to assess the relative toxicities of three chlorinated phenols. Effective concentrations, based on chlorophyll a content and cell growth, of 440 and 500 ug/l were obtained for 2,3,5,6-tetrachlorophenol. 2,4,5-Trichlorophenol and 4-chlorophenol were roughly two and seven times as potent, respectively, as 2,3,5,6-tetrachlorophenol.

D. Residues

Steady-state bioconcentration factors have not been calculated for the chlorinated phenols. However, based upon octanol/water partition coefficients, the following bioconcentration factors have been estimated for aquatic organisms with a lipid content of eight percent: 41 for 4-chlorophenol; 440 for 2,4,5-trichlorophenol; 380 for 2,4,6-trichlorophenol; 1,100 for 2,3,4,6-tetrachlorophenol; and 470 for 4-chloro-3-methylphenol (U.S. EPA, 1980).

E. Miscellaneous

The tainting of fish flesh by exposure of rainbow trout, Salmo gairdneri, to various chlorinated phenols has derived a range of estimated concentrations not impairing the flavor of cooked fish from 15 ug/l for 2-chlorophenol to 84 ug/l for 2,3-dichlorophenol (U.S. EPA, 1980).

II. EXISTING GUIDELINES AND STANDARDS

Water quality criteria recommended for chlorinated phenols by the U.S. EPA (1980) are given in the following table:

Recommended Water Quality Criteria

Compound	Human Health: Criterion from Organoleptic Effects (ug/l)	Human Health: Criterion from Toxicological Data (ug/l)	Aquatic Life (ug/l)
Monochlorophenols			
3-chlorophenol	0.1	none	29,700(b)
4-chlorophenol	0.1	none	
Dichlorophenols			
2,3-dichlorophenol	0.4	none	
2,4-dichlorophenol	0.3	3.09	365(a)
2,5-dichlorophenol	0.5	none	
2,6-dichlorophenol	0.2	none	
3,4-dichlorophenol	0.3	none	
Trichlorophenols			
2,4,5-trichlorophenol	1.0	1600	970(a)
2,4,6-trichlorophenol	2.0	12(c)	
Tetrachlorophenols			
2,3,4,6-tetrachlorophenol	1	none	440(b)
2,3,5,6-tetrachlorophenol			

(a) Chronic toxicity value, freshwater

(b) Acute toxicity value, saltwater

(c) Based on NCI carcinogenesis bioassay

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No. 40

Chloroacetaldehyde

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CHLOROACETALDEHYDE

Summary

No carcinogenic effects were observed in female ICR Ha Swiss mice following administration of chloroacetaldehyde via dermal application or subcutaneous injection. Mutagenic effects, varying from weak to strong, have been reported in the yeasts Schizosaccharomyces pombe and Saccharomyces cerivisiae and in certain Salmonella bacterial tester strains. There is no evidence in the available literature to indicate that chloroacetaldehyde produces teratogenic effects. Occupational exposure studies have shown chloroacetaldehyde to be a severe irritant of the eyes, mucous membranes and skin.

Data concerning the effects of chloroacetaldehyde on aquatic organisms were not found in the available literature.

CHLOROACETALDEHYDE

I. INTRODUCTION

Chloroacetaldehyde (C_2H_3ClO) is a clear, colorless liquid with a pungent odor. Its physical properties include: boiling point, 90.0-100.1°C (40 percent sol.); freezing point, -16.3°C (40 percent sol.); and vapor pressure, 100 mm at 45°C (40 percent sol.). Synonyms for chloroacetaldehyde are: monochloroacetaldehyde, 2-chloroacetaldehyde and chloroaldehyde. It is soluable in water, acetone and methanol. Primary uses of chloroacetaldehyde include: use as a fungicide, use in the manufacture of 2-aminothiazole, and use in the removal of bark from tree trunks.

II. EXPOSURE

No monitoring data are available to indicate ambient air or water levels of chloroacetaldehyde, nor is any information available on possible exposure from food.

Occupational routes of human exposure to chloroacetaldehyde are primarily through inhalation and skin absorption.

Bioaccumulation data on chloroacetaldehyde were not found in the available literature. However, 2-chloroacetaldehyde is known to be a chemically reactive compound and its half-life in aqueous solution has been reported as slightly greater than 24 hours (Van Duuren et al., 1972).

III. PHARMACOKINETICS

A. Absorption

Exposure to chloroacetaldehyde is primarily through inhalation and skin absorption.

Chloroacetaldehyde proved to be very lethal by inhalation. In an inhalation study conducted by Lawrence et al. (1972), mice were placed in a chloroacetaldehyde-free chamber and air containing chloroacetaldehyde vapor was then passed

through the chamber. The time of exposure required to kill 50% of the animals, LT_{50}, was 2.57 min. (the chamber atmosphere was calculated to have reached 45% equilibrium within that time.)

In comparison studies conducted on chloroacetaldehyde and 2-chloroethanol, chloroacetaldehyde was reported as exhibiting greater irritant activity, but having lesser penetrant capacity (Lawrence et al., 1972).

B. Distribution

Information on the distribution of chloroacetaldehyde was not found in the available literature.

C. Metabolism

Chloroacetaldehyde appears to be a metabolite of a number of compounds including 1,2-dichloroethane, chloroethanol and vinyl chloride (McCann et al., 1975).

Johnson (1967) conducted in vitro studies on rat livers, the results of which indicated that S-carboxymethylglutathione was probably formed via chloroacetaldehyde metabolic action. Based upon these studies, Johnson suggested that the same metabolic mechanism was operative in the in vivo conversion of chloroethanol to S-carboxymethylglutathione.

In recent studies, Watanabe et al. (1976a,b) reported that chloroacetaldehyde would conjugate with glutathione and cysteine leading ultimately to the types of urinary metabolites found in animals exposed to vinyl chloride. The authors reported that as nonprotein free sulfhydral concentrations are depleted, the alkylating metabolites, one of which is chloroacetaldehyde, are likely to react with protein, DNA and RNA, eliciting proportionally greater toxicity. This is in agreement with other studies conducted on vinyl chloride metabolism (Hefner et al., 1975; Bolt et al., 1977).

Chloroacetaldehyde was shown to cause the destruction of lung hemoprotein, cytochrome P450, as well as liver microsomal cytochrome P450, with no requirement for NADPH (Harper and Patel, 1978). The results suggested that the aldehydes tested, one of which was chloroacetaldehyde, were the toxic intermediates which inactivated pulmonary enzymes following exposure to some environmental agents.

D. Excretion

Information specifically on the rates and routes of chloroacetaldehyde elimination was not found in the available literature. Studies on vinyl chloride and ethylene dichloride, however, indicate that chloroacetaldehyde, as an intermediate metabolite, may ultimately convert to a number of urinary metabolites--including chloroacetic acid, S-carboxymethylcysteine and thiodiacetic acid--depending on the particular metabolic pathway involved in the biotransformation of the parent compound (Johnson, 1967; Yllner, 1971; Watanabe, 1976a,b).

IV. EFFECTS

A. Carcinogenicity

In a study on the carcinogenic activity of alkylating agents, Van Duuren et al. (1974) exposed female ICR Ha Swiss mice to 2-chloroacetaldehyde (assayed as diethylacetal). The routes of administration were via skin and subcutaneous injection. The authors reported no significant tumor induction. Later studies confirmed these findings (Goldschmidt, personal communication, 1977). However, in a report by McCann et al. (1975), the authors stated that previous reports of changes of respiratory epithelium in lungs of rats exposed to chloroacetaldehyde were suggestive of premalignant conditions.

B. Mutagenicity

Many studies have been reported which show that chloroacetaldehyde exhibits varying degrees of mutagenic activity (Huberman et al., 1975; Border

and Webster, 1976; Elmore et al., 1976; Rosenkranz, 1977). Loprieno et al. (1977) reported that 2-chloroacetaldehyde showed only feeble genetic activity when tested in the yeasts Schizosaccharomyces pombe and Saccharomyces cerevisiae. However, McCann et al. (1975) reported that chloroacetaldehyde was quite effective in reverting Salmonella bacterial tester strain TA 100, but did not revert TA 1535. In a later study, Rosenkranz (1977) found that 2-chloroacetaldehyde did display some mutagenic activity towards TA 1535.

In a study conducted by Elmore et al. (1976) the authors reported that the chloroacetaldehyde monomer and monomer hydrate were more mutagenically active that the dimer hydrate and the trimer.

Rannug et al. (1976) reported that the mutagenic effectiveness of chloroacetaldehyde is about 10^4 times higher than expected from kinetic data.

C. Teratogenicity and Other Reproductive Effects

Pertinent information could not be found in the available literature.

D. Chronic Toxicity

No chronic information could be found in the available literature. However, extensive toxicity studies conducted by Lawrence et al. (1972) revealed some subacute effects of chloroacetaldehyde on Sprague-Dawley and Black Bethesda rats. Groups of rats received .001879 and .003758 ml/kg of chloroacetaldehyde (representing 0.3 and 0.6 of the acute LD_{50} dose, respectively) daily for 30 consecutive days. Hematologic tests at the end of 30 days showed that there was a significant decrease in hemoglobin, hematocrit, and erthrocytes in the high dose group; the low dose group showed an increase in monocytes accompanied by a decrease in lymphocytes. The animals were sacrificed and organ-to-body weight ratios were calculated. Ratios for both brain and lungs were significantly greater in the low dose group, while the high dose group showed a significant increase in the brain, gonads, heart, kidneys, liver, lungs and spleen.

Histological examination did not reveal any abnormalities attributable to chloroacetaldehyde except for the lungs which showed more severe bronchitis, bronchiolitis and bronchopneumonia than were seen in controls.

In another subacute (subchronic) study, chloroacetaldehyde was administered to rats in doses of .00032, .00080, .00160 and .00320 ml/kg, three times a week for 12 weeks. Hematologic determinations showed no significant differences between controls and the two lower dose groups, while animals administered .0016 ml/kg showed a decrease in red cell count and lymphocytes and an increase in segmented neutrophiles; the highest dose group showed a significant decrease in red blood cells and hemoglobin with an increase in clotting time and segmented neutrophiles. Organ-to-body weight ratios were determined for several organs and, although there were some significant differences from controls, there were no apparent dose-related responses.

D. Acute Toxicity

Lawrence et al. (1972) conducted a series of acute toxicity tests on ICR mice, Sprague-Dawley and Black Bethesda rats, New Zealand albino rabbits and Hartlez strain guinea pigs. The results were reported as follows: the LD_{50}s (ml/kg) for chloroacetaldehyde administered intraperitoneally ranged from .00598 in mice to .00464 in rabbits; the LD_{50}s (ml/kg) for chloroacetaldehyde administered intragastrically were reported as .06918 in male mice, .07507 in female rats and .08665 in male rats; the dermal LD_{50} (ml/kg) in rabbits was reported as .2243; and the inhalation LT_{50} in mice was reported as 2.57 min.

E. Other Relevent Information

Case studies show that contact with a strong solution of chloroacetaldehyde in the human eye will likely result in permanent impairment of vision and skin contact with a potent solution will result in burns (Proctor and Hughes, 1978).

V. AQUATIC TOXICITY

Data concerning the effects of chloroacetaldehyde on aquatic organisms were not found in the available literature.

VI. EXISTING GUIDELINES

The 8-hour, TWA occupational exposure limit established for chloroacetaldehyde is 1 ppm. This TLV of 1 ppm was set to prevent irritation (ACGIH, 1976).

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No. 41

Chloroalkyl Ethers

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

41-1

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated chloroalkyl ethers and has found sufficient evidence to indicate that this compound is carcinogenic.

CHLOROALKYL ETHERS

SUMMARY

Bis(chloromethyl)ether (BCME), chloromethyl methyl ether (CMME), and bis(2-chloroethyl)ether (BCEE) have shown carcinogenic effects in animal studies following administration by various routes. Epidemiological studies in the United States, Germany, and Japan have indicated that workers exposed to BCME and CMME developed an increased incidence of respiratory tract tumors.

Testing of BCME, CMME, BCEE, and bis(2-chloroisopropyl)-ether (BCIE) in the Ames Salmonella assay and in E. coli have indicated that these compounds have mutagenic activity. Cytogenetic studies of lymphocytes from workers exposed to BCME and CMME have reported an increased frequency of aberrations, which appear to be reversible.

There is no available evidence to indicate chloroalkyl ethers produce adverse reproductive or teratogenic effects.

The information base for freshwater organisms and chloroalkyl ethers is limited to a few toxicity tests of 2-chloroethyl vinyl ether and bis(2-chloroethyl)ether. The reported 96-hour LC_{50} value for bis(2-chloroethyl)ether in the bluegill is greater than 600,000 µg/l. A "no effect" value of 19,000 µg/l was observed using the fathead minnow in an embryo-larval test. Bis(2-chloroethyl)ether has a reported bioconcentration factor of 11 in a 14-day exposure to bluegills. The half-life is from four to seven days. The reported 96-hour LC_{50} value for the bluegill and 2-chloroethyl vinyl ether is 194,000 µg/l.

CHLOROALKYL ETHERS

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for chloroalkyl ethers (U.S. EPA, 1979).

The chloroalkyl ethers are compounds with a hydrogen atom in one or both of the aliphatic ether chains substituted by a chlorine atom. The chemical reactivity of these compounds varies greatly, depending on the nature of the aliphatic groups and the placement of the chlorine atoms. The most reactive compounds are those with short aliphatic groups and those in which chlorine substitution is closest to the ether oxygen (alpha-chloro) (U.S. EPA, 1979).

As an indication of their high reactivity, chloromethyl methyl ether (CMME), bis(chloromethyl)ether (BCME), 1-chloroethyl ethyl ester, and 1-chloroethyl methyl ether decompose rapidly in water. The beta-chloroethers, bis(2-chloroethyl)-ether (BCEE) and bis(2-chloroisopropyl)ether (BCIE) are more stable in aqueous systems; they are practically insoluble in water but miscible with most organic solvents (U.S. EPA, 1979).

The chloroalkyl ethers have a wide variety of industrial and laboratory uses in organic synthesis, textile treatment, the manufacture of polymers and insecticides, in the preparation of ion exchange resins, and as degreasing agents (U.S. EPA, 1979).

While the short chain alpha-chloroalkyl ethers (BCME,, CMME) are very unstable in aqueous systems, they appear to be relatively stable in the atmosphere (Tou and Kallos, 1974). Bis(chloromethyl)ether will form spontaneously in the pres-

ence of both hydrogen chloride and formaldehyde (Frankel, et al. 1974).

II. EXPOSURE

The beta-chloroalkyl ethers have been monitored in water. Industrial effluents from chemical plants involved in the manufacture of glycol products, rubber, and insecticides may contain high levels of these ethers (U.S. EPA, 1979). The highest concentrations in drinking water of bis(2-chloroethyl)ether, bis(2-chloroisopropyl)ether, and bis-1,2-(2-chloroethoxy)ethane (BCEXE) reported by the U.S. EPA (1975) are 0.5, 1.58, and 0.03 µg/l, respectively. The average concentration of these compounds in drinking water is in the nanogram range (U.S. EPA, 1979). Chloroalkyl ethers have been detected in the atmosphere, and human inhalation exposure appears to be limited to occupational settings.

The chloroalkyl ethers have not been monitored in food (U.S. EPA, 1979). The betachloroalkyl ethers, because of their relative stability and low water solubility, may have a tendency to be bioaccumulated. The U.S. EPA (1979) has estimated the weighted bioconcentration factor to be 25 for the edible portions of fish and shellfish consumed by Americans. This is based on the measured steady-state bioconcentration studies in bluegills. Bioconcentration factors for BCME (31) and BCIE (106) have been derived using a proportionality constant related to octanol/water partition coefficients (U.S. EPA, 1979). Dermal exposure for the chloroalkyl ethers has not been determined (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Experiments with radio-labelled BCIE and BCEE in female rats and monkeys have indicated that both compounds are readily absorbed in the blood following oral administration (Smith, et al., 1977; Lingg, et al., 1978). Pertinent data could not be located in the available literature retrieved on dermal or inhalation absorption of the alkyl ethers.

B. Distribution

Species differences in the distribution of radio-labelled BCIE have been reported by Smith, et al. (1977). Monkeys, as compared to rats, retain higher amounts of radioactivity in the liver, muscle, and brain. Urine and expired air from the rat contained higher levels of radioactivity than those found in the monkey. Blood levels of BCIE in monkeys reached a peak within two hours following oral administration and then declined in a biphasic manner ($t_{1/2}$'s = 5 hours and 2 days for the first and second phases, respectively).

C. Metabolism

The biotransformation of BCEE in rats following oral administration appears to involve cleavage of the ether linkage and subsequent conjugation (Lingg, et al., 1978). Thiodiglycolic acid and chloroethanol-D-glucuronide were identified as urinary metabolites of BCEE. Metabolites of BCIE identified in the rat included 1-chloro-2-propanol, propylene oxide, 2-(1-methyl-2-chloroethoxy)-propionic acid, and carbon dioxide (Smith, et al., 1977).

D. Excretion

BCEE administered orally to rats was excreted rapidly, with more than 60 percent of the compound excreted within 24 hours. Virtually all of this elimination was via the urine (Lingg, et al., 1978).

IV. EFFECTS

A. Carcinogenicity

There are several studies with bis(chloromethyl)-ether (BCME), chloromethyl methyl ether (CMME), and bis(2-chloroethyl)ether (BCEE) that show carcinogenic effects. BCME induced malignant tumors of the male rat respiratory tract following inhalation exposure (Kuschner, et al., 1975). Application of BCME and BCEXE to the skin of mice produced skin tumors (Van Duuren, et al., 1968), while subcutaneous injection of BCME to newborn mice induced pulmonary tumors (Gargus, et al., 1969).

Oral administration of bis(2-chloroethyl)ether (BCEE) to mice has been shown to increase the incidence of hepatocellular carcinomas in males (Innes, et al., 1969).

Epidemiological studies of workers in the United States, Germany, and Japan who were occupationally exposed to BCME and CMME have indicated these compounds are human respiratory carcinogens (U.S. EPA, 1979).

Both BCME and CMME have been shown to accelerate the rate of lung tumor formation in Strain A mice following inhalation exposure (Leong, et al., 1971). BCME and BCEE have shown tumor initiating activity for mouse skin, while CMME showed only weak initiating activity (U.S. EPA, 1979).

Preliminary results of a National Cancer Institute study indicate that oral administration of BCIE does not produce an increase in tumor incidence (U.S. EPA, 1979).

B. Mutagenicity

Testing of the chloroalkyl ethers in the Ames Salmonella assay on E. coli have indicated that BCME, CMME, BCIE, and BCEE all produced mutagenic effects (U.S. EPA, 1979). BCEE has also been reported to induce mutations in Saccharomyces cerevisiae (U.S. EPA, 1979). Neither BCEE nor BCIE showed mutagenic effects in the heritable translocation test in mice (Jorganson, et al. 1977). An increase in cytogenetic aberrations in the lymphocytes of workers exposed to BCME and CMME was reported by Zudova and Landa (1977); the frequency of aberrations decreased following the removal of workers from exposure.

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Chronic occupational exposure to CMME contaminated with BCME has produced bronchitis in workers (U.S. EPA, 1979). Cigarette smoking has been found to act synergistically with CMME exposure to produce bronchitis (Weiss, 1976, 1977).

Animal studies have indicated that chronic exposure to BCIE produces liver necrosis in mice. Exposure in rats causes major effects on the lungs, including congestion and pneumonia (U.S. EPA, 1979).

E. Other Relevant Information

The initiating activity of several chloroalkyl ethers indicates that these compounds may interact with other agents to produce skin papillomas (Van Duuren, et al., 1969, 1972).

V. AQUATIC TOXICITY

A. Acute Toxicity

The reported static 96-hour LC_{50} value for the bluegill (Lepomis macrochirus) with 2-chloroethyl vinyl ether (concentration unmeasured) is 194,000 µg/l (U.S. EPA, 1978). The 96-hour LC_{50} values for the bluegill could not be determined in a static test for bis(2-chloroethyl)ether with exposure concentrations as high as 600,000 µg/l. The concentration of the ether was not monitored during the bioassay. Pertinent data could not be located in the available literature on saltwater species.

B. Chronic Toxicity

An embryo-larval test was conducted with bis(2-chloroethyl)ether and the fathead minnow, (Pimephales promelas). Adverse effects were not observed at test concentrations as high as 19,000 µg/l.

C. Plant Effects

Pertinent data could not be located in the available literature.

D. Residues

Using bis(2-chloroethyl)ether, a bioconcentration factor of 11 was determined during a 14-day exposure of bluegills (U.S. EPA, 1979). The half-life was observed to be between four and seven days.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on animal carcinogenesis bioassays, and using a linear, nonthreshold model, the U.S. EPA (1979) has estimated the following ambient water levels of chloroalkyl ethers which will produce an increased cancer risk of 10^{-5}: BCIE, 11.5µg/l; BCEE, 0.42 µg/l; and BCME 0.02 ng/l.

Eight-hour TWA exposure values (TLV) for the following chloroalkyl ethers have been recommended by the American Conference of Governmental and Industrial Hygienists (ACGIH, 1978): BCME, 1 ppb; BCEE, 5 ppm.

B. Aquatic

Freshwater and saltwater drafted criteria have not been derived for any chloroalkyl ethers because of insufficient data (U.S. EPA, 1979).

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No. 42

Chlorobenzene

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CHLOROBENZENE

Summary

There is little data on the quantities of chlorobenzene in air, water and food, although this compound has been identified in these media. Chronic exposure to chlorobenzene appears to cause a variety of pathologies under different experimental regimens; however, the liver and kidney appear to be affected in a number of species. There have been no studies conducted to evaluate the mutagenic, teratogenic, or carcinogenic potential of chlorobenzene.

Four species of freshwater fish have 96-hour LC_{50} values ranging from 24,000 to 51,620 µg/l. Hardness does not significantly affect the values. In saltwater, a fish and shrimp had reported 96-hour LC_{50} values of 10,500 µg/l and 6,400 µg/l, respectively. No chronic data involving chlorobenzene are available. Algae, both fresh and saltwater, are considerably less sensitive to chlorobenzene toxicity than fish and invertebrates.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Benzenes (U.S. EPA, 1979).

Chlorobenzene, most often referred to as monochlorobenzene (MCB; C_6H_5Cl; molecular weight 112.56), is a colorless liquid with a pleasant aroma. Monochlorobenzene has a melting point of -45.6°C, a boiling point of 131-132°C, a water solubility of 488 mg/l at 25°C, and a density of 1.107 g/ml. Monochlorobenzene has been used as a synthetic intermediate in the production of phenol, DDT, and aniline. It is also used as a solvent in the manufacture of adhesives, paints, polishes, waxes, diisocyanates, pharmaceuticals and natural rubber (U.S. EPA, 1979).

Data on current production derived from U.S. International Trade Commission reports show that between 1969 and 1975, the U.S. annual production of monochlorobenzene decreased by 50 percent, from approximately 600 million pounds to approximately 300 million pounds (U.S. EPA, 1977).

II. EXPOSURE

A. Water

Based on the vapor pressure, water solubility, and molecular weight of chlorobenzene, Mackay and Leinonen (1975) estimated the half-life of evaporation from water to be 5.8 hours. Monochlorobenzene has been detected in ground water, "uncontaminated" upland water, and in waters contaminated either by industrial, municipal or agricultural waste. The concentrations ranged from 0.1 to 27 µg/l, with raw waters having the lowest concentration and municipal waste the highest (U.S. EPA, 1975, 1977). These estimates should be considered as gross estimates of exposure, due to the volatile nature of monochlorobenzene.

B. Food

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of monochlorobenzene to be 13 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on octanol/-water partition coefficients.

C. Inhalation

Data have not been found in the available literature which deal with exposure to chlorobenzene outside of the industrial working environment.

III. PHARMACOKINETICS

A. Absorption

There is little question, based on human effects and mammalian toxicity studies, that chlorobenzene is absorbed through the lungs and from the gastrointestinal tract (U.S. EPA, 1977).

B. Distribution

Because chlorobenzene is highly lipophilic and hydrophobic, it would be expected that it would be distributed throughout total body water space, with body lipid providing a deposition site (U.S. EPA, 1979).

C. Metabolism

Chlorobenzene is metabolised via an NADPH-cytochrome P-448 dependent microsomal enzyme system. The first product, and rate limiting step, is a epoxidation; this is followed by formation of diphenolic and monophenolic compounds (U.S. EPA, 1979). Various conjugates of these phenolic derivatives are the primary excretory products (Lu, et al. 1974). Evidence indicates that the metabolism of monochlorobenzene results in the formation of toxic intermediates (Kohli, et al. 1976). Brodie, et al. (1971) induced microsomal enzymes with phenobarbital and showed a potentiationin in 'the toxicity of monochlorobenzene. However, the use of 3-methylcho-

lanthrene to induce microsomal enzymes provided protection for rats (Oesch, et al. 1973). The metabolism of chlorobenzene may also lead to the formation of carcinogenic active intermediates (Kohli, et al. 1976).

D. Excretion

The predominant route of elimination is through the formation of conjugates of the metabolites of monochlorobenzene and elimination of these conjugates by the urine (U.S. EPA, 1979). The types of conjugates formed vary with species (Williams, et al. 1975). In the rabbit, 27 percent of an administered dose appeared unchanged in the expired air (Williams, 1959).

IV. EFFECTS

Pertinent data could not be located in the available literature on the carcinogenicity, mutagenicity, teratogenicity, or other reproductive effects of chlorobenzene.

A. Chronic Toxicity

Data on the chronic toxicity of chlorobenzene is sparse and somewhat contradictory. "Histopathological changes" have been noted in lungs, liver and kidneys following inhalation of monochlorobenzene (200, 475, and 1,000 ppm) in rats, rabbits and guinea pigs (Irish, 1963). Oral administration of doses of 12.5, 50 and 250 mg/kg/day to rats produced little pathological change, except for growth retardation in males (Knapp, et al. 1971).

B. Other Relevant Information

Chlorobenzene appears to increase the activity of microsomal NADPH-cytochrome P-450 dependent enzyme systems. Induction of microsomal enzyme activity has been shown to enhance the metabolism of a wide variety of drugs, pesticides and other xenobiotics (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

Pickering and Henderson (1966) reported observed 96-hour LC_{50} values for goldfish, Carassius auratus, guppy, Poecilia reticulatus, and bluegill, Lepomis macrochirus, to be 51,620, 45,530, and 24,000 µg/l, respectively, for chlorobenzene. Two 96-hour LC_{50} values for chlorobenzene and fathead minnows, Pimephales promelas, are 33,930 µg/l in soft water (20 mg/l) and 29,120 µg/l in hard water (360 mg/l), indicating that hardness does not significantly affect the acute toxicity of chlorobenzene (U.S. EPA, 1978). With Daphnia magna, an observed 48-hour EC_{50} value of 86,000 µg/l was reported. In saltwater studies, sheepshead minnow had a reported unadjusted LC_{50} (96-hour) value of 10,500 µg/l, with a 96-hour EC_{50} of 16,400 µg/l for mysid shrimp (U.S. EPA, 1978).

B. Chronic Toxicity

No chronic toxicity studies have been reported on the chronic toxicity of chlorobenzene and any salt or freshwater species.

C. Plant Effects

The freshwater alga Selenastrum capricornutum is considerably less sensitive than fish and Daphnia magna. Based on cell numbers, the species has a reported 96-hour EC_{50} value of 224,000 µg/l. The saltwater alga, Skeletonema costatum, had a 96-hour EC_{50}, based on cell numbers of 341,000 µg/l.

D. Residues

A bioconcentration factor of 44 was obtained assuming an 8 percent lipid content of fish.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) threshold limit value for chlorobenzene is 350 mg/m^3. The acceptable daily intake (ADI) was calculated to be 1.008 mg/day. The U.S. EPA (1979) draft water criterion for chlorobenzene is 20 µg/l, based on threshold concentration for odor and taste.

B. Aquatic

For chlorobenzene, the drafted criterion to protect freshwater aquatic life is 1,500 µg/l as a 24-hour average; the concentration should not exceed 3,500 µg/l at any time. To protect saltwater aquatic life, a draft criterion of 120 µg/l as a 24-hour average with a concentration not exceeding 280 µg/l at any time has been recommended (U.S. EPA, 1979).

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No. 43

p-Chloro-m-cresol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SUMMARY

p-Chloro-m-cresol has been found to be susceptible to biodegradation under aerobic conditions in a synthetic sewage sludge. It has been found to be formed by the chlorination of waters receiving effluents from electric power-generating plants and by the chlorination of the effluent from a domestic sewage treatment facility.

Very little information on the health effects of p-chloro-m-cresol was located. p-Chloro-m-cresol has been characterized as very toxic in humans, although support for this statement is limited. In rats, a subcutaneous LD_{50} of 400 mg/kg and an oral LD_{Lo} of 500 mg/kg have been reported.

I. INTRODUCTION

p-Chloro-m-cresol (4-chloro-3-methylphenol; C_7H_7ClO; molecular weight 142.58) is a solid (dimorphous crystals) at room temperature. The pure compound is odorless, but it has a phenolic odor in its most common, impure form. Its melting point is 55.5°C and its boiling point is 235°C. It is soluble in water and many organic solvents (Windholz 1976).

A review of the production range (includes importation) statistics for p-chloro-m-cresol (CAS No. 59-50-7) as listed in the initial TSCA Inventory (U.S. EPA 1979) shows that between 10,000 and 90,000 pounds of this chemical were produced/imported in 1977.*

p-Chloro-m-cresol is used as an external germicide and as a preservative for glues, gums, paints, inks, textiles and leather goods (Hawley 1971). It is also used as a preservative in cosmetics (Wilson 1975, Liem 1977). EPA (1973) indicates that p-chloro-m-cresol is "cleared for use in adhesives used in food packaging."

*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

II. EXPOSURE

A. Environmental Fate

Voets et al. (1976) reported that p-chloro-m-cresol was quite susceptible to microbial breakdown under aerobic conditions in an organic medium (synthetic sewage sludge), while degradation under aerobic conditions in a mineral solution (simulating oligotrophic aquatic systems) was relatively difficult. No degradation was observed in either system under anaerobic conditions.

B. Bioconcentration

No studies on the bioconcentration potential of this compound were found. Based on its solubility, p-chloro-m-cresol would not be expected to have a high bioconcentration potential.

C. Exposure

Human exposure to p-chloro-m-cresol occurs through its presence in certain cosmetics and in a variety of other consumer products in which it is used as a preservative (Wilson 1975, Liem 1977).

p-Chloro-m-cresol has been found to be formed by the chlorination of water from a lake and a river receiving cooling waters from electric power-generating plants, at concentrations of 0.2 ug/l and 0.7 ug/l, respectively. It has also been found to be formed by the chlorination of the effluent from a domestic sewage treatment facility at a concentration of 1.5 ug/l (Jolley et al. 1975).

III. PHARMACOKINETICS

No information was found.

IV. HEALTH EFFECTS

Very little toxicological data for p-chloro-m-cresol was available. The subcutaneous LD_{50} for p-chloro-m-cresol in rats is 400 mg/kg (NIOSH 1975). The oral LD_{Lo} for p-chloro-m-cresol in rats is 500 mg/kg. In mice the intraperitoneal LD_{Lo} is 30 mg/kg and the subcutaneous LD_{Lo} is 200 mg/kg

(U.S. DHEW 1978). One author has rated p-chloro-m-cresol as very toxic, with a probable lethal dose to humans of 50-500 mg/kg. (Von Oettingen as quoted in Gosselin et al. 1976). p-Chloro-m-cresol was also reported as non-irritating to skin in concentrations of 0.5 to 1.0% in alcohol.

V. AQUATIC TOXICITY

A. Acute

The only information available is that for Daphnia pulex. The 96-hour LC_{50} for p-chloro-m-cresol exposure is 3.1 mg/L (Jolley et al. 1977).

VI. GUIDELINES

No guidelines for exposure to p-chloro-m-cresol were located.

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No. 44

Chloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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CHLOROETHANE

SUMMARY

There is no available evidence which indicates that monochloroethane produces carcinogenic, mutagenic, or teratogenic effects. Symptoms produced by human poisoning with monochloroethane include central nervous system depression, respiratory failure, and cardiac arrhythmias. The results of animal studies indicate that liver, kidney, and cardiac toxicity may be produced by monochloroethane.

Data examining the toxic effects of chloroethane on aquatic organisms were not available.

CHLOROETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms have been replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. Monochloroethane (chloroethane, M.W. 64.52) is a gas at room temperature. The compound has a boiling point of 13.1°C, a melting point of -138.7°C, a specific gravity of 0.9214, and a solubility of 5.74 g/l in water (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds.

The 1976 production of monochloroethane was 335×10^3 tons/year (U.S. EPA, 1979a).

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes present in raw and finished waters are due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water

or treatment of sewage. Air levels of chloroethanes are produced by evaporation of these volatile compounds widely used as degreasing agents and in dry cleaning operations (U.S. EPA, 1979a).

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976). Data on the levels of monochloroethanes in foods is not available.

An average bioconcentration factor for monochloroethane in fish and shellfish has not been derived by the EPA.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature on monochloroethane for absorption, distribution, metabolism, and excretion. However, the reader is referred to a more general treatment of chloroethanes (U.S. EPA, 1979b), which indicates rapid absorption of chloroethanes following oral or inhalation exposure; widespread distribution of the chloroethanes throughout the body; enzymatic dechlorination and oxidation to the alcohol and ester forms; and excretion of the chloromethanes primarily in the urine and expired air. Specifically for monochloroethane, absorption following dermal application is minor; and excretion appears to be rapid, with the major portion of the injected compound excreted in the first 24 hours (U.S. EPA, 1979a)

IV. EFFECTS

Pertinent data could not be located in the available literature on monochloroethane for carcinogenicity, mutagenicity, teratogenicity and other reproductive effects.

A. Chronic Toxicity

Human symptons of monochloroethane poisoning indicate central nervous system depression, respiratory failure, and cardivascular symptoms, including cardiac arrhythmias (U.S. EPA, 1979a). Animal toxicity has indicated kidney damage and fatty infiltration of the liver, kidney, and heart (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDLINES AND STANDARDS

A. Human

The eight-hour TWA standard prepared by OSHA for monochloroethane is 1,000 ppm.

Sufficient data are not available to derive a criterion to protect human health from exposure to monochloroethane in ambient water.

B. Aquatic

There are not sufficient toxicological data to calculate exposure criteria.

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No. 45

Chloroethene

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

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CHLOROETHENE

(VINYL CHLORIDE)

Summary

Vinyl chloride has been used for over 40 years in the production of polyvinyl chloride. Animal studies indicate that vinyl chloride is not teratogenic, but it has been found to be mutagenic in several biologic test systems. Vinyl chloride has been found to be carcinogenic in laboratory animals and has been positively associated with angiosarcoma of the liver in humans. Recently "vinyl chloride disease", a multisystem disorder, has been described in workers exposed to vinyl chloride.

Data are lacking concerning the effects of vinyl chloride in freshwater and saltwater aquatic life.

CHLOROETHENE

(VINYL CHLORIDE)

I. INTRODUCTION

Vinyl chloride (CH_2CHCl; molecular weight 62.5) is a highly flammable chloro-olefinic hydrocarbon which emits a sweet or pleasant odor, and has a vapor density slightly more than twice that of air. Its physical properties include: melting point, -153.8°C; and solubility in water, 0.11g/100 g at 28°C. It is soluble in alcohol and very soluble in ether and carbon tetrachloride (Weast, 1972). Many salts of metals (including silver, copper, iron, platinum, iridium) have the ability to complex with vinyl chloride resulting in its increased solubility in water. Conversely, alkali metal salts, such as sodium or potassium chloride, may decrease the solubility of vinyl chloride in aqueous solutions (Fox, 1978).

Vinyl chloride has been used for over 40 years in the production of polyvinyl chloride (PVC), which in turn is the most widely used material in the manufacture of plastics. Production of vinyl chloride in the U.S. reached slightly over 5 billion pounds in 1977 (U.S. Int. Trade Comm, 1978).

Vinyl chloride and polyvinyl chloride are used in the manufacture of numerous products in building and construction, the automotive industry, for electrical wire insulation and cables, piping, industrial and household equipment, packaging for food products, medical supplies, and are depended upon heavily by the rubber, paper and glass industries (Maltoni, 1976a).

In the U.S. about 1500 workers were employed in monomer synthesis and an additional 5000 in polymerization operations (Falk,

et al. 1974). As many as 350,000 workers were estimated to be associated with fabricating plants (U.S. EPA, 1974). By 1976, it was estimated that worldwide nearly one million persons were associated with manufacturing goods derived from PVC (Maltoni, 1976a). Potential sources of population exposure to vinyl chloride are emissions from PVC fabricating plants, release of monomers from various plastic products, and emissions from the incineration of PVC products (U.S. EPA, 1975).

II. EXPOSURE

A. Water

Small amounts of vinyl chloride may be present in public water supplies as a result of industrial waste water discharges. The levels of vinyl chloride in effluents vary considerably depending on the extent of in-plant treatment of waste water. Vinyl chloride in samples of waste water from seven areas ranged from 0.05 ppm to 20 ppm, typical levels being 2-3 ppm (U.S. EPA, 1974). The low solubility and high volatility of vinyl chloride tend to limit the amounts found in water; however, the presence of certain salts may increase the solubility and therefore could create situations of concern (U.S. EPA, 1975).

Polyvinyl chloride pipe used in water distribution systems provides another source of low levels of vinyl chloride in drinking water. In a study by the U.S. EPA of five water distribution systems which used PVC pipes, water from the newest, longest pipe system had the highest vinyl chloride concentration (1.4 µg/l) while the two oldest systems only had traces of vinyl chloride (0.3 µg/l and 0.6 µg/l) (Dressman and McFarren, 1978). The National

Science Foundation (NSF) has adopted a voluntary standard of 10 ppm or less of residual monomer in finished pipe and fittings. Three times a year NSF samples water supplies in several cities. In 1977, more than 95 percent of the samples conformed to the standard; however, levels of 5.6 μg/l and 0.27 μg/l vinyl chloride have been detected in at least two cities.

B. Food

Small quantities of vinyl chloride are ingested by humans when the entrained monomer migrates into foods packaged in PVC wrappings and containers. The solubility of vinyl chloride in foods packaged in water is low (0.11 percent); however, the monomer is soluble in alcohols and mineral oil. In 1973, the U.S. Treasury Department banned the use of vinyl chloride polymers for packaging alcoholic beverages (Int. Agency Res. Cancer, 1974). The FDA analyzed a number of PVC packaged products in 1974. The concentrations ranged from "not detectable" to 9,000 ppb.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of vinyl chloride to be 1.9 for the edible portions of fresh and shellfish consumed by Americans. This estimate was based on the octanol/water coefficient of vinyl chloride.

C. Inhalation

Inhalation of vinyl chloride is the principal route of exposure to people working in or living near vinyl chloride industries. After 1960, Dow Chemical Co. was successful in reducing exposures to workers to about 25 ppm level, though levels up to 500 ppm still occurred. Inhalation exposures drastically dropped after appropriate controls were instituted following case reports of vinyl chloride induced angiosarcoma of the liver in workers and experimental animals (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Vinyl chloride is rapidly absorbed through the lungs and enters the blood stream (Duprat, et al. 1977).

B. Distribution

The liver of rats accumulates the greatest percentage of vinyl chloride and/or metabolites of vinyl chloride 72 hours after a single oral dose (Watanabe, et al. 1976). Ten minutes after a 5-minute inhalation exposure to vinyl chloride at 10,000 ppm, the compound was found in the liver, bile duct, stomach, and kidney of rats (Duprat, et al. 1977). Immediately after exposure by inhalation to ^{14}C-vinyl chloride at 50 ppm for 5 hours, the percent incorporated as ^{14}C/radioactivity per gram of tissue was highest for kidney (2.13), liver (1.86), and spleen (0.73). Forty-eight hours after the beginning of exposure, labeled material could still be detected in these tissues.

C. Metabolism

Detoxification of vinyl chloride takes place primarily in the liver by oxidation to polar compounds which can be conjugated to glutathione and/or cysteine (Hefner, et al. 1975). These covalently bond metabolites are then excreted in the urine.

Vinyl chloride is metabolized extensively by rats in vivo and the metabolic pathways appear to be saturable. The postulated primary metabolic pathway involves alcohol dehydrogenase and, for rats, appears to be saturated by exposures to concentrations exceeding 220 to 250 ppm. In rats exposed to higher concentrations, metabolism of vinyl chloride is postulated to occur via a secondary

pathway involving epoxidation and/or peroxidation. Present data indicates that vinyl chloride is metabolized to an activated carcinogen electrophile and is capable of covalent reaction with nucleophilic groups or cellular macromolecules (U.S. EPA, 1979).

There is ample evidence that the mixed function oxidase (MFO) system may be involved in the metabolism of vinyl chloride. Rat liver microsomes catalyze the covalent binding of vinyl chloride metabolites to protein and nucleic acids; chloroethylene oxide is thought to be the primary microsomal metabolite capable of alkylating these cellular macromolecules (Kappus, et al. 1975; 1976; Laib and Bolt, 1977). Hathway (1977) reports in vitro depurination of calf thymus DNA by chloroacetaldehyde identical to that observed in hepatocyte DNA following the administration of vinyl chloride to rats in vitro.

D. Excretion

Watanabe, et al. (1976) monitored the elimination of vinyl chloride for 72 hours following a single oral dose administered to rats. The total ^{14}C-activity recovered at each dose level ranged from 82-92 percent. At a dose level of 1 mg/kg, 2 percent was exhaled as vinyl chloride, 13 percent was exhaled as carbon dioxide, 59 percent was eliminated in the urine and 2 percent in the feces. Excretion of vinyl chloride at a dose level of 100 mg/kg was 66 percent exhaled as vinyl chloride, 2.5 percent as carbon dioxide, 11 percent in the urine and 0.5 percent in the feces. Administration by inhalation produced almost the same results.

Green and Hathway (1975) found that more than 96 percent of 250 µg ^{14}C-vinyl chloride administered via intragastric, intra-

venous or intraperitoneal routes was excreted within 24 hours. The rats given vinyl chloride by the intragastric route exhaled 3.7 percent as vinyl chloride, 12.6 percent as CO_2; 71.5 percent of the labeled material was in the urine and 2.8 percent in the feces. Intravenous injections resulted in 9.9 percent exhaled as vinyl chloride, 10.3 percent as CO_2; 41.5 percent in the urine and 1.6 percent in the feces.

IV. EFFECTS

A. Carcinogenicity

The carcinogenicity of vinyl chloride has been investigated in several animal studies. Viola, et al. (1971) induced skin epidermoid carcinomas, lung carcinomas or bone steochrondromas in 24/25 male rats exposed to 30,000 ppm vinyl chloride intermittently for 12 months. Tumors appeared between 10 and 11 months. Caputo, et al. (1974) observed carcinomas and sarcomas in all groups of male and female rats inhaling various concentrations of vinyl chloride except those exposed to 50 ppm.

Maltoni and Lefemine (1974a,b; 1975) reported on a series of experiments concerning the effects on rats, mice, and hamsters of inhalation exposure to vinyl chloride at concentrations ranging from 50 to 10,000 ppm for varying periods of time. The animals were observed for their entire lifetime. Angiosarcomas of the liver occurred in all three species, as well as tumors at several other sites. A differential response between the sexes was not reported.

Maltoni (1976b) observed four subcutaneous angiosarcomas, four zymbal gland carcinomas, and one nephroblastoma in

66 offspring of rats exposed by inhalation 4 hours/day to 10,000 or 6,000 ppm vinyl chloride from the 12th to 18th day of gestation. Liver angiosarcomas were also observed in rats administered vinyl chloride via stomach tube for 52 weeks.

Recent experiments by Lee, et al. (1977) with rats and mice confirm the carcinogenicity of vinyl chloride. Each species was exposed to 50,250 or 1000 ppm vinyl chloride or 55 ppm vinylene chloride 6 hr/day, 5 days/week for 1-12 months. After 12 months, bronchioalveolar adenomas, mammary gland tumors, and angiosarcomas in the liver and other sites developed in mice exposed to all three dose levels of vinyl chloride. Rats exposed to 250 ppm or 100 ppm vinyl chloride developed angiosarcoma in the liver, lung and other sites (Lee, et al. 1978).

The primary effect associated with vinyl chloride exposure in man is an increased risk of cancer in several organs including angiosarcoma of the liver. Liver angiosarcoma is an extremely rare liver cancer in humans, with 26 cases reported annually in the U.S. (Natl. Cancer Inst., 1975). Human data on the carcinogenic effects of vinyl chloride have been obtained primarily from cases of occupational exposures of workers. The latent period has been estimated to be 15-20 years; however, recent case reports indicate a longer average latent period (Spirtas and Kaminski, 1978).

A number of epidemiological studies of vinyl chloride have been reported (U.S. EPA, 1979). Tabershaw/Cooper Associates (1974) found no increase in the overall mortality rate for vinyl chloride workers nor significant increases in standard mortality

rates (SMR's) for malignant neoplasms. Reexamination of this data by Ott, et al. (1975) including more clearly defined exposure levels confirmed the previous findings: no increase over that expected for malignant neoplasms in the low exposure group (TWA 10-100 ppm vinyl chloride) and a non-significant increase in deaths due to malignant neoplasms in the high exposure group (TWA, greater than 200 ppm).

However, liver cancer death were twelve-fold, and brain cancer deaths were five-fold greater than that expected in a study by Wagoner (1974). Likewise, Monson, et al. (1974) found death due to cancer to be 50 percent higher than expected in vinyl chloride workers who died from 1947-1973, including a 900 percent increase in cancers of the liver and biliary tract.

In the most recent update of the NIOSH register, a total of 64 cases of hepatic angiosarcoma have been identified worldwide among vinyl chloride exposed industrial workers (Spirtas and Kaminski, 1978). Twenty-three of these cases were reported in the United States. Six cases were documented since 1975.

B. Mutagenicity

Vinyl chloride has been found to be mutagenic in a number of biological systems including: metabolically activated systems using Salmonella typhimurium; back mutation systems using Escherichia coli; forward mutation and gene coversion in yeast; and germ cells of Drosophila and Chinese hamster V79 cells (U.S. EPA, 1979).

The dominant lethal assay was used to test the mutagenicity of inhaled vinyl chloride in mice. Levels as high as 30,000

ppm (6 hours/day for 5 days) yielded negative results (Anderson, et al. 1976).

Several investigators have observed a significantly higher incidence of chromosomal aberrations in the lymphocytes of workers chronically exposed to high levels of vinyl chloride (Ducatman, et al. 1975; Purchase, et al. 1975; Funes-Cravioto, et al. 1975).

C. Teratogenicity

Animal studies using mice, rats and rabbits, indicate that inhalation of vinyl chloride does not induce gross teratogenic abnormalities in offspring of mothers exposed 7 hours daily to concentrations ranging from 50 to 2,500 ppm (John, et al. 1977); however, excess occurrences of minor skeletal abnormalities were noted. Increased fetal death was noted at the higher exposure levels. These findings were confirmed by Radike, et al. (1977a) who exposed rats to 600-6,000 ppm vinyl chloride, 4 hours daily on the 9th to the 21st day of gestation.

Further examination is needed of reported high rates of congenital defects in three small communities in which vinyl chloride polymerization plants are located (U.S. EPA, 1979).

D. Other Reproductive Effects

No effect on fertility in mice was noted in a dominant lethal assay conducted by Anderson, et al. (1976).

E. Chronic Toxicity

There are numerous clinical indications that chronic exposure to vinyl chloride is toxic to humans (U.S. EPA, 1979). Hepatitis-like changes, angioneurosis, Raynaud's syndrome, derma-

titis, acroosteolysis, thyroid insufficiency, and hepatomegaly have been reported around the world. Other long term effects include functional disturbances of the central nervous system with adrenergic sensory polyneuritis (Smirnova and Granik, 1970); thrombocytopenia, splenomegaly, liver malfunction with fibrosis, pulmonary changes (Lange, et al. 1974); and alterations in serum enzyme levels (Makk, et al. 1976).

F. Other Relevant Information

Pretreatment of rats with pyrazole (an alcohol dehydrogenose inhibitor) and ethanol inhibits the metabolism of vinyl chloride (Hefner, et al. 1975). This indicates the involvement of alcohol dehydrogenose in the metabolism of vinyl chloride.

The chronic ingestion of alcohol was found to increase the incidence of liver tumors and tumors in other sites in individuals exposed to vinyl chloride (Radike, 1977b).

Jaeger (1975) conducted experiments to determine the interaction between vinylidene chloride (1,1-DCE) and vinyl chloride. In this experiment, the effects of 4-hour exposures to 200 ppm of 1,1-DCE and 1,000 ppm vinyl chloride were less than if 1,1-DCE was given alone.

V. AQUATIC TOXICITY

A. Pertinent information relevant to acute and chronic toxicity, plant effects and residues for vinyl chloride were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The current federal OSHA standard for vinyl chloride is 1 ppm (TWA) with a maximum of 5 ppm for a period of no longer than 15 minutes in 1 day. (39 FR 35890 (Oct. 4, 1979)).

In 1974, a notice to cancel registrations of pesticide spray products containing vinyl chloride as a propellant was issued (39 FR 14753 (April 26, 1974)). Other aerosol products, such as hair spray, utilizing vinyl chloride as a propellant were banned from the market in the U.S. and other countries (Int. Agency Res. Cancer, 1974). The U.S. EPA proposed in 1975 and 1976 an emission standard of 10 ppm vinyl chloride at the stack for industry.

The draft ambient water quality criterion for vinyl chloride has been set to reduce the human lifetime cancer risk level to 10^{-5}, 10^{-6} and 10^{-7} (U.S. EPA, 1979). The corresponding criteria are 517 µg/l, 51.7 µg/l and 5.17 µg/l, respectively. The data base from which this criterion has been derived is currently being reviewed, therefore, this criteria to protect human health may change.

B. Aquatic

Fresh or salt water criteria could not be derived because of insufficient data (U.S. EPA, 1979).

CHLOROETHENE
(VINYL CHLORIDE)

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No. 46

2-Chloroethyl Vinyl Ether

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

2-CHLOROETHYL VINYL ETHER

SUMMARY

Very little information is available for 2-chloroethyl vinyl ether. It appears to be relatively stable except under acidic conditions. There is some potential for bioconcentration of the compound in exposed organisms. No exposure data were available, although 2-chloroethyl vinyl ether has been identified in industrial effluent discharges.

The acute toxicity of 2-chloroethyl vinyl ether is relatively low: oral LD_{50}: 250 mg/kg; dermal LD_{50} 3.2 mL/kg; LC_{LO}: 250 ppm (4 hrs). Eye irritation has been reported following exposure to 2-chloroethyl vinyl ether. No other data on health effects were available.

I. INTRODUCTION

2-Chloroethyl vinyl ether ($ClCH_2CH_2OCH=CH_2$; molecular weight 106.55) is a liquid having the following physical/chemical properties (Windholz, 1976; Weast, 1972; U.S. EPA, 1979c):

Boiling point (760 mm Hg):	109°C
Melting point:	-70°C
Density:	1.0475^{20}
Solubility:	Soluble in water to the extent of 6g/L; very soluble in alcohol and ether

The compound finds use in the manufacture of anesthetics, sedatives, and cellulose ethers (Windholz, 1976).

A review of the production range (includes importation) statistics for 2-chloroethyl vinyl ether (CAS No. 110-75-8) which is listed in the initial TSCA inventory (1979a) has shown that none of this chemical was produced or imported in 1977*.

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*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise confidential business information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40CFR710).

II. EXPOSURE

A. Environmental Rate

The β-chloroalkyl ethers have been shown to be quite stable to hydrolysis and to persist for extended periods without biodegradation (U.S. EPA, 1979b). 2-Chloroethyl ethyl ether (a β-chloroalkyl other) is stable to sodium hydroxide solutions but will undergo hydrolysis in the presence of dilute acids to acetaldehyde and 2-chloroethanol (Windholz 1976). Conventional treatment systems may be inadequate to sufficiently remove the β-chloroalkyl ethers once present in water supplies (U.S. EPA 1979b; U.S. EPA 1975).

B. Bioconcentration

A calculated bioconcentration factor of 34.2 (U.S. EPA, 1979b) points to some potential for 2-chloroethyl vinyl ether accumulation in exposed organisms.

C. Environmental Occurrence

There is no specific information available on general population exposure to 2-chloroethyl vinyl ether. The compound has been identified three times in the water of Louisville, Kentucky (3/74): twice in effluent facturing plants and once in the effluent from a latex plant (U.S. EPA 1976). No concentration levels were given.

NIOSH, utilizing data from the National Occupational Hazards Survey (NOHS 1977) has compiled a listing summarizing occupational exposure to 2-chloroethyl vinyl ether (Table 1). As shown, NIOSH estimates 23,473 people are exposed annually to the compound. The number of potentially exposed individuals is greatest for the following areas: fabricated metal products; wholesale trade; leather, rubber and plastic, and chemical products.

III. PHARMACOKINETICS

Vinyl ethers readily undergo acid catalysed hydrolysis to give alcohols and aldehydes, e.g., 2-chloroethyl vinyl ether is hydrolyzed to 2-chloroethanol and acetaldehyde (Salomaa et al. 1966).

TABLE 1

PROJECTED NUMBERS BY INDUSTRY

HAZARD DESCRIPTION

84673 Chloroethyl Vinyl Ether, 2-

SIC CODE	DESCRIPTION	ESTIMATED PLANTS	ESTIMATED PEOPLE	ESTIMATED EXPOSURES
25	Furniture and fixtures	193	920	920
28	Chemicals and allied products	103	1,683	1,683
30	Rubber and plastic products	89	1,669	1,669
31	Leather and leather products	45	2,279	2,279
34	Fabricated metal products	61	9,149	9,149
35	Machinery, except electrical	35	35	35
36	Electrical equipment and supplies	54	432	432
37	Transportation equipment	92	553	553
38	Instruments and related products	24	299	299
39	Miscellaneous manufacturing industries	119	240	240
50	Wholesale trade	1,239	6,194	6,194
73	Miscellaneous business services	5	20	20
TOTAL		2,059	23,473	23,473

IV. HEALTH EFFECTS

A. Mutagenicity

Although no information on the mutagenicity of 2-chloroethyl vinyl ether was available, its hydrolysis product, 2-chloroethanol, has been shown to be mutagenic in Salmonella typhimurium TA 1535 (Rannug et al. 1976), TA100 and TA98 (McCann et al. 1976), as well as Klebsiella pneumonia (Voogd et al. 1972).

B. Other Toxicity

Very little toxicological data for 2-chloroethyl vinyl ether is available. The oral LD_{50} for 2-chloroethyl vinyl ether in rats is 250 mg/kg (U.S. EPA, 1975, Patty 1963). Dermal exposure to the shaven skin of rabbits for 24 hours resulted in an LD_{50} of 3.2 mL/kg (U.S. EPA, 1976). The acute inhalation toxicity of 2-chloroethyl vinyl ether in rats was determined following single four-hour exposures. The lowest lethal concentration was 250 ppm (U.S. EPA, 1975). In a similar inhalation study, 1/6 rats exposed by inhalation to 500 ppm died during the 14-day observation period (U.S. EPA, 1975).

Primary skin irritation and eye irritation studies have also been conducted for 2-chloroethyl vinyl ether. Dermal exposure to undiluted 2-chloroethyl vinyl ether did not cause even slight erythema. Application of 0.5 mL undiluted 2-chloroethyl vinyl ether to the eyes of rabbits resulted in severe eye injury (U.S. EPA, 1975).

V. AQUATIC TOXICITY

A. Acute

The adjusted 96-hour LC_{50} for blue gill exposure to 2-chloroethyl vinyl ether is 194,000 ug/L (U.S. EPA, 1979b). Dividing by the species sensitivity factor (3.9), a Final Fish Acute Value of 50,000 ug/L is obtained (Table 1). There is no data on invertebrate or plant exposure.

VI. EXISTING GUIDELINES

No guidelines were located.

Table 2. Freshwater fish acute values (U.S. EPA, 1979b)

Organism	Bioassay Method	Test Conc.**	Chemical Description	Time (hrs)	LC_{50} (ug/L)	Adjusted LC_{50} (ug/L)
Bluegill, *Lepomis macrochirus*	S	U	2-chloroethyl vinyl ether	96	354,000	194,000

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* S = static

** U = unmeasured

Geometric mean of adjusted values: 2-chloroethyl vinyl ether = 194,000 ug/L

$$\frac{194,000}{3.9} = 50,000 \text{ ug/L}$$

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No. 47

Chloroform (Carbon Trichloromethane)

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated chloroform and has found sufficient evidence to indicate that this compound is carcinogenic.

CHLOROFORM

SUMMARY

Chloroform has been found to induce hepatocellular carcinomas in mice and kidney epithelial tumors in rats. Hepatomas have also been induced in mice, but necrosis may be a prerequisite to tumor formation. Bacterial assays involving chloroform have yielded no mutagenic effects. Chloroform has produced teratogenic effects when administered to pregnant rats.

Reported 96-hour LC_{50} values for two common freshwater fish range from 43,800 to 115,000 µg/l in static tests. A 48-hour static test with Daphnia magna yielded an LC_{50} of 28,900 µg/l. The observed 96-hour LC_{50} for the saltwater pink shrimp is 81,500 µg/l. In a life cycle chronic test, the chronic value was 2,546 µg/l for Daphnia magna. Pertinent information on chloroform toxicity to plants could not be located in the available literature. In the only residue study reported, the bluegill concentrated chloroform six times after a 14-day exposure. The tissue half-life was less than one day suggesting that residues of chloroform would not be an environmental hazard to aquatic life.

CHLOROFORM

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chloroform (U.S. EPA, 1979a).

Chloroform ($CHCl_3$; molecular weight 119.39) is a clear, colorless liquid with a pleasant, etheric, non-irritating odor and taste (Hardie, 1964; Windholz, 1976). It has the following physical/chemical properties (Hardie, 1964; Irish, 1972; Windholz, 1976):

Boiling Point:	61-62°C
Melting Point:	-63.5°C
Flash Point:	none (none-flammable)
Solubility:	Water - 7.42×10^6 µg/l at 25°C Miscible with alcohol, benzene, ether, petroleum ether, carbon tetrachloride, carbon disulfide, and oils.
Vapor Pressure:	200 mm Hg at 25°C

Current Production: 1.2×10^5 metric tons/year (U.S. EPA, 1978a).

Chloroform is currently used either as a solvent or as an intermediate in the production of refrigerants (principleus), plastics, and pharmaceuticals (U.S. EPA, 1975).

Chloroform is relatively stable under normal environmental conditions. When exposed to sunlight, it decomposes slowly in air but is relatively stable in water. The measured half-life for hydrolyis was found to be 15 months (Natl. Acad. Sci., 1978a). Degradation in water can occur in the presence of metals and is accelerated by aeration (Hardie, 1964).

For additional information regarding halomethanes as a class the reader is referred to the Hazard Profile on halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

Chloroform appears to be ubiquitous in the environment. A major source of chloroform contamination is from the chlorination of water and wastewater (U.S. EPA, 1975; Bellar, et al., 1974). Industrial spills may occasionally be a pulse source of transient high level contamination (Nat. Acad. Sci., 1978a; Neely, et al., 1976; Brass and Thomas, 1978).

Based on available monitoring data including information from the National Organics Monitoring Survey (NOMS), the U.S. EPA (1978b) has estimated the uptake of chloroform by adult humans from air, water, and food:

Source	Adult mg/yr	Percent uptake
	Maximum Conditions	
Atmosphere	204	36
Water	343	61
Food Supply	16	3
Total	563	100.00
	Minimum Conditions	
Atmosphere	0.41	13
Water	0.73	23
Food Supply	2.00	64
Total	3.14	100.00
	Mean Conditions	
Atmosphere	20.0	22
Water	64.0	69
Food Supply	9.00	10
Total	93	100.00

A similar estimate, not using NOMS data, has been made by the National Academy of Sciences (Nat. Acad. Sci., 1978a).

The U.S. EPA (1979a) has estimated the bioconcentration factor for chloroform to be 14 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

III. PHARMACOKINETICS

A. Absorption

The efficiency of chloroform absorption by the gastrointestinal tract is virtually 100 percent in humans (Fry, et al., 1972). The corresponding value by inhalation is 49 to 77 percent (Lehmann and Hassegawa, 1910). Quantitative estimates of dermal absorption efficiency were not encountered. Since chloroform was used as an anesthetic via dermal administration, some dermal absorption by humans can be assumed (U.S. EPA, 1979a).

B. Distribution

Chloroform is transported to all mammalian body organs and is also transported across the placenta. Strain differences for chloroform distribution in mice have been documented by Vessell, et al., (1976).

C. Metabolism

Most absorbed chloroform is not metabolized by mammals. Toxication, rather than detoxication, appears to be the major consequence of metabolism and probably involves mixed-function oxidase (MFO) enzyme systems. This observa-

tion is based on enhancement of chloroform toxicity by MFO inducers and the diminution of toxicity by MFO inhibitors (Ilett, et al., 1973, McLean, 1970). At least in the liver, covalent binding of a metabolite to tissue is associated with tissue damage (Lavigne and Marchand, 1974). Limited human data (two people) suggest that about 50 percent of absorbed chloroform is metabolized to CO_2 (Fry, et al., 1972; Chiou, 1975).

D. Excretion

In humans, the half-life of chloroform in the blood and expired air is 1.5 hours (Chiou, 1975). Most unchanged chloroform and CO_2 generated from chloroform are eliminated via the lungs. Chlorine generated from chloroform metabolism is eliminated via the urine (Taylor, et al., 1974; Fry, et al., 1972).

IV. EFFECTS

A. Carcinogenicity

Eschenbrenner and Miller (1945) demonstrated that oral doses of chloroform administered over a 16-month period induced hepatomas in strain A mice. Based on variations in dosing schedules, these researchers concluded that necrosis was prerequisite to tumor induction.

In the National Cancer Institute bioassay of chloroform (NCI, 1976), hepatocellular carcinomas were induced in mice (Table 1) and kidney epithelial tumors were induced in male rats (Table 2), following oral doses over extended periods of time.

Ten epidemiologic studies have been conducted on the association of human exposure to chloroform and/or other trihalomethanes with cancer. A review of these studies by the National Academy of Sciences (NAS, 1978b) indicated that these studies suggest that higher concentrations of trihalomethanes in drinking water may be associated with an increased frequency of cancer of the bladder. One of these studies (McCabe, 1975) claimed to demonstrate a statistically significant correlation between age, sex, race, adjusted death rate for total cancer, and chloroform levels.

B. Mutagenicity

Chloroform yielded negative results in the Ames assay (Simmon, et al. 1977).

C. Teratogenicity

At oral dose levels causing signs of maternal toxicity, chloroform had fetotoxic effects on rabbits (100 mg/kg/day) and rats (316 mg/kg/day) (Thompson, et al., 1974). Fetal abnormalities (acaudia, imperforate anus, subcutaneous edema, missing ribs, and delayed ossification) were induced when pregnant rats were exposed to airborne chloroform at 489 and 1,466 mg/m^3, 7 hrs/day, on days 6 to 15 of gestation. At 147 mg/m^3, the only effects were significant increases in delayed skull ossification and wavy ribs (Schwetz, et al., 1974).

Table 1. Hepatocellular Carcinoma Incidence in Mice[a]

	Controls		Low Dose	High Dose
	Colony	Matched		
Male	5/77 (6%)	1/18 (6%)	138 mg/kg 18/50 (30%)	277 mg/kg 44/45 (98%)
Female	1/80 (1%)	0/20 (0%)	238 mg/kg 36/45 (80%)	477 mg/kg 39/41 (95%)

Table 2. Statistically Significant Tumor Incidence in Rats[a]

	Males			
	Controls		Low Dose	High Dose
	Colony	Matched		
Kidney epithelial tumors/animals	0/99	0/19	90 mg/kg 4/50 (8%)	180/mg/kg 12/50 (24%)
P value	0.0000	0.0016		

[a]Source: National Cancer Institute, 1976.

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

The NIOSH Criteria Document (1974) tabulates data on the effect of chronic chloroform exposure in humans. The primary target organs appear to be the liver and kidneys, with some signs of neurological disorders. These effects have been documented only with occupational exposures.

With the exception of the possible relationship to cancer (Section IV.A), chronic toxic effects in humans, attributable to ambient levels of chloroform, have not been documented.

The chronic effects of chloroform in experimental mammals is similar to the effects seen in humans: liver necrosis and kidney degeneration (Torkelson, et al., 1976; U.S. EPA, 1979a).

F. Other Relevant Information

Ethanol pretreatment of mice reportedly enhances the toxic effects of chloroform on the liver (Kutob and Plaa, 1961); as does high fat and low protein diets (Van Oettingen, 1964; McLean, 1970). These data were generated using experimental mammals.

V. AQUATIC TOXICITY

A. Acute Toxicity

Bentley, et al. (1975) observed the 96-hour LC_{50} values for rainbow trout, (Salmo gairdneri), of 43,800 and 66,800 µg/l and for bluegills (Lepomis macrochirus), 100,000 to 115,000 µg/l, all in static tests. A 48-hour static test with Daphnia magna resulted in an LC_{50} of 28,900 µg/l (U.S. EPA 1979a). The observed 96-hour LC_{50} for the pink shrimp (Panaeus duorarum) is 81,500 µg/l. (Bentley, et al., 1975).

B. Chronic Toxicity

The chronic effects of chloroform on Daphnia magna were determined using flow-through methods with measured concentrations. The chronic effect level was 2,546 µg/l (U.S. EPA, 1979a). No other chronic data were available.

C. Plant Effects

Pertinent information could not be located in the available literature concerning acute chronic toxicity of chloroform to plants.

D. Residues

In the only residue study reported, the bluegill (Lepomis macrochirus) bioconcentrated chloroform six times after a 14-day exposure (U.S. EPA, 1979a). The tissue half-life was less than one day.

VI. EXISTING GUIDELINES AND STANDARDS

Both the human health and aquatic criteria derived by U.S. EPA (1979a), which are summarized below, are being reviewed; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on the NCI mice data, and using the "one-hit" model, the EPA (1979a) has estimated levels of chloroform in ambient water which will result in specified risk levels of human cancer:

Exposure Assumption (per day)	Risk Levels and Corresponding Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.021 µg/l	0.21 µg/l	2.1 µg/l
Consumption of fish shellfish only.	0	0.175 µg/l	1.75 µg/l	17.5 µg/l

The above risks assume that drinking water treatment and distribution will have no impact on the chloroform concentration.

The NIOSH time-weighted average exposure criterion for chloroform is 2 ppm or 9.8 mg/m^3.

The FDA prohibits the use of chloroform in drugs, cosmetics, or food contact material (14 FR 15026, 15029 April 9, 1976).

Refer to the Halomethane Hazard Profile for discussion of criterion derivation (U.S. EPA, 1979b).

B. Aquatic

For chloroform, the draft criterion to protect freshwater aquatic life, based on chronic invertebrate toxicity, is 500 µg/l as a 24-hour average and the concentration should not (based on acute effects) exceed 1,200 µg/l at any time (U.S. EPA, 1979a). To protect saltwater aquatic life, the concentration of chloroform should not exceed 620 µg/l as a 24-hour average and the concentration should not exceed 1,400 µg/l at anytime (U.S. EPA, 1979a). These were calculated from an experiment on a marine invertebrate.

CHLOROFORM

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No. 48

Chloromethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CHLOROMETHANE

SUMMARY

Chloromethane is toxic to humans by its action on the central nervous system. In acute toxicity, symptoms consist of blurring vision, headache, vertigo, loss of coordination, slurring of speech, staggering, mental confusion, nausea, and vomiting. Information is not available on chronic toxicity, teratogenicity, or carcinogenicity. Chloromethane is highly mutagenic to the bacteria, Salmonella typhimurium.

Only three toxicity tests have been conducted on three species of fish yielding acute values ranging from 147,000 to 300,000 µg/l. Tests on aquatic invertebrates or plants have not been conducted.

CHLOROMETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Halomethanes (U.S. EPA, 1979a).

Chloromethane (CH_3Cl; methyl chloride; molecular weight 50.49) is a colorless, flammable, almost odorless gas at room temperature and pressure (Windholz, 1976). Chloromethane has a melting point of -97.7°C, a boiling point of -24.2°C, a specific gravity of 0.973 g/ml at -10°C, and a water solubility of 5.38×10^6 µg/l. It is used as a refrigerant, a methylating agent, a dewaxing agent, and catalytic solvent in synthetic rubber production (MacDonald, 1964). However, its primary use is as a chemical intermediate (Natl. Acad. Sci., 1978). Chloromethane is released to the environment by manufacturing and use emissions, by synthesis during chlorination of drinking water and municipal sewage, and by natural synthesis, with the oceans as the primary site (Lovelock, 1975). For additional information regarding the halomethanes as a class, the reader is referred to the Hazard Profile on Halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

The U.S. EPA (1975) has identified chloromethane qualitatively in finished drinking waters in the U.S. However, there are no data on its concentration in drinking water, raw water, or waste-water (U.S. EPA, 1979a), probably because it is more reactive than other chlorinated methanes (Natl. Acad. Sci., 1978).

B. Food

There is no information on the presence of chloromethane in food. There is no bioconcentration factor for chloromethane (U.S. EPA, 1979a).

C. Inhalation

Saltwater atmospheric background concentrations of chloromethane averaging about 0.0025 mg/m^3 have been reported (Grimsrud and Rasmussen, 1975; Singh, et al. 1977). This is higher than reported average continental background and urban levels and suggests that the oceans are a major source of global chloromethane (National Acad. Sci., 1978). Localized sources, such as burning of tobacco or other combustion processes, may produce high indoor-air concentrations of chloromethane (up to 0.04 mg/m^3) (Natl. Acad. Sci., 1978). Chloromethane is the predominant halomethane in indoor air, and is generally in concentrations two to ten times ambient background levels.

III. PHARMACOKINETICS

A. Absorption

Chloromethane is absorbed readily via the lungs, and to a less significant extent via the skin. Poisonings involving gastrointestinal absorption have not been reported (Natl. Acad. Sci., 1977; Davis, et al., 1977).

B. Distribution

Uptake of chloromethane by the blood is rapid but results in only moderate blood levels with continued exposure. Signs and pathology of intoxications suggest

wide tissue (blood, nervous tissue, liver, and kidney) distribution of absorbed chloromethane (Natl. Acad. Sci., 1978).

C. Metabolism

Decomposition and sequestration of chloromethane result primarily by reaction with sulfhydryl groups in intracellular enzymes and proteins (Natl. Acad. Sci., 1977).

IV. EFFECTS

A. Carcinogenicity

Pertinent information could not be located in the available literature.

B. Mutagenicity

Simmon and coworkers (1977) reported that chloromethane was mutagenic to Salmonella tryphimurium strain TA 100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required, and the number of revertants per plate was directly dose-related. Also, Andrews, et al. (1976) have demonstrated that chloromethane was mutagenic to S. typhimurium strain TA1535 in the presence and absence of added liver homogenate preparations.

C. Teratogenicity and Other Reproductive Effects

Information on positive evidence of teratogenisis or other reproductive effects was not available in the literature.

D. Chronic Toxicity

Under prolonged exposures to chloromethane (duration not specified) increased mucous flow and reduced mucosta-

tic effect of other agents (e.g., nitrogen oxides) were noted in cats (Weissbecker, et al., 1971).

E. Other Relevant Information

In acute human intoxication, chloromethane produces central nervous system depression, and systemic poisoning cases have also involved hepatic and renal injury (Hansen, er al., 1953; Spevac, et al., 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

A single 96-hour static renewal test serves as the only acute study for freshwater providing an adjusted LC_{50} value of 550,000 µg/l for the bluegill sunfish (Lepomis macrochirus). (Dawson, et al., 1977). Studies on freshwater invertebrates were not found. For the marine fish, the tidewater silversides (Menidia beryllina), a 96-hour static renewal assayed provided an LC_{50} value of 270,000 µg/l (Dawson, et al., 1977). Acute studies on marine invertebrates were not found.

B. Chronic Toxicity

In a review of the available literature, chronic testing with chloromethane has not been reported.

C. Plant Effects

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human nor the aquatic criteria derived by U.S. EPA, 1979a, which are summarized below, have gone

through the process of public review; therefore, there is a possibly that these criteria may be changed.

A. Human

OSHA (1976) has established the maximum acceptable time-weighted average air concentrations for daily eight-hour occupational exposure at 210 mg/m^3. The U.S. EPA (1979a) Draft Water Quality Criteria for Chloromethane is 2 µg/l. Refer to the Halomethanes Hazard Profile for discussion of criteria derivation (U.S. EPA, 1979b).

B. Aquatic

Criterion recommended to protect freshwater organisms have been drafted as 7,000 µg/l, not to exceed 16,000 µg/l for a 24-hour average concentration. For marine life, the criterion has been drafted as 3,700 µg/l, not to exceed 8,400 µg/l as a 24-hour average concentration.

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No. 49

2-Chloronaphthalene

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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2-CHLORONAPHTHALENE

SUMMARY

Monochlorinated naphthalenes are relatively insoluble in water. They can be slowly degraded by bacteria and are subject to photochemical decomposition. Monochlorinated naphthalenes appear to bioconcentrate in plants and animals exposed to the substances. 2-Chloronaphthalene has been identified as a pollutant in a variety of industries.

No information was located on the carcinogenicity, mutagenicity, or teratogenicity of 2-chloronaphthalene or other monochlorinated naphthalenes. The metabolism of some chlorinated naphthalenes, however, proceeds through an epoxide mechanism. If an epoxide is formed as an intermediate in the metabolism of 2-chloronaphthalene, it could react with cellular macromolecules possibly resulting in cytotoxicity, mutagenicity, oncogenicity, or other effects.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Naphthalenes (U.S. EPA, 1979b).

2-Chloronaphthalene ($C_{10}H_7Cl$; molecular weight 162) is a crystalline solid with a melting point of 61°C and a boiling point of 256°C. Its density at 16°C is 1.27. It is insoluble in water and soluble in many organic solvents (Weast; 1972 and Hardie, 1964).

A review of the production range (includes importation) statistics for 2-chloronaphthalene (CAS. No. 91-58-7) which is listed in the inital TSCA Inventory (1979a) has shown that between 1,000 and 9,000 pounds of this chemical were produced/imported in 1977.*/

Monochloronaphthalenes and mixtures of mono- and dichloronaphthalenes have been used for chemical-resistant gauge fluids and instrument seals, as heat exchange fluids, high-boiling specialty solvents (e.g., for solution polymerization), color dispersions, engine crankcase additives to dissolve sludges and gums, and as ingredients in motor tuneup compounds. Monochloronaphthalene was formerly used as a wood preservative (Dressler, 1979).

II. EXPOSURE

A. Environmental Fate

Polychlorinated naphthalenes do not occur naturally in the environment. Potential environmental accumulation can occur around points of manufacture of the compounds or products containing them, near sites of disposal of polychorinated naphthalene-containing wastes, and, because polychlorinated

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

biphenyls (PCBs) are to some extent contaminated by polychlorinated naphthalenes (Vos et al. 1970; Bowes et al. 1975) near sites of heavy PCB contamination.

Because polychlorinated naphthalenes are relatively insoluble in water, they are not expected to migrate far from their point of disposition. The use of mono- and dichlorinated naphthalenes as an engine oil additive and as a polymerization solvent in the fabric industry suggests possible contamination of soil or water.

Walker and Wiltshire (1955) found that soil bacteria when first grown on naphthalene could also grow on 1-chloronaphthalene, producing a diol and chlorosalicylic acid. Canonica et al. (1957) found similar results for 2-chloronaphthalene. Okey and Bogan (1965) studied the utilization of chlorinated substrates by activated sludge and found that naphthalene was degraded at a fairly rapid rate, while 1-and 2-chloronaphthalenes were handled more slowly.

Ruzo et al. (1975) studied the photodegradation of 2-chloronaphthalene in methanol. The major reaction pathways seen were dechlorination and dimerization. Jaffe and Orchin (1966) indicated that any 2-chloronaphthalene present at the surface of water could be degraded by sunlight to naphthalene. In the aquatic environment, 2-chloronaphthalene can exist as a surface film, be adsorbed by sediments, or accumulated by biota.

B. Bioconcentration

Monochlorinated naphthalenes appear to bioconcentrate in the aquatic environment. Adult grass shrimp (Palaemonetes pugio) were exposed to a mixture of mono- and dichloro naphthalenes for 15 days. The concentration of chloronaphthalenes detected in the shrimp was 63 times that of the experimental environment. When removed from the contaminated environment, however, the concentration in the shrimp returned to virtually zero within 5 days (Green and Neff, 1977).

Erickson et al. (1978a) reported a higher relative bioconcentration of the lower chlorinated naphthalenes in the fruit of apple trees grown on contaminated soil. The soil was found to have a polychlorinated naphthalene level of 190 ug/kg of which 1.6 ug/kg consisted of monochloronaphthalenes. While the apples grown on this soil had only 90 ug/kg of polychlorinated naphthalenes, the level of monochloronaphthalene was 62 ug/kg.

C. Environmental Occurrence

2-Chloronaphthalene has been identified as a pollutant in a variety of industries, e.g. organic chemical, rubber, power generation, and foundries (U.S. EPA, 1979c).

Chlorinated naphthalenes have been found more consistently in air and soil samples than in associated rivers and streams (Erickson et al., 1978b). The air samples contained mainly the mono-, di- and trichlorinated naphthalenes, while soil contained mostly the tri-, tetra- and pentachlorinated derivatives.

To date polychlorinated naphthalenes have not been identified in either drinking water or market basket food. The Food and Drug Administration has had polychlorinated naphthalene

monitoring capability for foods since 1970, but has not reported their occurrence in food (U.S. EPA, 1975).

III. PHARMACOKINETICS

Ruzo et al. (1976b) reported the presence of 2-chloronaphthalene in the brain, kidney, and liver of pigs six hours after injection. Small concentrations of 3-chloro-2-naphthol, a metabolite , were seen in the kidney and liver with large amounts occurring in the urine and bile. The metabolism of some chlorinated napthalenes proceeds through an epoxide mechanism (Ruzo et al. 1975, 1976ab; Chu et al., 1977ab).

IV. HEALTH EFFECTS

A. Teratogenicity, Mutagenicity, and Carcinogenicity

No information was located on the carcinogenicity, mutagenicity, or teratogenicity of polychlorinated naphthalenes.

If an epoxide is formed as an intermediate in the metabolism of 2-chloronaphthalene, it could react with cellular macromolecules. Binding might occur with protein, RNA, and DNA resulting in possible cytotoxicity, mutagenicity, oncogenicity, or other effects (Garner, 1976; Heidelberger, 1973; Wyndham and Safe, 1978).

B. Other Toxity

In man, the first disease recognized as being associated with occupational exposure to higher polychlorinated naphthalenes was chloracne. Occurrence of this disease was associated with the manufacture or use of polychloronaphthalene-treated electrical cables. Kleinfeld et al. (1972) noted that workers at

an electric coil manufacturing plant had no cases of chloracne while using a mono- and dichloronaphthalene mixture. When a tetra-/pentachlorinated naphthalene mixture was substituted for the original mixture, 56 of the 59 potentially exposed workers developed chloracne within a "short" time.

The lower chlorinated naphthalenes appear to have low acute toxicity. Mixtures of mono-/dichloronaphthalenes and tri-/tetrachloronaphthalenes at 500 mg/g in a mineral oil suspension applied to the skin of the human ear caused no response over a 30-day period. A mixture of penta-/hexachloronaphthalenes given under the same conditions caused chloroacne (Shelley and Kligman, 1957).

The oral LD50 for rats and mice is 2078 mg/kg and 886 mg/kg respectively (NIOSH, 1978). No mortality or illness was reported in rabbits given 500 mg/kg orally (Cornish and Block, 1958).

V. AQUATIC EFFECTS

The LC50 (ppb) of a mixture of 60% mono- and 40% dichloronaphthalenes in grass shrimp (Palaemonetes pugio)is as follows:

	72-hr	96-hr
post larval stage	-	449
adult	370	325

(Green and Neff, 1977)

VI. EXISTING GUIDELINES

There are no existing guidelines for 2-chloronaphthalene.

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No. 50

2-Chlorophenol

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

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2-CHLOROPHENOL

SUMMARY

Insufficient data exist to indicate that 2-chlorophenol is a carcinogenic agent. 2-Chlorophenol appears to act as a nonspecific irritant in promoting tumors in skin painting studies. No information is available on mutagenicity, teratogenicity, or subacute and chronic toxicity. 2-Chlorophenol is a weak uncoupler of oxidative phosphorylation and a convulsant.

2-Chlorophenol is acutely toxic to freshwater fish at concentrations ranging from 6,590 to 20,170 µg/l. No marine studies are available. Concentrations greater than 60 µg/l have been reported to taint cooked rainbow trout flesh in flavor impairment studies.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for 2-Chlorophenol (U.S. EPA, 1979).

2-Chlorophenol (ortho-chlorophenol) is a liquid having the empirical formula C_6H_5Cl (molecular weight: 128.56). It has the following physical/chemical properties (Rodd, 1954; Judson and Kilpatrick, 1949; Sax, 1975; Stecher, 1968; Henshaw, 1971):

Melting Point:	8.7°C
Boiling Point Range:	175-176°C
Vapor Pressure:	1 mm Hg at 12.1°C
Solubility:	Slightly soluble (1g/l) in water at 25°C and neutral pH

2-Chlorophenol is a commercially produced chemical used as an intermediate in the production of higher chlorophenols and phenolic resins and has been utilized in a process for extracting sulfur and nitrogen compounds from coal (U.S. EPA, 1979).

2-Chlorophenol undergoes photolysis in aqueous solutions as a result of UV irradiaton (Omura and Matsuura, 1971; Joschek and Miller, 1966). Laboratory studies suggest that microbial oxidation could be a degradation route for 2-chlorophenol (Loos, et al., 1966; Sidwell, 1971; Nachtigall and Butler, 1974). However, studies performed by Ettinger and Ruchhoft (1950) on the persistency of 2-chlorophenol in sewage and polluted river water indicated that the removal of monochlorophenols requires the presence of an adapted microflora.

II. EXPOSURE

A. Water

The generation of waste from the commercial production and use of 2-chlorophenol (U.S. EPA, 1979) and the inadvertent synthesis of 2-chlorophenol due to chlorination of water contaminated with phenol (Aly, 1968: Barnhart and Campbell, 1972; Jolley, 1973; Jolley, et al., 1975) are potential sources of contamination of water with 2-chlorophenol. However, no data regarding 2-chlorophenol concentrations in finished drinking water are available (U.S. EPA, 1979).

B. Food

Information on levels of 2-chlorophenol in foods is not available. Any contamination of foods is probably indirect as a result of use and subsequent metabolism of phenoxyalkanoic herbicides (U.S. EPA, 1979). Although residues of 2,4-dichlorophenol were found in tissues of animals fed 2,4-D and nemacide containing food (Clark, et al. 1975); Sherman, et al. 1972), no evidences were cited to indicate the presence of 2-chlorophenol; moreover, there was no contamination of 2-chlorophenol in milk and cream obtained from cows fed 2,4-D treated food (Bjerke, et al. 1972).

The potential for airborne exposure to 2-chlorophenol in the general environment, excluding occupational exposure, has not been reported (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for 2-chlorophenol and the edible portion of fish and shellfish consumed by Americans at

490. This estimate is based on measured steady state bioconcentration studies in bluegills.

C. Inhalation

Pertinent data regarding concentrations of 2-chlorophenol in ambient air could not be found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Data dealing directly with the absorption of 2-chlorophenol by humans and experimental animals has not been found. Chlorophenol compounds are generally considered to be readily absorbed, as would be expected from their high lipid solubility and low degree of ionization at physiological pH (Doedens, 1963; Farquharson, et al., 1958). Toxicity studies indicate that 2-chlorophenol is absorbed through the skin.

B. Distribution

Pertinent data regarding tissue distribution of 2-chlorophenol was not located in the available literature.

C. Metabolism

Data regarding the metabolism of 2-chlorophenol in humans was not available (U.S. EPA, 1979). Based on experimental work in two species, it appears that the metabolism of 2-chlorophenol in mammals is similar to that of phenol in regard to the formation and excretion of sulfate and glucuronide conjugates (Von Oettingen, 1949; Lindsay-Smith, et al. 1972) Conversion of chlorobenzene to monochlorophenols, including 2-chlorophenol, has been shown in vitro with rat

liver (Selander, et al. 1975) and *in vivo*, with rabbits (Lindsay-Smith, et al. 1972).

D. Excretion

Studies on rate and route of excretion for 2-chlorophenol in humans were not available. Dogs excreted 87 percent of administered 2-chlorophenol in the urine as sulfate and glucuronide conjugates (Von Oettingen, 1949). The same metabolites were found in the urine of rabbits after administration of chlorobenzene (Lindsay-Smith, et al. 1972); however, out of the total free and conjugated chlorophenols only 6 percent were present as 2-chlorophenol.

IV. EFFECTS

A. Carcinogenicity

Insufficient data exist to indicate that 2-chlorophenol is a carcinogen. In the only study found (Boutwell and Bosch, 1959), 2-chlorophenol promoted skin cancer in mice after initiation with dimethylbenzanthracene and when repeatedly applied at a concentrations high enough to damage the skin. 2-Chlorophenol was not carcinogenic when applied repeatedly without initiation with dimethylbenzanthracene, but did induce a high incidence of papillomas and no carcinomas.

Information regarding mutagenicity, teratogenicity, other reproductive effects and chronic toxicity could not be found in the available literature.

F. Other Relevant Information

2-Chlorophenol is a weak uncoupler of oxidative phosphorylation (Mitsuda, et al., 1963) and a convulsant (Farquharson, et al., 1958; Angel and Rogers, 1972).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute studies on four species of fish have produced 96-hour static LC_{50} values ranging from 6,590 µg/l in the bluegill (Lepomis macrochirus) (U.S. EPA, 1978) to 20,170 µg/l to the guppy (Poecilia reticulatus). Juvenile bluegills were more sensitive in a static renewal assay with an LC_{50} value of 8,400 µg/l. The fathead minnow (Pimephales promelas) was the only freshwater fish tested in a flow through system and gave an LC_{50} value of 12,380 µg/l. Daphnia magna has been found to have 48-hour static LC_{50} values of 2,580 µg/l and 7,430 µg/l. No data concerning the effects of 2-chlorophenol to marine fish or invertebrates are available.

B. Chronic Toxicity

Effects were not obtained in a chronic embryo-larval test of 2-chlorophenol at concentrations as high as 1,950 µg/l for the freshwater fathead minnow. Additional chronic studies are not available.

C. Plant Effects

The only plant assay available provides an effective concentration of 500,000 µg/l in chlorophyll reduction in the algae, Chlorella pyrenoidosa.

D. Residues

A measured bioconcentration factor of 214 has been obtained for the bluegill. The half-life was less than one day, indicating a rapid depuration rate for 2-chlorophenol.

E. Miscellaneous

Flavor impairment of the edible portion of fish exposed to 2-chlorophenol has been reported. The highest concentration of 2-chlorophenol in the exposure water which would not impair the flavor of cooked rainbow trout (Salmo gairdneri) has been estimated at 60 µg/l Shumway and Palensky, 1973).

VI. EXISTING GUIDLINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on the prevention of adverse organoleptic effects, the U.S. EPA (1979) draft interim criterion recommended for 2-chlorophenol in ambient water is 0.3 µg/l. There are no other standards or guidelines for exposure to 2-chlorophenol.

B. Aquatic

Based on the tainting of fish, the draft criterion to protect freshwater organisms from 2-chlorophenol is 60 µg/l as a 24-hour average, not to exceed 180 µg/l at any time. No criterion was derived for marine life (U.S. EPA, 1979).

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No. 51

Chromium

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject material. This document has undergone scrutiny to ensure its technical accuracy.

CHROMIUM

Summary

Hexavalent chromium (CrVI), at low concentrations in water, has a deleterious effect on the growth of fish, aquatic invertebrates, and certain species of algae. For the most sensitive aquatic species, Daphnia magna, a final chronic no-effect level of less than 10 ug/l has been derived by the U.S. EPA. For trivalent Cr(CrIII) toxic effects are more pronounced in soft than in hard water; chronic no-effect levels are derived as a function of water hardness.

Several hexavalent Cr compounds have produced tumors in animal studies. Human epidemiology studies indicate a possible etiology of Cr exposure in the production of lung tumors in occupationally exposed workers. Trivalent Cr has not shown carcinogenic effects.

Mutagenic effects, including cytogenetic effects in exposed workers, have been reported for hexavalent chromium compounds. Trivalent chromium compounds were not mutagenic in the Ames bacterial assay. Teratogenic effects of chromium have been reported in a single study and have not been confirmed.

Impairment of pulmonary function has been reported in chrome electroplating workers subject to chronic chromium exposure. However, exposure to multiple agents complicates the interpretation of this finding.

CHROMIUM

I. INTRODUCTION

This profile is in large part based on the Ambient Water Quality Criteria Document for Chromium (U.S. EPA, 1980).

Chromium (Cr) is a steel gray, lustrous, hard metal that melts at 1857 ± 20°C, boils at 2672°C, and has a specific gravity of 7.18 to 7.20 at 20°C (Weast, 1974). Cr compounds exist in a variety of oxidation states; the most commonly occurring are those of the trivalent and hexavalent states. Physical properties of some Cr compounds are summarized in Table 1.

Cr compounds are utilized in the paint and dye industries as pigments and mordants, in metallurgy for the production of stainless steel and other alloys, in the chrome tanning of leather goods, in the production of high melting refractory materials, and for chrome plating.

Hexavalent Cr compounds are relatively water soluble and are readily reduced to more stable and insoluble trivalent forms by reaction with organic reducing matter. Trivalent chromium forms stable hexacoordinate complexes with a great variety of ligands (water, ammonia, urea, halides, sulfates, ethylene diamine, organic acids). In neutral and basic solutions, trivalent Cr may form polynuclear bridge compounds that eventually precipitate. Hexavalent Cr exists in solution as a component of an anion (hydrochromate, chromate, or dichromate) and does not precipitate from alkaline solution.

The specific anionic form of hexavalent Cr is dependent on pH - in the acid range hydrochromate predominates, while in the alkaline range the predominant form is chromate (Trama and Benoit, 1960). Cr VI occurs naturally in alkaline soft waters (Robertson, 1975) and in aerated sea water (Fukai, 1967; Cutshall et. al., 1965; Emerson et. al., 1979). The oxidation of CR III is expected to occur on energetic grounds (Carlin, 1965; U.S. EPA, 1977). In fact, however, oxidation takes place only very slowly in natural waters, except in the presence of MnO_2 (Schroeder and Lee, 1975; U.S. EPA, 1978). Under laboratory conditions oxidation does occur (Schroeder and Lee, 1975; Stephens, 1977). In contrast, the reduction of Cr VI to Cr III occurs rapidly in lake waters (Schroeder and Lee, 1975).

It seems probable that in most waters, especially under neutral or slightly acid conditions, Cr VI is reduced to Cr III, the hydroxy complexes of which precipitate out and/or are absorbed onto clays and other soil elements (N.A.S., 1974; U.S. EPA, 1978).

Since Cr is an element, it persists indefinitely in the environment in some form. Trivalent Cr compounds are more likely to accumulate in sediments, while hexavalent forms remain soluble and dissipate with the water flow (U.S. EPA, 1980).

II. EXPOSURE

Large amounts of hexavalent Cr are produced and utilized

in industry, primarily as chromates and dichromates (U.S. EPA, 1980). Industrial processes consumed 320,000 metric tons of Cr metal alone in 1972.

Much of the detectable chromium in air and water is presumably derived from industrial processes. Levels of total Cr in the air exceeding 0.10 mg/m^3 were reported from 59 of 186 urban areas examined (U.S. EPA, 1973). Air levels in non-urban areas generally fall below detection limits. Mean concentration of Cr in 1577 samples of surface water was determined as 9.7 ug/l (Kopp, 1969). Cr is naturally distributed in the continental crust at an average concentration of 125 mg/kg (N.A.S., 1974).

Based on available monitoring data, the U.S. EPA (1980) has estimated the uptake of Cr by adult humans from air, water and food:

Source	Uptake ug/day
Atmosphere	1
Water	20
Food Supply	50-100
	121

A different estimate for self-selected diets was 280ug/day (NAS, 1974). It is often stated that the American diet may be marginally deficient in Cr. Since a MDR has not yet been established (Mertz, 1978), and since absorption factors (see below) are as yet poorly understood, this statement is open to question.

Table 1. Physical Properties of Typical Chromium Compounds

Compound	Formula	Appearance	Crystal system and space group	Density (g/cm^3)	Melting point (^oC)	Boiling point (^oC)	Solubility
Oxidation state 0							
Chromium carbonyl	$(Cr(CO)_6$	Colorless crystals	Orthorhombic, C^9_{2r}	1.77_{18}	150 (decomposed) (sealed tube)	151 (decomposed)	Slightly soluble in CCl_4; insoluble in H_2O, $(C_2H_5)_2O$, C_2H_5OH, C_6H_6
Dibenzene chromium(0)	$(C_6H_6)_2Cr$	Brown crystals	Cubic, Pa_3	1.519	284-285	Sublimes 150 (vacuum)	Insoluble in H_2O; soluble in C_6H_6
Oxidation state + 1							
bis(biphenyl)-chromium (I) iodide	$(C_6H_5C_6H_5)_2CrI$	Orange plates		1.617_{16}	178	Decomposes	Soluble in C_2H_5OH, C_5H_5N
Oxidation state + 2							
Chromous acetate	$Cr_2(C_2H_3O_2)_4 \cdot 2H_2O$	Red crystals	Monoclinic, C2/c	1.79			Slightly soluble in H_2O; soluble in solids
Chromous chloride	$CrCl_2$	White crystals	Tetragonal, D^{14}_{4h}	2.93	815	1120	Soluble in H_2O to blue solution, absorbs O_2
Chromous ammonium sulfate	$CrSO_4 \cdot (NH_4)_2SO_4 \cdot 6H_2O$	Blue crystals	Monoclinic, C^5_{2h}				Soluble in H_2O, absorbs O_2
Oxidation state + 3							
Chromic chloride	$CrCl_3$	Bright purple plates	Hexagonal, D^{3or5}_3	2.87_{25}	Sublimes	885	Insoluble in H_2O, soluble in presence of Cr^{2+}
Chromic acetyl-acetonate	$Cr(CH_3COCHCOCH_3)_3$	Red-violet crystals	Monoclinic	1.34	208	345	Insoluble in H_2O; soluble in C_6H_6
Chromic potassium sulfate (chrome alum)	$KCr(SO_4)_2 \cdot 12H_2O$	Deep purple crystals	Cubic, A^6_n	1.826_{15}	89 (incongruent)		Soluble in H_2O
Chromic chloride hexahydrate	$(Cr(H_2O)_4Cl_2)Cl \cdot 2H_2O$	Bright green crystals	Triclinic or monoclinic	1.835_{25}	95		Soluble in H_2O, green solution turning green-violet
Chromic chloride hexahydrate	$(Cr(H_2O)_6)Cl_3$	Violet crystals	Rhombohedral, D^6_{3d}		90		Soluble in H_2O, violet solution turning green-violet

Compound	Formula	Appearance	Crystal system and space group	Density (g/cm^3)	Melting point (^oC)	Boiling point (^oC)	Solubility
Chromic oxide	Cr_2O_3	Green powder or crystals	Rhombohedral, D_{3d}^6	5.22_{25}	2435	ca. 3000	Insoluble
Oxidation state + 4							
Chromium (IV) oxide	CrO_2	Dark Brown or black powder	Tetragonal, D_{4h}^{14}	4.98 (calculated)		Decomposes to Cr_2O_3	Soluble in acids to Cr^{3+} and Cr^{6+}
Chromium(IV) chloride	$CrCl_4$		Stable only at high temp.			830	
Oxidation state + 5							
Barium chromate(IV)	$Ba_3(CrO_4)_2$	Black-green crystals	Same as $Ca_3(PO_4)_2$				Slightly decomposes in H_2O; soluble in dilute acids to Cr^{3+} and Cr^{6+}
Oxidation state + 6							
Chromium(VI) oxide	CrO_3	Ruby-red crystals	Orthorhombic, C_{2v}^{16}	2.7_{25}	197	Decomposes	Very soluble in H_2O; soluble in CH_3COCH_3, $(CH_2CO)_2O$
Chromyl chloride	CrO_2Cl_2	Cherry-red liquid		1.9145_{25}	-96.5	115.8	Insoluble in H_2O; hydrolyzes; soluble in CS_2, CCl_4
Ammonium dichromate	$(NH_4)_2Cr_2O_7$	Red-orange crystals	Monoclinic	2.155_{25}	Decomposes		Soluble in H_2O
Potassium dichromate	$K_2Cr_2O_7$	Orange-red crystals	Triclinic	2.676_{25}	398	Decomposes	Soluble in H_2O
Sodium dichromate	$Na_2Cr_2O_7 \cdot 2H_2O$	Orange-red crystals	Monoclinic	1.348_{25}	84.6 (incongruent)	Decomposes	Very soluble in H_2O
Potassium chromate	K_2CrO_4	Yellow crystals	Orthorhombic	2.732_{18}	971		Soluble in H_2O
Sodium chromate	Na_2CrO_4	Yellow crystals	Orthorhombic, D_{2h}^{17}	2.723_{25}	792		Soluble in H_2O
Potassium chlorochromate	$KCrO_3Cl$	Orange crystals	Monoclinic	2.497_{39}	Decomposes		Soluble in H_2O, hydrolyzes
Silver chromate	Ag_2CrO_4	Maroon crystals	Monoclinic	5.625_{25}			Very slightly soluble in H_2O; soluble in dilute acids
Barium chromate	$BaCrO_4$	Main yellow solid	Orthorhombic	4.498_{25}	Decomposes		Very slightly soluble in H_2O; soluble in strong acids

Compound	Formula	Appearance	Crystal system and space group	Density (g/cm^3)	Melting point (^oC)	Boiling point (^oC)	Solubility
Strontium chromate	$SrCrO_4$	Yellow solid	Monoclinic, C_{2h}^5	3.895_{15}	Decomposes		Slightly soluble in H_2O; soluble in dilute acids
Lead chromate	$PbCrO_4$	Yellow solid Orange solid	Orthorhombic Monoclinic, C_{2h}^5	6.12_{15}	844		Practically insoluble in H_2O; soluble in strong acids
		Red solid	Tetragonal				

Source: Adapted from U.S. EPA, 1978.

The U.S. EPA (1980) has derived a bioconcentration factor (BCF) of 11 for chromium.

III. PHARMACOKINETICS

A. Absorption

The efficiency of Cr absorption by the gastrointestinal tract is a function of the oxidation and chemical forms of the compound and the presence of other dietary constituents, and poorly understood intestinal epithelial barriers (U.S. EPA, 1980; Mertz, 1978). Oral administration of trivalent Cr results in little absorption. In order to be assimilated chromium must be present in the form of an organic complex with nicotinic acid termed glucose tolerance factor (GTF) (Mertz, 1969; 1971; 1978). Inorganic Cr is poorly assimilated (a few per cent) (Mertz, 1969; 1971). Cr from animal sources is much better utilized than that from vegetables, in which it may occur in high concentrations (Mertz, 1978). Dermal absorption of Cr does not contribute greatly to total body load, except in situations where toxic external concentrations have produced ulceration (U.S. EPA, 1980). Pulmonary exposure to Cr, which can be significant in some industrial situations, leads to prolonged retention at this site (Baetjer, et al. 1959). Under most conditions, however, the contribution of the inhalation route to total absorbed Cr is small (U.S. EPA, 1980).

B. Distribution

Analysis of the metabolism and distribution of Cr

is complicated by the fact that the methods available for the estimation of Cr at low levels do not adequately distinguish between its different forms (U.S. EPA 1980; 1978). In addition, difficulties of interpretation arise from the fact that cellular constituents reduce Cr to the trivalent form (Petrilli and DeFlora 1978; Nakamuro 1978).

Absorbed Cr is primarily transported bound to siderophilin, a metal transport protein which predominantly binds iron.

The organ distribution of Cr is highly dependent on the chemical form administered. For instance, while trivalent Cr does not extensively cross the placental barrier, when administered to pregnant rats in complexed form (GTF), it is taken up by the fetus. The highest concentrations of Cr accumulate in skin, lung, muscle and fat (Mertz 1969, Casarett and Doull, 1979). Pulmonary Cr arises from inhalation, and does not equilibrate with other body stores. Cr concentration in tissues other than lungs decline somewhat with age (Mertz 1969).

Hexavalent Cr is reduced to the trivalent form in skin. In the blood little hexavalent Cr is detected. The reticulo-endothelial system, liver, spleen, testis and bone marrow have an affinity for trivalent Cr, (Mertz 1969); chromates are bound largely to red blood cells (Mertz 1969). Inside cells, about half of the Cr is in the nucleus.

C. Metabolism

Analysis of chromium metabolism is complicated by the extensive binding of chromium to tissue components

(enzymes, proteins, nucleic acids) and by the inability of analytical methods to distinguish between the different forms of chromium (U.S. EPA, 1978; 1980).

Studies of the kinetics of radiochromium distribution in humans indicated three major accumulation and clearance components (Lim, 1978). Animal studies with radioactive chromium trichloride injected intravenously showed that heart, lung, pancreas, and brain retain only 10 to 31 percent of their initial radioactivity after four days. Spleen, kidney, testis and epididymis concentrate chromium (Hopkins, 1965). Average urinary and blood concentrations are 0.4 and 2.8 ug/100g, respectively (Casarett and Doull, 1979). Because of rapid clearance, blood concentration is not an indicator of Cr intake (Mertz, 1971).

D. Elimination

Chromium turnover in humans appears to be very slow (National Academy of Sciences, 1974). One component of chromium elimination has been calculated to have a half-life of 616 days (Taylor, 1975). In rats, three compartments for trivalent chromium have been estimated to have half-lives of 0.5, 5.9, and 83.4 days, respectively (Mertz, et al. 1965).

Chromium is excreted in both urine and feces. Urinary excretion is the major route of elimination, accounting for recovery of 80 percent of injected chromium (Mertz, 1969). Up to 20 percent of intravenously injected trivalent chromium was found in the feces of rats (Visek, et al. 1953). Milk

also contributes to excretion (Casarett, 1979).

IV. EFFECTS

A. Carcinogenicity

Carcinogenicity of various hexavalent Cr compounds in humans has been well documented (U.S. EPA, 1980). EPA's Carcinogen Assessment Group (CAG) has determined that there is substantial evidence that hexavalent Cr compounds are carcinogenic in man. Six epidemiologic studies, conducted at five different locations, of 1200 chromate workers provide strong evidence that inhalation of Cr VI produces lung cancer (U.S. EPA, 1978; 1980). One study (Taylor, 1966) also showed an increase in digestive cancer. In rats and hamsters inhalation studies using calcium chromates have produced cancer (Laskin, 1973), and Cr VI is carcinogenic when implanted in intrabronchial pellets, as well as by subcutaneous and intramuscular injection in mice and rats. However, the carcinogenicity of Cr VI has not been tested by oral administration (U.S. EPA, 1980).

The determination of the carcinogenicity of Cr VI compounds rests mainly on epidemiologic studies (see above) of employees in industries which use or produce chromates. Cr III compounds are used principally in the manufacture of ferrochrome, chromite bricks and steel, in leather tanning and in lithography. Data on the carcinogenicity of trivalent Cr are felt to be inadequate (Heimann, 1976). Rats showed a weak carcinogenic response to chromic (Cr III) acetate (Hueper and Payne, 1962;

Maltoni, 1974). Cr may be a co-carcinogen or promoter: chromium carbonyl is a mild synergist for benzo(a)pyrene in the production of carcinomas in tracheal grafts in rats (Lave and Mass, 1977). Such effects could be important in the development of lung cancer following pulmonary exposure to chromates.

B. Mutagenicity

Cytogenetic effects in workers exposed to welding fumes have been attributed to inhaled chromium (Hedenstedt, et al., 1977). These effects have also been reported in chromate production workers (Bigalief, et al., 1977).

Cr compounds induce chromosomal aberrations in human and animal leukocytes, and mutations in bacteria and yeasts (U.S. EPA, 1980; Petrilli and DeFlora, 1978a,b; Nakumoro 1978). In these tests Cr VI compounds have much higher activity than Cr III compounds. Under some assay conditions cellular reducing agents (ascorbic acid, NADH, NADPH, GSH) prevent Cr VI mutagenicity by reducing it to CR III (Petrilli and DeFlora, 1977; 1978a, b). Nakamuro, however (1978) found that Cr (III) acetate, nitrate and chloride induce chromosomal damage in cultured human leukocytes, and are bacterial mutagens.

C. Teratogenicity

Embryonic abnormalities have been produced in the developing chicken by direct injection of trivalent or hexavalent chromium into the yolk sac or onto the chorioallantoic membrane (Ridgway and Karnofsky, 1952). This effect

has not been further investigated, and is worrisome because of the reported placental permeability to complexed Cr (Mertz 1969).

D. Other Reproductive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

Except as regards the carcinogenicity of Cr VI, the concentrations of Cr encountered in the normal environment do not constitute a human health hazard. However, acute and chronic toxicity problems associated with exposure to Cr are of concern in the industrial environment. These effects have been reviewed (NIOSH, 1975; EPA, 1980), and include damage to liver, kidney, skin, respiratory passages and lungs (U.S. EPA, 1978, 1980; NAS 1974, 1977; NIOSH, 1975). Allergic dermatitis is a pronounced property of both tri- and hexavalent Cr compounds (EPA, 1980; Casarett and Doull, 1979).

Subtle changes in pulmonary function have been observed in workers employed in electroplating (Bovett et. al., 1977). Cr VI causes ulceration and perforation of the nasal systems, chronic rhinitis and pharyngitis, but these effects have been observed only in workers chronically exposed to relatively high concentrations of chromates (NIOSH, 1975).

V. AQUATIC TOXICITY

A. Chronic Toxicity

No data for chronic toxicity of trivalent chromium

for freshwater fishes is available. The geometric mean of chronic toxicity values for the freshwater invertebrate Daphnia magna is based on data from a single study, and is reported as 445 ug/l. No chronic data for trivalent chromium for freshwater algae are available.

Chronic embryo-larval tests on six species of fresh water fish exposed to Cr VI resulted in values ranging from 37 to 72 ug/l for rainbow trout (Salmo gairdneri) and lake trout, Salvelinus mamaycush. White suckers, Catostomus commersoni, and channel catfish, Ictalurus punctatus, were intermediate in sensitivity and northern pike, Esox lucius, and bluegills, Lepomis macrochirus, were least sensitive with chronic values of 360 and 368 ug/l respectively. In life cycle or partial life cycle tests, both the rainbow trout and snook trout, Salvelinus fontinalis, were sensitive with chronic values of 265 ug/l. Chronic testing of hexavalent chromium in Daphnia magna found significant survival and fecundity changes at concentrations as low as 10 ug/l. The effects of hexavalent chromium on the freshwater algae, Chlamydomonas reinhardi, were recorded at levels as low as 10 ug/l. The Eurasian watermilfoil displayed the greatest resistance to hexavalent chromium, even at levels as high as 9,900 ug/l.

There are no chronic toxicity data available for trivalent chromium compounds in marine fish, invertebrates or algae.

The only available bioconcentration data for freshwater

species are from studies on rainbow trout, and indicate a bioconcentration factor of 1 for potassium chromate. Marine bioconcentration factors in three species of bivalve molluscs, Mytilus edulis, (34), Crassostrea Virginia (166), and Mya arenaria, (152), give a geometric mean of 114. The weighted average BEF is 11 (U.S. EPA, 1980).

B. Acute Toxicity

The acute toxicity of trivalent chromium compounds has been examined extensively. The 96-hour LC_{50} values for 14 tests ranged from 3,330 to 71,900 ug/l and correlates with the hardness of water over a range of 20 to 360 ug/l (as $CaCO_3$) in 11 species of freshwater fish. The guppy Poecilia reticulata was most sensitive and the bluegill the most resistant. Among eight species of freshwater invertebrates, acute 96-hour LC_{50} values ranged from 2,000 to 64,000 ug/l.

For hexavalent chromium 96-hour LC_{50} values ranged from 17,600 ug/l in the fathead minnow, Pimephales promelas, in soft water to 195,--- ug/l for large mouth bass, Micropteus salmoider, in hard water. The 96-hour LC_{50} values for freshwater invertebrates exposed to hexavalent chromium ranged from 3,100 ug/l in the rotifer, Philodina acuticornis, to 12,000 ug/l in the rotifer, Philodina roseola.

There are no pertinent acute toxicity data available regarding the toxicity of Cr III compounds to marine species.

The acute toxicity data for hexavalent chromium to marine fishes resulted in 96-hour LC_{50} values of 30,000 to 30,000

ug/l for the speckled sanddab, Citharichthys stigmaeus, and 91,000 ug/l for the mummichog, Fundulus heteroclitus. Invertebrates appeared more sensitive to hexavalent chromium than marine fish. The 96 hour LC_{50} values for hexavalent chromium ranged from 2,000 ug/l for the polychaete worm, Nereis vinens, to 105,000 ug/l for the mud snail, Nassarius obsoleutus, in static bioassays.

The U.S. EPA (1978) offers an extensive review of the environmental effects of chromium compounds in freshwater and marine organisms.

VI. EXISTING GUIDELINES

Standards promulgated by various U.S. agencies are summarized in Table I.

Based on animal data indicating carcinogenic effects of chromium VI and estimates of lifetime exposures from consumption of both drinking water and aquatic life forms, the U.S. EPA (1980) has estimated that the concentrations of hexavalent chromium in ambient water should be no greater than 7.1 ng/l to keep the lifetime risk of cancer below 1 in 100,000. This risk calculation is based on the conservative assumption that ingestion of Cr VI can cause cancer. EPA's Water Quality Criteria Document (U.S. EPA 1980) discusses this and alternative assumptions.

The OSHA time-weighted average exposure criterion for chromium (carcinogenic compounds) is 1 ug/m^3; for the "non-carcinogenic" classification of chromium compounds the criterion is 25 ug/m^3 (OSHA 1979).

TABLE 1

Recommended or Established Standards for Cr in the United States

MEDIUM	CHEMICAL SPECIES	REFERENCE	STANDARD
Drinking Water	Cr VI	U.S. Public Health Service (1962)	50 ug/l
Domestic Water Supply	total chromium	U.S. EPA (1976)	50 ug/l
Fresh Water (aquatic life)	total chromium	U.S. EPA (1976)	100 ug/l
Ambient Water Quality Criteria	total chromium[c]	U.S. EPA (1980)	50 ug/l
	Cr VI[c]	U.S. EPA (1980)	0.007 ug/l
Livestock Water	Cr VI	Nat'l. Acad. Sci. (1972) and Nat'l. Acad. Eng. (1972)	1 mg/l
Work Place AIR	carcinogenic Cr VI[a]	Nat'l. Inst. Occup. Safety and Health (1975)	1 ug/m^3
	noncarcinogenic Cr VI[a]	Nat'l. Inst. Occup. Safety and Health (1975)	25 ug/m^3 TWA[b] 50 ug/m^3 ceiling
	soluble chromic and chromous salts	29 CFR 1910.1000	0.5 mg/m^3
	metal and insoluble salts	29 CFR 1910.000	1.0 mg/m^3

[a]Carcinogenic compounds are here taken to include all forms of Cr VI other than CrO_3 and mono-or dichromates of H, Li, Na, K, Rb, Cs, and NH_4.

[b]ime-weighted average

For the protection of aquatic species, proposed water criteria for both trivalent and hexavalent chromium in freshwater and marine environments have been prepared in accordance with the Guidelines for Deriving Water Quality Criteria (Federal Register 43:21506, May 18, 1975 and Federal Register 43:29028, July 5, 1978). In freshwater environments the proposed criterion for hexavalent chromium is 10 ug/l, not to exceed 110 ug/l, and the proposed criterion for trivalent Cr is given a Chronic Final Value represented by the following equation:

$$C.F.V. = e\ (0.83\ \ln(\text{water hardness}) = 2.94)$$

The proposed criterion for trivalent chromium in marine environments could not be determined by criteria established in the Guidelines.

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No. 52

Chrysene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated chrysene and has found sufficient evidence to indicate that this compound is carcinogenic.

CHRYSENE

Summary

Chrysene is a member of the polynuclear aromatic hydrocarbons (PAH) class. Numerous compounds in the PAH class are well-known as potent animal carcinogens. However, chrysene is generally regarded as only a weak carcinogen to animals. There are no reports available concerning the chronic toxicity of chrysene. Although exposure to chrysene in the environment occurs in conjunction with exposure to other PAH, it is not known how these compounds may interact in human systems.

No standard toxicity data for chrysene are available for freshwater or marine organisms.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multi-media Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Chrysene ($C_{18}H_{12}$) is one of the family of polynuclear aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Its physical/chemical properties have not been well-characterized, other than a reported melting point of 254°C and a boiling point of 448°C (U.S. EPA, 1979b).

PAH, including chrysene, are ubiquitous in the environment, being found in ambient air, food, water, soils, and sediment (U.S. EPA, 1979b). The PAH class contains a number of potent carcinogens (e.g., benzo(a)pyrene), moderately active carcinogens (e.g., benzo(b)fluoranthene), weak carcinogens (e.g., chrysene), and cocarcinogens (e.g., fluoranthene), as well as numerous non-carcinogens (U.S. EPA, 1979b).

PAH which contain more than three rings (such as chrysene) are relatively stable in the environment and may be transported in air and water by adsorption to particulate matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment.

The reader is referred to the PAH Hazard Profile for more general discussion of PAH (U.S. EPA, 1979c).

II. EXPOSURE

A. Water

Levels of chrysene are not routinely monitored in water. However, the concentration of six representative PAH (benzo(a)pyrene, fluoranthene, benzo(k)fluoranthene, benzo(j)fluoranthene, benzo(g,h,i)perylene, and indeno(1,3-cd)pyrene) in U.S. drinking water averaged 13.5 ng/l (Basu and Saxena, 1977,1978).

B. Food

Chrysene has been detected in a wide variety of foods such as coconut oil (12 ppb), and smoked or cooked meats (up to 66 ppb) (U.S. EPA, 1979b). Although it is not possible to accurately estimate the human dietary intake of chrysene, it has been concluded (U.S. EPA, 1979b) that the daily dietary intake for all types of PAH is in the range of 1.6 to 16 ug. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for chrysene to be 3,100 for the edible portion of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient for chrysene.

C. Inhalation

Chrysene is commonly found in ambient air. Measured concentrations of chrysene have reportedly been in the range of 0.6 to 4.8 ng/m^3 (Gordon, 1976; Fox and Staley, 1976). Thus, the human daily intake of chrysene by inhalation of ambient air may be in the range of 11.4 to 91.2 ng, assuming that a human breathes 19 m^3 of air per day.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature concerning the pharmacokinetics of chrysene or other PAH in humans. Nevertheless, it is possible to make limited assumptions based on the results of animal research conducted with several PAH, particularly benzo(a)pyrene.

A. Absorption

The absorption of chrysene in humans has not been studied. However, it is known (U.S. EPA, 1979a) that, as a class, PAH are well-absorbed across the respiratory and gastrointestinal epithelia. In particular, chrysene was reported to be readily transported across the gastrointestinal mucosa (Rees, et al. 1971). The high lipid solubility of compounds in the PAH class supports this observation.

B. Distribution

The distribution of chrysene in mammals has not been studied. However, it is known (U.S. EPA, 1979a) that other PAH are widely distributed throughout the body following their absorption in experimental rodents. Relative to other tissues, PAH tend to localize in body fat and fatty tissues (e.g., breast).

C. Metabolism

Limited work on the metabolism of chrysene has been conducted, as part of an investigation into the mechanism of its bioactivation to a mutagen/carcinogen (Wood, et al. 1977).

Chrysene, like other PAH, is apparently metabolized by the microsomal mixed-function oxidase enzyme system in mammals (U.S. EPA, 1979b). Metabolic attack on one or more of the aromatic double bonds leads to the formation of phenols, and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed-function oxidases to yield diol epoxides, compounds which are known to be biologically reactive intermediates for certain PAH. Removal of activated intermediates by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

The excretion of chrysene by mammals has not been studied. However, the excretion of closely related PAH is rapid, and occurs mainly via the feces (U.S. EPA, 1979a). Elimination in the bile may account for a significant percentage of administered PAH. However, the rate of disappearance of various PAH from the body, and the principal routes of excretion, are in-

fluenced both by the structure of the parent compound and the route of administration (U.S. EPA, 1979b). It is unlikely that PAH will accumulate in the body with chronic low-level exposures.

IV. EFFECTS

A. Carcinogenicity

Chrysene is regarded as a weak animal carcinogen (U.S. EPA, 1979b). LaVoie and coworkers (1979) reported that chrysene can act as both a tumor initiator and as a complete carcinogen on the skin of mice.

B. Mutagenicity

Chrysene is positive in the Ames Salmonella assay in the presence of a metabolizing enzyme system (LaVoie, et al. 1979; Wood, et al. 1977). Chrysene is also positive in the induction of sister-chromatid exchanges in Chinese hamster cells (Roszinsky-Kocher, et al. 1979).

C. Teratogenicity

Pertinent data could not be located in the available literature concerning the possible teratogenicity of chrysene. Other related PAH are apparently not significantly teratogenic in mammals (U.S. EPA, 1979a).

D. Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature regarding other reproductive effects and chronic toxicity.

V. AQUATIC TOXICITY

The only data concerning the effects of chrysene to aquatic organisms is a single bioconcentration factor of 8.2 (24-hour) for the marine clam (Rangia cuneata) (Neff, et al. 1976). No standard aquatic toxicity data for chrysene either in acute or chronic studies are available for freshwater or marine species.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

There are no established exposure criteria for chrysene. However, PAH as a class are regulated by several authorities. The World Health Organization has recommended that the concentration of PAH in drinking water (measured as the total of fluoranthene, benzo(g,h,i)perylene, benzo(b)fluoranthene, benzo(h)fluoranthene, indeno(1,2,3-cd)pyrene, and benzo(a)pyrene) not exceed 0.2 µg/l. Occupational exposure criteria have been established for coke oven emissions, coal tar products, and coal tar pitch volatiles, all of which contain large amounts of PAH including chrysene (U.S. EPA, 1979a).

The U.S. EPA (1979a) draft recommended criteria for PAH in water are based upon the extrapolation of animal carcinogenicity data for benzo(a)pyrene and dibenz(a,h)anthracene.

B. Aquatic

Data is insufficient for drafting freshwater or marine criterion.

CHRYSENE

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No. 53

Creosote

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated creosote and has found sufficient evidence to indicate that this compound is carcinogenic.

CREOSOTE

I. INTRODUCTION

Creosote is a coal-tar distillate used mainly as a wood preservative. It is highly toxic to wood-destroying organisms and has a low evaporation rate (Farm Chemicals Handbook, 1977). In 1972, an estimated 521,000 tonnes (575,000 tons) were produced by six companies at 25 sites in the United States (von Rumker, et al. 1974). About 90 percent of the creosote is sold to the wood-preservation industry; the remainder is burned as fuel (von Rumker, et al. 1974).

Creosote's other pesticidal uses are as an herbicide, an insecticide, an acaricide, an arachnicide, a fungicide, a tree dressing, a disinfectant, and a horse repellent (Table 1).

TABLE 1.

USES AND SITES FOR CREOSOTE
(Cummings, 1977)

Use	Site
Preservative	Wood
Insecticide (screwworm)	Horses and mules
Acaricide (mites)	Poultry and horses
Arachnicide (ticks)	Poultry and horses
Herbicide	Along roads, highways, and fences; farms; flower beds
Fungicide	Rope, canvas, tarpaulins, tree wounds
Insecticide (Certain insects, worms, moths and borers)	Tree dressing
Horse repellent	Wood stalls, mangers, gates, fence rails, posts, trees, trailer sites
Disinfectant	Outhouses, water closets, garbage cans, feeding and watering equipment

Creosote is produced by the distillation of coal tar obtained from the coking of coal. The composition of creosote is highly variable and depends on the composition of the coal used to make the tar, the design and operating conditions of the coke oven (e.g., gas collection system, temperature, coking time), and the design and operating condition of the still (e.g., feed rate, temperature, and blending of tar distillation fractions) (43 FR 48154, 1978).

Continuous tar distillation at temperatures of up to 400°C produces fractions typically ranging from crude benzene to residue pitches (von Rumker, et al. 1974). A common distillation temperature for creosote is about 200 to 400°C (Hawley, 1977; von Rumker, et al. 1974). The creosote fraction is a mixture of organic compounds, mainly liquid and solid cyclic hydrocarbons, including two-ring and polynuclear aromatic hydrocarbons (PAH) (Table 2). Among the PAH, phenanthrene represents 12 to 14 percent of the composition of creosote (Considine, 1976). Benzo(a)pyrene (BaP) is present at a concentration of about 200 ppm (Guerin, 1977).

II. EXPOSURE

A. Water

Each year an estimated 60 to 115 million pounds (27,000-52,000 tonnes) of creosote are discharged in wastewater treatment sludges by creosote producers. At large tar distillation plants, wastewater streams containing creosote are treated on-site and/or conveyed to public sewage treatment facilities. Wastewater sludges treated on-site are transferred to landfill or burial sites (von Rumker, et al. 1974). The estimated flux of creosote from these disposal sites ranges from 0.75 $kg/m^2/hr$ to 11.0 $kg/m^2/yr$ (U.S. EPA, 1980). In 1972, about one billion pounds (455,000

TABLE 2.

PHYSICAL AND CHEMICAL PROPERTIES OF CREOSOTE

Synonyms: Brick oil, coal tar oil, creosote oil, creosotum, cresylic creosote, dead oil, heavy oil, liquid pitch oil, naphthalene oil, tar oil, wash oil

Structural and Empirical Formula: Consists principally of liquid and solid cyclic hydrocarbons; contains substantial amounts of naphthalene and anthracene; 12-14 percent phenanthrene; 200 ppm benz(a)pyrene

Molecular Weight: ---

Description: Dark brown green, yellowish or colorless above 38°C, naphthenic odor; soluble in alcohol, benzene toluene; immiscible with water

Specific Gravity and/or Density: d^{25}_{25} more than 1.076

Melting and/or Boiling Points: Common distillation range 200 to 400°C

Stability: Overall degradation rate (0.48/day) = same as microbial degradation

Solubility (water): approx. 5 g/l; $\frac{sed}{H_2O} \cdot \frac{.2}{1}$

Vapor Pressure: ---

Bioconcentration Factor (BCF) and/or
Octanol/water partition coefficient (K_{ow}): BCF = 0.6
K_{ow} = 1.0

Source: Hawley, G.G., 1977; Windholz, 1976; U.S. EPA, 1980; Lopedes, 1978

tonnes) of creosote were used to preserve railroad ties, marine pilings and utility poles (NIOSH, 1977a).

Some of the organics present in creosote are moderately soluble. Creosote partitions between sediments and water in a ratio of 1:5. It is considered stable in groundwater, but decomposes at an estimated rate of 90 percent in five days in river water flowing 50-250 miles. About 99 percent decomposed in a lake environment in one year (U.S. EPA, 1980).

Creosote migrates from treated wood into the environment, but the impact of this migration is unknown. Creosote was found to have a vapor loss of 27.5 and 15.2 percent from the outer two inches of seasoned and green poles, respectively; high residue creosote was estimated to have a 10.3 and 4.4 vapor loss, respectively. Creosote losses to the aquatic environment are the greatest during the first years after installation. One eight-year study is summarized below (43 FR 48154, 1978).

Year	Creosote Loss pounds/linear foot
1	0.31
2	0.05
3	0.06
4	0.22
4-8	0.15 (average)

B. Food

Naiussat and Auger (1970) found that PAHs in a contaminated lagoon accumulated to the greatest extent in species near the top of the food chain. One of these compounds, BaP, has been reported to accumulate in mussels (about 50 µg/kg; 20 times background) taken from creosote-treated pilings (43 FR 48154, 1978). Elevated levels of BaP in mussels growing near creosoted timbers or pilings suggest that creosote is a significant source of BaP in the marine environment. This suggestion was supported by compari-

sons of gas chromatography profiles of polycyclic aromatic hydrocarbons isolated from mussels and creosoted wood (Dunn and Stich, 1976).

High levels of PAH have been found in commercial seafoods grown in impoundments constructed of creosoted wood. Commercial samples of oysters, clams, and mussels were found to contain BaP at concentrations generally less than 10 ng/g (wet weight). PAHs were also found in cockels, abalone, scallops, lobster, and shrimp. Levels of BaP and other related PAHs were found to be inversely related to the ability of the species to metabolize PAH, except in the case of lobster. Unexpectedly high levels were found in all edible meat of lobsters maintained in commercial tidal compounds constructed of creosoted timber: up to 281 ng/g BaP, 303 ng/g chrysene, 222 ng/g benzo(a)anthracene, 261 ng/g benzo(b)fluoranthene, 153 ng/g dibenz-(a,h)anthracene, and 137 ng/g indeno(1,2,3-cd)pyrene (Dunn and Fee, 1979).

III. PHARMACOKINETICS

A. Absorption

Creosote is (readily) absorbed through the skin and mucous membranes (NIOSH, 1977b).

IV. EFFECTS

A. Carcinogenicity

Creosote has been associated with several occupational cases of skin cancer over a 50-year period (Farm Chemicals Handbook, 1977); its role in human cancer is still not clearly understood (NIOSH, 1977b).

Henry (1947), Lenson (1956), O'Donovan (1920), Cookson (1924), and Mackenzie (1898) described various kinds of workers who were occupationally exposed to creosote and developed skin tumors. Dermal application of creosote produced skin tumors in mice (Woodhouse, 1950; Poel and Kammer, 1957; Lijinsky, et al. 1956; Boutwell and Bosch, 1958; Roe, et al. 1958). Roe, et

al. (1958) also found that dermal application of creosote to mice produced lung tumors. Boutwell and Bosch (1958) found that creosote had the ability to initiate tumor formation when applied for a limited period prior to treatment with croton oil. Sall and Shear (1940) found that the number of skin tumors was increased by dermal treatment with creosote and benzo(a)pyrene over the number of tumors produced by benzo(a)pyrene or creosote alone. There is considerable evidence to show that creosote produces tumors in mice; that creosote, when applied dermally, is a tumor-initiating agent when followed by dermal treatment with croton oil (Boutwell and Bosch, 1958); that creosote accelerates the tumor production caused by benzo(a)pyrene (Sall and Shear, 1940); and that workers occupationally exposed to creosote developed tumors (Table 3). These studies have not yet demonstrated a correlation between the carcinogenic potency of creosote oils and the content of benzpyrene (Patty, 1963).

Results from dose response studies are summarized below (NIOSH, 1977a).

Concentration and duration	Effects
100% 3x/wk 28 wk	Skin carcinomas in 82%, tumors in 92%
20-80% 3x/wk 6-44 wk	Skin carcinomas in 88%, tumors in 100%
100% 2x/wk 21 wk	Skin and lung tumors in 74%
100% 3x/wk 70 wk	Skin tumors in 50%
10-100% 2x/wk* 70 wk	Skin tumors in 38-74%
2% 2x/wk* 70 wk	No tumors

*Creosote plus 1 percent 7,12-dimethylbenz(a)anthracene.

TABLE 3.

SUMMARY TABLE ON ONCOGENICITY OF CREOSOTE

A. Human Case Reports

Authors	Year	Substance and Type of Exposure	Occupation of Exposed Individual(s)	Type of Tumor Response
Mackenzie	1896	Handling of Creosote	Worker who dipped railway ties in creosote	Warty elevation on arms; papillomatous swellings on scrotum
O'Donovan	1920	Handling of Creosote	Workers who creosoted timbers	Skin cancer
Cookson	1924	Handling of Creosote	Creosote factory worker	Squamous epitheliomata on hand; epitheliomatous deposits in liver, lungs, kidneys and heart walls
Henry	1947	Handling of Creosote	37 men of various occupations	Cutaneous epitheliomata
Lenson	1956	Painting of Creosote	Shipyard worker	Malignant cutaneous tumors of the face

B. Animal Studies

Dermal Exposure

Authors	Year	Substance Tested	Animal and Strain	Type of Tumor Response
Sall and Shear	1940	Creosote and benzo(a)pyrene	Mice (Strain A)	Accelerated tumor formation
Woodhouse	1950	Creosote oil	Mice (Albino; Undefined strain)	Papillomas and carcinomas
Lijinsky, et al.	1956	#1 creosote oil	Mice - Swiss	Papillomas and carcinomas
Poel and Kammer	1957	Blended creosote oils;	Mice (C57L Strain)	Papillomas and carcinomas metastatic growths in lungs and lymph nodes
		Light creosote oil	Mice (C57L Strain)	Papillomas
Boutwell and Bosch	1958	Creosote (Carbasota)	Mice (Albino - random bred)	Papillomas and carcinomas
Roe, et al.	1958	Creosote oil (Carbasota)	Mice (Strain Undefined)	Skin and lung tumors

B. Mutagenicity

Simmon and Poole (1978) found that, following metabolic activation by Arochlor 1254-stimulated rat liver homogenate, both the creosote P1 and the coal tar-creosote P2 produced a mutagenic dose-response and a doubling above background mutation rate with Salmonella typhimurium strains TA 1537, TA 98, and TA 100. Mitchell and Tajiri (1978) found that, following metabolic activation by Arochlor 1254-stimulated rat liver homogenate, creosote P1 and coal tar creosote P2 increased the number of forward mutations at the thymidine kinase locus of L5178Y mouse lymphoma cells in a dose-related manner. There is considerable evidence which proves that creosote P1 and P2 cause mutations in Salmonella typhimurium strains TA 1537, TA 98 and TA 100, and in L5178Y mouse lymphoma cells.

C. Teratogenicity and Other Reproductive Effects

Investigations utilizing pregnant swine indicate that direct contact with lumber freshly treated with creosote would produce acute toxicosis, resulting in extensive mortality in newborn swine. The direct contact of the pregnant sow with lumber freshly treated with creosote provides sufficient dermal absorption to cause fetal deaths and weak pigs at birth. Creosote is extremely toxic to young swine; the degree of toxicity lessens as the pigs become older (Schipper, 1961).

D. Chronic and Acute Toxicity

Skin contact with creosote or exposure to its vapors may cuase burning, itching, papular and vasicular eruptions, or gangrene. Eye injuries can include keratitis, conjunctivitis, and corneal abrasion (Patty, 1963). Exposed skin shows increased susceptibility to sunburn, an effect attributed to photo-toxic substances usually present in commercial grades of creosote. Eventually, exposed skin areas become hyperpigmented (NIOSH, 1977b).

Serious systemic effects, including cardiovascular collapse and death, have been observed only after ingestion (NIOSH, 1977b). Fatalities have occurred within 14 to 36 hours after ingestion of 7 grams by adults or 1 to 2 grams by children. Symptoms of systemic illness include salivation, vomiting, respiratory difficulties, vertigo, hypothermia, cyanosis, and mild convulsion (Patty, 1963). Once widely used in medicine, occasional instances of self-medication are still reported and sometimes lead to chronic visual disturbances, hypertension, and gastrointestinal bleeding (NIOSH, 1977b).

The oral LD_{50} in rats is estimated at 725 mg creosote per kilogram body weight (mg/kg). The reported LD_{Lo} for dogs, cats, and rabbits is 600 mg/kg (Fairchild, 1977).

V. AQUATIC TOXICITY

Ellis (1943) found fish kills occurring at creosote concentrations as low as 6.0 mg/l in less than 10 hours. Applegate, et al. (1957), using small numbers of subjects, found that concentrations of 5.0 mg/l produced no mortalities in rainbow trout (Salmo gainneri), bluegill (Lepomis macrochirus), or lamprey larvae (Petromyzon marinus).

The 8-day LD_{50} of a 60:40 mixture of creosote and coal tar in bobwhite quail (Colinus virginianus) was reported to be about 1,260 ppm; in the mallard duck (Anas platyrhynchos), 10,388 ppm. The 24-hour 50 percent medium tolerance limit (TL_{50}) of the creosote/coal tar mixture was 3.72 ppm in rainbow trout (Salmo gainneri) and 4.42 ppm in the bluegill (Lepomis macrochirus). The 24-hour TL_{50} concentrations in goldfish (Carrasius auratus) and rainbow trout were 3.51 and 2.6 ppm, respectively (Webb, 1975).

VI. EXISTING GUIDELINES AND STANDARDS

The Office of Toxic Substances of EPA has issued RPAR on creosote and is continuing preregulatory assessment under Section 6 of the Federal Insecticide, Fungicide and Rodenticide Act.

A time-weighted average creosote concentration of 0.1 mg/m^3 has been recommended for occupational air exposure.

The aquatic toxicity rating for creosote is reported as TLm_{96} = 10-1 ppm (Fairchild, 1977).

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No. 54

Cresols and Cresylic Acid

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

Cresol and Cresylic Acid

I. INTRODUCTION

Cresols are methyl phenols with methyl group at the o-, p-, m- position. It has a molecular weight of 108, a melting point of between 11-35°C and a boiling point of between 191-203°C. It is slightly soluble in water, but soluble in alcohols, glycols, dilute alkalis, ether and chloroform. Cresylic acid is the refined product from coal tar and contains the three isomers of cresol (the crude product from coal tar is creosote).

Cresols are quite stable in soil due to their antimicrobial properties. o-cresol is degraded in air to quinones and dihydroxybenzene by O_3 with an estimated half-life of 1 day. The m- and p- isomers are expected to behave similarly.

Cresols are used as disinfectants, agricultural chemicals, solvents, chemical intermediates, metal cleaners, and motor oil additives. p-cresol is permitted in U.S. as a food flavoring and for fragrance in soaps, lotions and perfumes. Annual production if 150 million pounds. NIOSH[1] estimates that the annual environmental release of the mixed isomers is 30 million pounds.

II. PHARMACOKINETICS

Cresols are rapidly metabolized and thus unlikely to bioaccumulate in mammals.[2]

III. EFFECTS ON MAMMALS

A. Carcinogenicity: CAG[2] concluded that the data base

for this chemical is weak. No data exist on which to determine carcinogenesis in mice. The literature cites three case reports of cancer in humans occupationaly exposed.

B. Mutagenicity: CAG[2] concluded that cresols cause chromosome fragmentation in plants. No other mutagenicity studies have been done.[2]

C. Toxicity: They are corrosive to the skin and mucuous membranes and moderately toxic by ingestion and dermal exposure. The organs affected are CNS, liver, lung, kidneys, stomach, eyes, and heart. No epidemiological studies of workers have been done.[1]

IV. EXISTING GUIDELINES

The current occupational standard (TWA) is 5 ppm. NIOSH[1] recommends a lowering to 2.3 ppm.

DOSSIER

ON

CRESOLS

BY

Clement Associates, Inc.
1055 Thomas Jefferson Street, NW
Washington, D.C. 20007

December, 1977

Contract No. NSF-C-ENV77-15417

Prepared for

TSCA Interagency Testing Committee
Washington, D.C.

54-5
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FOREWORD

This dossier has been prepared by Clement Associates, Inc. (Clement), in partial fulfillment of Contract NSF-C-ENV77-15417, sponsored by the National Science Foundation, to provide technical support to the Toxic Substances Control Act (TSCA) Interagency Testing Committee. The Committee is charged with the responsibility for making recommendations to the Administrator of the Environmental Protection Agency (EPA) regarding chemical substances or mixtures which should be given priority by EPA for testing to determine adverse effects on man or the environment.

The dossier was designed to provide the Committee with information on the chemical's physical and chemical properties, exposure characteristics, and biological properties in sufficient detail to support an informed judgment on whether the substance should be given priority for testing. The dossier is not intended to represent a comprehensive critical review. Such a review could not be performed with the constraints imposed upon the Committee (and, therefore, the contractor) by the statutory deadlines of TSCA.

Faced with the task of preparing dossiers which could be quickly assembled and yet contain sufficient information for the Committee's purposes, Clement proceeded along the following lines.

Literature searches were conducted using the National Library of Medicine's TOXLINE and the Environmental Mutagen Information Center (EMIC) automated data banks. Each reference on a list of sources of general information (see "General References" in bibliography) was reviewed. Further references and information were obtained from monographs, criteria documents, reviews, and reports available from government agency files and trade association libraries. Information received in response to the Committee's July 1977 Federal Register notice requesting information on certain substances was reviewed. Clement scientists relied upon their own knowledge of the literature to augment the data sources.

In general, secondary sources were relied upon in preparing the dossiers. When an article was judged to contain information of major significance or to require a critical review the primary source was consulted. The text makes clear whether a primary or secondary source of information was used.

KEY TO ABBREVIATIONS

TCLo - Lowest published toxic concentration
- the concentration of a substance in air which has been reported to produce any toxic effect in animals or humans over any given exposure time.

TDLo - Lowest published toxic dose
- the lowest dose of a substance introduced by any route other than inhalation over any given period of time that has been reported to produce any toxic effect in animals or humans.

LCLo - Lowest published lethal concentration
- the lowest concentration of a substance, other than an LC50, in air that has been reported to have caused death in humans or animals over any given exposure time.

LDLo - Lowest published lethal dose
- the lowest dose of a substance other than LD50 introduced by any route other than inhalation over any given period of time that has been reported to have caused death in humans or animals.

LC50 - Median lethal concentration
- the concentration of a test material that kills 50 per cent of an experimental animal population within a given time period.

LD50 - Median lethal dose
- the dose of a test material, introduced by any route other than inhalation, that kills 50 percent of an experimental animal population within a given time period.

LT50 - Median Lethal Response Time
-Statistical estimate of the time from dosage to the death of 50 percent of the organisms in the population subjected to a toxicant under specified conditions.

TLm - Median tolerance limit
- the concentration of a test material at which 50 per cent of an experimental animal population are able to survive for a specified time period.

TLV® - Threshold limit value
- the airborne concentration of a substance to which nearly all workers may be repeatedly exposed day after day without adverse effect.

TLV®-TWA - Threshold limit value - time weighted average
- the time-weighted average concentration of a substance for an 8-hour workday or 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

TLV®-STEL- Threshold limit value - short term exposure limit-
- the maximal concentration of a substance to which workers can be exposed for up to 15 minutes without suffering acute or chronic toxic effects. No more than four excursions per day are permitted. There must be at least 60 minutes between exposure periods. The daily TLV-TWA must not be exceeded.

BOD - Biochemical oxygen demand
- a measure of the presence of organic materials which will be oxidized biologically in bodies of water.

NOHS Occupational Exposure:

- Rank
  - an ordering of the approximately 7000 hazards occurring in the workplace from most common to least common

- Estimated number of persons exposed
  - includes full- and part-time workers. For hazards ranked 1 through 200, the figure projected to national statistics by NIOSH is given; for the remaining hazards the number of people exposed given in the survey was multiplied by a fixed number to give a rough estimate of national exposure. The fixed number used, --30--, is derived from the statistical sampling technique used in this survey.

i - insoluble

ss - slightly soluble

s - soluble

vs - very soluble

∞ - soluble in all proportions

bz - benzene

chl - chloroform

eth - ether

peth - petroleum ether

ace - acetone

lig - ligroin

alc - alcohol

CCl_4 - carbon tetrachloride

dil. alk. - dilute alkalis

CS_2 - carbon disulfide

os - organic solvents

oos - ordinary organic solvents

CRESOLS

AN OVERVIEW

There are three isomers of cresol: o-cresol, m-cresol, and p-cresol. All three isomers as well as mixtures are articles of commerce. Cresols are solid or liquid at room temperature (melting points 11-35°C). They are slightly soluble in water and soluble in organic solvents.

Total annual production of cresols in the United States is probably in excess of 100 million pounds. They are used for a wide variety of purposes, including uses as disinfectants, solvents, in ore flotation, and as intermediates in the production of phosphate esters and phenolic resins. The number of persons occupationally exposed to cresols is estimated to be two million. They are also present in a number of consumer products, including disinfectants, metal cleaners, and motor oil additives.

Cresols are manufactured both from petroleum and from coal. The composition of the commercial products depends on the method of production and upon the degree of refining. Cresols are sold in a wide variety of grades, varying in composition, color, and boiling range. Technical grade cresols commonly contain xylenols and phenol. A less refined product called creosote oil contains 10-20% by volume of tar from the coking process.

Cresols are relatively easily metabolized by mammals and micro-organisms and are unlikely to undergo significant bio-accumulation. They are moderately toxic to mammals by ingestion and dermal exposure, and are corrosive to skin and other tissues. No data are available on their toxicity by inhalation. Little information is available on effects of chronic exposure.

In one experiment all three isomers of cresol were reported to promote the carcinogenicity of dimethylbenzanthracene on mouse skin. m-Cresol caused developmental abnormalities in toad embryos. Otherwise, no significant information is available on the potential carcinogenicity, mutagenicity, or teratogenicity of cresols.

Cresols have a broad spectrum of toxicity to micro-organisms and are used as disinfectants and fungicides. There is little other information on their potential toxicity to wildlife.

CRESOLS

PART I

GENERAL INFORMATION

I. Cresol (mixed isomers)

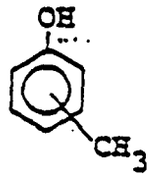
1.1 Identification — CAS No. 001319773
NIOSH No. GO59500

1.2 Synonyms and Trade Names

Cresylic acid; methyl phenol; hydroxytoluene; tricresol; cresylol

(G23,G21,G16)

1.3 Chemical Formula and Molecular Weight



C_7H_8O Mol. Wt. 108.15

(G23)

1.4 Chemical and Physical Properties

1.4.1 Description: A mixture of isomers in which m-isomer predominates, obtained from coal tar or petroleum; colorless, yellow or pinkish liquid; phenolic odor; combustible; becomes darker with age and on exposure to light.

(G21,G23)

1.4.2 Boiling Point: 191 - 203° C (G21)

1.4.3 Melting Point: 11 - 35° C (G21)

1.4.4 Absorption Spectrometry:

No information found in sources searched

1.4.5 Vapor Pressure: No information found in sources searched

1.4.6 Solubility: Soluble in alcohol, glycol, dilute alkalis, ether, chloroform; Slightly soluble in water

(G21,G25)

1.4.7 Octanol/Water Partition Coefficient:

Log P_{oct} = 2.70 (estimate)

1.5 Production and Use

1.5.1 Production: ~60 Million lbs (1968)
~80 Million lbs (1973)
(G25)

1.5.2 Use: As a disinfectant; intermediate in manufacturing of phenolic resins, tricresyl phosphate, salicylaldehyde, coumarin, and herbicides; as an ore flotation agent; as a textile scouring agent; as an organic intermediate; as a surfactant
(G21)

Quantitative Distribution of Uses:

	Percent
Phosphate esters	22
Magnet wire	15
Antioxidants	15
Resins	15
Exports	10
Cleaning and disinfectant compounds	6
Ore flotation	6
Miscellaneous	11
	100 (G25)

Consumer Product Information:

Cresol is present in:

automotive parts cleaner
metal cleaner, stripper, degreaser
disinfectant
motor oil additive
carbon remover
embalming supplies (G35)

1.6 Exposure Estimates

1.6.1 Release Rate: 30.4 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 105

Estimates no. of persons exposed: 1,914,000
(G29)

II. m-Cresol

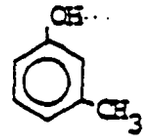
1.1 Identification CAS No.: 000108394
NIOSH No.: GO61250

1.2 Synonyms and Trade Names

m-Cresylic acid; m-methylphenol; 3-methylphenol; 1-hydroxy-3-methyl-benzene; m-kresol; m-oxytoluene

(G16)

1.3 Chemical Formula and Molecular Weight



C_7H_8O Mol. wt. 108.15

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless to yellowish liquid; phenol-like odor (G21)

1.4.2 Boiling Point: 202.2° C (G22)

1.4.3 Melting Point: 11.5° C (G22)

1.4.4 Absorption Spectrometry:

λ_{max}^{hexane} = 214, 271, 277

log ϵ = 3.79, 3.20, 3.27 (G22)

1.4.5 Vapor Pressure: 1 mm at 52.0° C (G22)

1.4.6 Solubility: Slightly soluble in water; Soluble in hot water, organic solvents; Soluble in all proportions in alcohol, ether, acetone, benzene and carbon tetrachloride

(G22)

1.4.7 Octanol/Water Partition Coefficient:

$\log P_{oct} = 2.37$ (G15)

1.5 Production and Use

1.5.1 Production:

No information found in sources searched

1.5.2 Use:

In disinfectants and fumigants; in photographic developers, explosives (G23)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

Rank: 2781

Estimated no. of persons exposed: 9,000*

*rough estimate (G29)

1.7 Manufacturers

Koppers Co., Inc. (G24)

III. o-Cresol

1.1 Identification

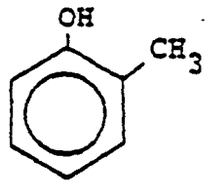
CAS No. 000095487
NIOSH No. GO63000

1.2 Synonyms and Trade Names

o-Cresylic acid; o-methyl phenol; 2-methyl phenol; orthocresol; 1-hydroxy-2-methylbenzene; o-hydroxy-toluene; o-methylphenol; o-oxytoluene; 2-hydroxy-toluene

(G16)

1.3 Chemical Formula and Molecular Weight



C_7H_8O Mol. Wt. 108.15

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: White crystals; phenol-like odor; combustible; becomes dark with age and exposure to air and light. (G23,G21)

1.4.2 Boiling Point: 190.95° C (G22)

1.4.3 Melting Point: 30.94° C (G22)

1.4.4 Absorption Spectrometry:

$\lambda^{\text{Water}}_{\text{Max}}$ = 219, 275 nm

log ϵ = 3.71, 3.22 (G22)

1.4.5 Vapor Pressure: 1 mm at 38.2° C (G22)

1.4.6 Solubility: Soluble in water and ordinary organic solvents; Very soluble in alcohol and ether; Soluble in all proportions in acetone, benzene, carbon tetrachloride

(G22)

1.4.7 Octanol/Water Partition Coefficient:

$$\text{Log } P_{oct} = 3.40 \qquad \text{(G15)}$$

1.5 Production and Use

1.5.1 Production:

49.700	Million lbs	(1972)	(G28)
20.481	Million lbs	(1975)	(G24)
22.187	Million lbs	(1976)	(G24)

1.5.2 Use: Disinfectant; solvent (G23)

1.6 Exposure Estimates

1.6.1 Release Rate: 15.6 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 1480

Estimates no. of persons exposed: 52,000*

*rough estimate (G29)

1.7 Manufacturers

from coal tar:

Koppers Co., Inc.
Ferro Corp.

from petroleum:

Merichem Co.
Ferro Corp.
Sherwin-Williams Co.

(G24)

IV. p-Cresol

1.1 Identification CAS No.: 000106445
NIOSH No.: GO64750

1.2 Synonyms and Trade Names

4-Cresol; p-cresylic acid; 1-hydroxy-4-methylbenzene; p-hydroxytoluene; 4-hydroxytoluene; p-kresol; 1-methyl-4-hydroxybenzene; p-methylphenol; 4-methylphenol; p-oxytoluene; para-cresol; paramethyl phenol

(G16)

1.3 Chemical Formula and Molecular Weight

C_7H_8O Mol. wt. 108.15

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Crystalline mass; phenol-like odor

(G21)

1.4.2 Boiling Point: 201.9° C (G22)

1.4.3 Melting Point: 34.8° C (G22)

1.4.4 Absorption Spectrometry:

$\lambda_{max}^{cyclohexane}$ = 280 nm

log ϵ = 3.23 (G22)

1.4.5 Vapor Pressure: 1 mm at 53.0° C (G22)

1.4.6 Solubility: Slightly soluble in water; Soluble in hot water, organic solvents; Soluble in all proportions in alcohol, ether, acetone, benzene and carbon tetrachloride

(G22)

1.4.7 Octanol/Water Partition Coefficient

Log P_{oct} = 2.35 (G15)

1.5 Production and Use

1.5.1 Production:

No information found in sources searched

1.5.2 Use:

As a chemical intermediate (G24)

1.6 Exposure Estimate

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure

Rank: 2466

Estimated no. of persons exposed: 14,000*

*rough estimate

(G29)

1.7 Manufacturers

Sherwin-Williams Co.

(G24)

CRESOLS

SUMMARY OF CHARACTERISTICS

Name	Solubility	Log P_{oct}	Estimated Environmental Release (Million lbs)	Production (Million lbs)	Estimated no. of persons exposed (occupational)	Use
Cresol (mixed isomers)	s in alc, glycol, dil. alk, eth, chl. ss in H_2O	2.70	30.4	~60 (1968) ~80 (1973)	1,914,000	Disinfectant; phenolic resins; tricresyl phosphate; ore flotation; textile scouring agent; organic intermediate; mfg. of salicylaldehyde coumarin, and herbicides surfactant
o-Cresol	s in H_2O and OOS. vs in alc and eth. oo in ace, bz, CCl_4.	3.40	15.6	49.7 (1972) 20.481(1975) 22.187(1976)	~ 52,000	Disinfectant, solvent
m-Cresol	ss in H_2O; s in hot H_2O, os; oo in alc, eth, bz, ace, CCl_4	2.37	*	*	~ 9,000	In disinfectants, fumigants, photographic developers, explosives
p-Cresol	ss in H_2O; s in hot H_2O, os; oo in alc, eth, bz, ace, CCl_4	2.35	*	*	~ 14,000	cyclic intermediate

No information found in sources searched.

CRESOLS

PART II.

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

Log octanol/water partition coefficients are 3.40, 2.37, and 2.35 for the o-, m-, and p-isomers, respectively (G15). The high partition coefficient of the o-isomer is due to the steric effect of the methyl group on the hydroxyl group. The high octanol/water partition coefficients of the cresols indicate that bioaccumulation in aquatic organisms is a possibility, but specific data on such bioaccumulation are not available. By analogy with phenol, which appears to be completely eliminated from the body within 24 hours (G19), it is expected that cresols would not be bioaccumulated in mammals. Cresols in waste waters near industrial plants are reported to undergo rapid biodegradation (G14), which indicates that cresols, like phenol, are relatively easily metabolized.

2.2 Contaminants and Environmental Degradation or Conversion Products

Cresols are sold in a wide variety of technical and special grades, classified by color and distillation range (G25). The composition of the various materials depends upon the starting material and the method of production. A major source of cresols is the tar-acid oil obtained as a by-product of coking of coal (G25).

Cresols (boiling above 204°C), available as a mixture of o-, m-, and p-isomers from tar acids are called cresylic acid. A less refined product called creosote oil contains 10-20% by volume of the tar from the coking process; it is used as a wood preservative (G25). Creosote oil may contain polynuclear aromatic hydrocarbons. Xylenols and phenol are common impurities (or ingredients) of technical grade cresols (G25).

The high environmental stability of the cresols in soils (owing to their antimicrobial properties) contributes to their widespread use as wood perservatives. o-Cresol is degraded by the hydroxyl radical and ozone in air and by organic peroxide radicals in water; half life estimates are less than 1 day in air and 10 days in water (G14). The m- and p-isomers are expected to behave similarly. Environmental degradation is likely to be by air oxidation to give quinones and dihydroxybenzenes (G14).

Biodegradation products of cresols by sewage microorganisms include carbon dioxide, methane, 3-methylcatechol, 2-hydroxy-6-oxahepta-2,4-dienoic acid, oxalic acid, pyrocatechol,carboxylic acid, and salicylic acid (G14). By analogy with phenol, cresols may be methylated in the environment to form the corresponding anisoles.

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the acute toxicity of cresols as follows:

Substance	Parameter	Dosage	Animal	Route
Cresol	LD50	1454 mg/kg	rat	oral
	LD50	861 mg/kg	mouse	oral
o-Cresol	LD50	121 mg/kg	rat	oral
	LD50	1100 mg/kg	rat	skin
	LD50	344 mg/kg	mouse	oral
	LDLo	410 mg/kg	mouse	subcutaneous
	LDLo	55 mg/kg	cat	subcutaneous
	LDLo	940 mg/kg	rabbit	oral
	LD50	1380 mg/kg	rabbit	skin
	LDLo	450 mg/kg	rabbit	subcutaneous
	LDLo	180 mg/kg	rabbit	intravenous
	LDLo	360 mg/kg	guinea pig	intraperitoneal
	LDLo	200 mg/kg	frog	subcutaneous
m-Cresol	LD50	242 mg/kg	rat	oral
	LD50	620 mg/kg	rat	skin
	LD50	350 mg/kg	rat	unknown
	LD50	828 mg/kg	mouse	oral
	LDLo	450 mg/kg	mouse	subcutaneous
	LDLo	180 mg/kg	cat	subcutaneous
	LDLo	1400 mg/kg	rabbit	oral
	LD50	2050 mg/kg	rabbit	skin
	LDLo	500 mg/kg	rabbit	subcutaneous
	LDLo	280 mg/kg	rabbit	intravenous
	LDLo	100 mg/kg	guinea pig	intraperitoneal
	LDLo	250 mg/kg	frog	subcutaneous

(continued)

Substance	Parameter	Dosage	Animal	Route
p-Cresol	LD50	207 mg/kg	rat	oral
	LD50	705 mg/kg	rat	skin
	LD50	344 mg/kg	mouse	oral
	LDLo	150 mg/kg	mouse	subcutaneous
	LD50	160 mg/kg	mouse	unknown
	LDLo	80 mg/kg	cat	subcutaneous
	LDLo	620 mg/kg	rabbit	oral
	LD50	301 mg/kg	rabbit	skin
	LDLo	300 mg/kg	rabbit	subcutaneous
	LDLo	180 mg/kg	rabbit	intravenous
	LDLo	100 mg/kg	guinea pig	intraperitoneal
	LDLo	150 mg/kg	frog	subcutaneous

Cresols are rated as moderately toxic to humans (G4). Acute exposures can cause muscular weakness, gastroenteric disturbances, severe depression, collapse, and death (G38). Organs attacked by cresols include the central nervous system, liver, kidneys, lungs, pancreas, spleen, eyes, heart, and skin (G38). The type of exposure to cresols determines, in part, the toxic effects. Cresols are highly corrosive to any tissues they contact (G5) and are readily absorbed by skin and mucous membranes. Systemic effects, including death, occur after dermal exposure. Because their vapor pressure is low at 25°C, cresols do not usually constitute an acute inhalation hazard. No data are available on the toxicity of cresol vapors to humans (G39).

In animals, cresol toxicity varies with the isomer, the species and the route of exposure. Reported LD50s vary from a low of 121 mg/kg in the rat (oral, o-cresol) to a high of 2050 mg/kg in the rabbit (skin, m-cresol) (G16). Evidence for different biological effects of the three isomers includes the observation that the ratios between the LD50s of the least toxic and most toxic isomers vary from as low as 1.8 (cutaneous, rat) to as high as 6.8 (cutaneous, rabbit). Furthermore, p-cresol, but neither o- nor m-cresol, produced permanent pigment loss in the hair of mice (1).

2.4 Other Toxic Effects

Chronic poisoning from absorption of cresols through the skin,

mucous membranes or respiratory tract has not been well studied. Campbell (2) presented incomplete studies showing that exposure of mice to an atmosphere saturated with cresylic acid vapors for 1 hr/day on consecutive days caused irritation of the nose and eyes, and death in some animals. Uzhdavini et al. (3) performed poorly documented studies on the chronic effects of o-cresol inhalation. In mice, they found evidence for: tail necrosis; slowed weight gain; cellular degeneration of the CNS; respiratory tract hyperemia, edema, proliferation of cellular elements, and hemorrhagic patches; myocardial fiber degeneration; and protein deposits in liver and kidney cells. In rats, they reported alterations in a conditioned reflex, and alterations in both peripheral blood and bone marrow elements.

The Threshold Limit Value established by the ACGIH for cresols is 5 ppm (G11).

2.5 Carcinogenicity

o, m, and p-Cresol have been reported to promote the carcinogenicity of dimethylbenzanthracene (DMBA) in skin tests with mice (4). They were slightly less active as promoters than phenol in this experiment (see table below).

Promoter*	No. mice survivors/ original no.	Avg. no. papillomas per survivor	% survivors with papilloma
Benzene Control	12/12	0	0
20% phenol	22/27	1.50	64
20% o-cresol	17/27	1.35	59
20% m-cresol	14/29	0.93	50
20% p-cresol	20/28	0.55	35

* Initiator: 0.3% DMBA in acetone. Promoter in benzene. Data at 12 weeks.

No carcinogenicity tests conducted with cresols alone have been found in the searched literature.

2.6 Mutagenicity

In onion root tips, however, m- and p-cresol produced cytological abnormalities including stickiness, erosion, pycnosis, C-mitosis, polyphoidy, and chromosome fragmentation(5). o-Cresol did not appear as active (5). These chromosomal effects do not necessarily imply that the cresols will have genetic activity in mammals. No other mutagenicity studies were found in the searched literature.

2.7 Teratogenicity

No systematic studies of the teratogenic potential of the cresols have been found. The only information available is on the effect of m-cresol on embryos of a toad (Xenopus laevis) at the neural tube stage of development (6). Concentrations of 20 to 80 ppm, m-cresol caused two developmental abnormalities: edema and tail flexion.

2.8 Metabolic Information

Very little is known about the metabolic fate of cresols in mammals. One study showed that the cresols are excreted in rabbit urine primarily as oxygen conjugates: 60-72% as ether glucuronides and 10-15% as ethereal sulphates (7). Paper chromatography showed that o- and m-cresol are hydroxylated and that p-cresol forms p-hydroxybenzoic acid (7). p-Cresol glucuronide was isolated from the urine of rabbits dosed by stomach tube with p-cresol, whereas o- and m-cresol were metabolized to 2,5-dihydroxytoluene (7). No studies have been traced of the biological effect of these and other possible metabolites of the cresols.

2.9 Ecological Effects

The 96-hour LC50 of o-cresol to channel catfish (Ictalurus punctatus) is reported to be 67 mg/l (8). In tests with perch and sunfish, lethal concentrations (not LC50s) were determined in 1 hour exposures. In perch (Perca fluviatilis), lethal concentrations for o-, m- and p-cresols were in the range 10-20 ppm (9). The Aquatic Toxicity Rating (96-hour TLm, species unspecified) for cresols is listed as 10-1 ppm (G16). Although o-cresol is less toxic to juvenile Atlantic salmon (Salmo salar) than p-cresol, the salmon avoided o-cresol more efficiently (10).

Cresols have a broad spectrum of toxicity to microorganisms. They are used as disinfectants and as fungicides to protect materials such as wood. They are also reported to be active against mycoplasmas (11), viruses (12), and plant galls (13).

2.10 Current Testing and Evaluation

A criteria document on cresols is planned for completion in 1977 by NIOSH.

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No. 55

Crotonaldehyde

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CROTONALDEHYDE

SUMMARY

Crotonaldehyde is not expected to be overly persistent in water or the atmosphere. It is not expected to bioconcentrate. It has been detected in finished drinking water and in sewage treatment plant effluents.

An increased incidence of malignant neoplasms has been observed in workers at an aldehyde factory who were exposed to crotonaldehyde, among other substances. There is, however, no indication that crotonaldehyde was the causative factor in the excess incidence of cancer.

Pathologic change was observed in the testes of mice receiving crotonaldehyde in the drinking water (0.2 g/l) for one month.

I. INTRODUCTION

Crotonaldehyde ($CH_3CH=CHCHO$; molecular weight 70.1) is a water-white, mobile liquid with a pungent, suffocating odor (Hawley, 1977). It has the following physical/chemical properties (U.S.EPA, 1979a; Hawley, 1977):

Boiling Point:	102°C
Melting Point:	-60°C
Vapor Pressure:	19 mm Hg at 20°C
Solubility:	very soluble in water; also soluble in many organic solvents.

A review of the production range (includes importation) statistics for crotonaldehyde (CAS No. 4170-30-3) which was listed in the initial TSCA Inventory (1979b) has shown that between 1 million and 8 million pounds of this chemical were produced/imported in 1977.*/

Crotonaldehyde is used as an intermediate in the manufacture of n-butanol and crotonic and sorbic acids; solvent in the purification of mineral oil; intermediate in resin and rubber antioxidant manufacture; and in organic syntheses (NCI, 1978). Other uses are as a warning agent in fuel-gas, insecticides, leather tanning, production of rubber accelerators, and as an alcohol denaturant (Hawley, 1977).

II. ENVIRONMENTAL FATE

Formaldehyde, the simplest aldehyde, is almost entirely hydrated in water, thus it is nonvolatile and is inactive toward photochemical dissociation. Higher aldehydes, such as crotonaldehyde, are less hydrated in water, more volatile, and somewhat active toward photochemical degradation (Calvert and Pitts, 1966). Crotonaldehyde is expected to be oxidized in water at the double bond to form keto aldehydes and cleavage products (U.S. EPA, 1977). Crotonaldehyde biodegrades at a slow to moderate

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

rate; acclimated bacteria can speed the degradation rate (U.S. EPA, 1979a). In general, neither crotonaldehyde nor its oxidation products are expected to be overly persistent in water (U.S. EPA, 1977).

In air, aldehydes are expected to photodissociate to RCO and H atoms rapidly and competitively with their oxidation by HO radical. The projected half-life is on the order of 2 to 3 hours (Calvert and Pitts, 1966). Oxidation of crotonaldehyde by HO radical should result in addition at the double bond to form a keto aldehyde (U.S. EPA, 1977). Crotonaldehyde is a reactive component of auto exhaust and may contribute to smog (Dimitriades and Wesson, 1972).

B. Bioconcentration

Crotonaldehyde is not expected to bioconcentrate (based on its similarity to acrolein) (U.S. EPA, 1977).

C. Environmental Occurrence

Crotonaldehyde has been detected in finished drinking water, sewage treatment plant effluents (U.S. EPA, 1976), in wastewater used for irrigation of potatoes (Dodolina et al., 1976), and the atmosphere (IARC, 1976).

Crotonaldehyde occurs naturally in essential oils extracted from the wood of oak trees (Egorov, 1976). It has also been found in the volatiles from cooking mutton (Nixon et al., 1979) and in tobacco and tobacco smoke constituents (Pilott, 1975).

III. PHARMACOKINETICS

Although no information was found specifically on the metabolism of crotonaldehyde, it is probably oxidized to an acid and subsequently to CO_2 in the same manner as other small aliphatic aldehydes. Crotonaldehyde is a potential alkylating agent by the metabolic formation of an activated epoxy derivative at the double bond and via reaction with amino groups of cellular macromolecules (NCI, 1978).

IV. HEALTH EFFECTS

A. Carcinogenicity

An increased incidence of malignant neoplasms has been observed in workers at an aldehyde factory who were exposed to acetaldehyde, butyraldehyde, crotonaldehyde, aldol, several alcohols, and longer chain aldehydes. Crotonaldehyde was found in concentrations of 1-7 mg/m^3. Of the 220 people employed in this factory, 150 had been exposed for more than 20 years. During the period 1967 to 1972, tumors were observed in nine males (all of whom were smokers). The tumor incidences observed in the workers exceeded incidences of carcinomas of the oral cavity and bronchogenic lung cancer expected in the general population and, for the age group 55-59 years, the incidence of all cancers in chemical plant workers. There is no indication that crotonaldehyde was the causative factor in the excess incidence of cancer (Bittersohl, 1974, 1975).

B. Mutagenicity

Schubert (1972) reported chromosome breakage in human lymphocytes exposed to crotonaldehyde *in vitro*. When tested in *Salmonella typhimurium* (tester strains TA1535, TA1537, TA1538, TA100, and TA98) both in the presence and absence of a metabolic activation system, crotonaldehyde was nonmutagenic. It also failed to increase the incidence of mitotic recombination in *Saccharomyces cerevisiae* D3 in the presence and absence of a metabolic activation system (NCI, 1978).

C. Reproductive Effects

Pathologic change was observed in the testes of mice one month following a single intraperitoneal injection of crotonaldehyde (1 mg/mouse). In a related study, similar changes were observed in the testes of mice receiving crotonaldehyde in the drinking water (0.2 g/l) for one month (Auerbach *et al.*, 1977; Moutschen-Dahmen *et al.*, 1975; Moutschen-Dahmen *et al.*, 1976).

D. Other Toxicity

Skog (1950) studied the effects of lower aliphatic aldehydes in rats and mice. When administered subcutaneously or by inhalation, crotonaldehyde caused lung edema and mild narcosis. Death was delayed and probably resulted from the lung damage.

With cats, similar effects were seen, with death due to lung edema or bronchial pneumonia occurring within 24 hours for injection and between 6 and 48 hours for inhalation studies (Skog, 1950).

The oral LD_{50} for crotonaldehyde in the rat is 300 mg/kg; the 30-minute LC_{50} in the rat is 4000 mg/kg. The rabbit dermal LD_{50} is 380 mg/kg (NIOSH, 1979).

E. Other Relevant Information

A case of apparent sensitization to crotonaldehyde has been reported in a laboratory worker who handled "small" amounts of the material (ACGIH, 1971).

Crotonaldehyde is a strong mucous membrane irritant (NIOSH, 1978).

V. AQUATIC EFFECTS

The 96-hour LC_{50} (partial flow-through system) for crotonaldehyde in bluegill sunfish is 3.5 ppm; in tidewater silversides the 96-hour LC_{50} is 1.3 ppm (Dawson, 1975/1977).

VI. EXISTING GUIDELINES

The OSHA standard for crotonaldehyde in air is a time weighted average (TWA) of 2 ppm (39CFR23540).

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No. 56

Cyanides

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CYANIDES

SUMMARY

Cyanide is well-known as an acute, rapidly acting poison which has caused numerous deaths, primarily in occupational situations. The mechanism of cyanide intoxication is attributable to the biochemical inhibition of cellular respiration, which produces a condition resembling acute hypoxia. Despite the considerable potency of cyanide as an acute poison, repeated sublethal exposures do not result in cumulative adverse effects in animals or man. In a chronic feeding study in rats, a no observable adverse effect level (NOAEL) was found to be 12 mg/kg/day. Extrapolation of this value to humans, using the application of a safety factor of 100, results in an acceptable daily intake for man (ADI) of 8.4 mg.

Cyanide exists in water in the free form (CN^- and HCN), which is extremely toxic, or in a form bound to organic or inorganic moieties which is less toxic. Cyanide is lethal to freshwater fishes at concentrations near 50 µg/l and has been shown to adversely affect invertebrates and fishes at concentrations near 10 µg/l. Very few saltwater data have been generated. Cyanide affects fish and invertebrates by inhibiting utilization of available oxygen for metabolism at the cellular level of respiration.

CYANIDES

I. INTRODUCTION

This profile is based primarily upon the Ambient Water Quality Criteria Document for Cyanides (U.S. EPA, 1979). The National Institute for Occupational Safety and Health (NIOSH, 1976) has also prepared a recent comprehensive review of health hazards associated with hydrogen cyanides (HCN) and commercially important cyanide salts (NaCN, KCN, and $Ca(CN)_2$).

The toxicologic effects of cyanides are based upon their potential for rapid conversion by mammals to HCN. Cyanide production in the United States is now over 700 million pounds per year and appears to be increasing steadily (Towill, et al. 1978). The major industrial users of cyanide in the United States are the producers of steel, plastics, synthetic fibers and chemicals, and the electroplating and metallurgical industries (NIOSH, 1976; Towill, et al. 1978).

II. EXPOSURE

A. Water

Cyanide exists in water in the free form (CN^- and HCN), or bound to organic or inorganic moieties. Cyanide is not commonly found in United States water supplies. Among 2,595 water samples tested, the highest cyanide concentration found was 8 ppb (Towill, et al. 1978). The volatility of HCN, the predominant form in water, accounts in part for the low levels usually measured. The U.S. EPA (1979) has estimated the bioconcentration factor of cyanide at 2.3.

B. Food

Except for certain naturally occurring organonitriles in plants (e.g., cyanogenic glycosides, such as amygdalin), it is uncommon to find cyanide in foods.

C. Ambient Air

There is insufficient information available to estimate population exposures to cyanide via ambient air (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

The common inorganic cyanides are rapidly absorbed across the skin (Drinker, 1932; Potter, 1950; Tovo, 1955; Walton and Witherspoon, 1926), stomach and duodenum, and lungs (Goesselin, et al. 1976). Quantitative estimates of the rate of penetration by various routes of exposure are unavailable, however. The rapid absorption of cyanide is evidenced by the fact that death may be produced within a matter of minutes following inhalation or ingestion.

B. Distribution

Cyanide is distributed to all organs and tissues via the blood, where its concentration in red cells is greater than that in plasma by a factor of two or three. This may be due, at least in part, to a preferential binding of cyanide to methemoglobin (Smith and Olson, 1973). Although quantitative data are lacking, it is predicted that cyanide may readily cross the placenta.

C. Metabolism

By far, the major pathway for the metabolic detoxification of cyanide involves its conversion to thiocyanate via the enzyme rhodanase (deDuve, et al. 1955). A minor pathway for cyanide metabolism involves nonenzymatic conjugation with cysteine, a reaction which accounts for no more than 15 percent of cyanaide metabolism in the rat (Wood and Cooley, 1956). Very small amounts of cyanide can be excreted unchanged (as HCN) or converted to carbon dioxide (Friedberg and Schwarzkopf, 1969).

D. Excretion

Among rats given 30 mg of sodium cyanide intraperitoneally over eight days, it was estimated that 80 percent of the total dose was excreted in the urine in the form of thiocyanate (Wood and Cooley, 1956). Cyanide does not appear to accumulate significantly in any body compartment with chronic exposures.

IV. EFFECTS

A. Carcinogenicity

Pertinent data confirming the carcinogenicity of cyanide were not found in the available literature.

B. Mutagenicity

Pertinent data concerning the mutagenicity of cyanide were not found in the available literature.

C. Teratogenicity

Cyanide is not known to be teratogenic. However, thiocyanate, the major metabolic product of cyanide in vivo,

has produced developmental abnormalities in the chick (Nowinski and Pandra, 1946) and ascidian embryo (Ortolani, 1969) at high concentrations.

D. Other Reproductive Effects

Pertinent information regarding the possible effect of cyanide on fertility or reproductive success was not found in the available literature.

E. Chronic Toxicity

Human inhalation of 270 ppm HCN brings almost immediate death, while 135 ppm is fatal after 30 minutes of exposure (Dudley, et al. 1942). The mean lethal dose of HCN and its alkali metal salts by ingestion in humans is in the range of 50 to 200 mg (1 to 3 mg/kg), with death coming in less than one hour (Gosselin, et al. 1976). In non-fatal poisonings, recovery is generally rapid and complete. The mechanism of acute cyanide intoxication can be attributed to the biochemical inhibition of cytochrome c oxidase, the terminal enzyme complex in the respiratory electron transport chain of mitochondria (Gosselin, et al. 1976). The major feature of cyanide poisoning resembles the effects of acute hypoxia, which results in a decreased utilization of oxygen by the tissues. Cyanide poisoning differs from other types of hypoxia in that the oxygen tension in peripheral tissues usually remains normal or may even be elevated (Brobeck, 1973).

Despite the high lethality of large single doses or acute inhalation exposures to high vapor concentrations

of cyanide, repeated sublethal doses do not result in cumulative adverse effects (Hertting, et al. 1960; Hayes, 1967; American Cyanamid, 1959).

F. Other Relevant Information

Since cyanide acts by inhibiting cytochrome c oxidase, it is reasonable to assume that any other inhibitor of the same enzyme (e.g. sulfide or azide) would have toxic effects synergistic with (or additive to) those of cyanide. This has not been demonstrated experimentally, however.

Cyanide poisoning is specifically antagonized by any chemical agent capable of rapidly generating methemoglobin in vivo, such as sodium nitrite, or other aromatic nitro and amino compounds (Smith and Olson, 1973).

V. AQUATIC TOXICITY

A. Acute Toxicity

There have been numerous studies investigating the toxicity of cyanide in freshwater fish. Free cyanide concentrations in the range of about 50 to 200 µg/l have eventually proven fatal to most species. Certain life stages and species of fish appear to be more sensitive to cyanide than others. Eggs, sac fry, and warmwater species tended to be the most resistant.

Several authors have reported increased cyanide toxicity with the reduction of dissolved oxygen or with a rise in water temperature. However, water alkalinity, hardness, and pH below 8.3 have not been shown to have a pronounced effect on the acute toxicity of cyanide to fish. The reported range for LC_{50} values for freshwater fish is

from 52 µg/l, for juvenile brook trout, to 507 µg/l, for sac fry brook trout, Salvelinus fontinalis. For the freshwater invertebrates, the results from 11 acute tests on 6 species have shown a range of LC_{50} values from 83 µg/l for cladoceran, Daphnia pulex to 760,000 µg/l for snail, Goniobasis livescens.

The only saltwater species to be studied is the oyster. A short exposure of an oyster to cyanide resulted in supression of activity after 10 minutes of exposure to 150 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

Based on long-term tests with bluegills (embryo-larval) and reproduction by brook trout and fatheads, the geometric mean of the chronic effect level concentrations is 9.6 µg/l (Koenst, et al. 1977; Lind, et al. 1977; Kimball, et al. 1978). Life cycle tests on the scud, Gammarus pseudolimnaeus, and the isopod, Ascellus communis, show the chronic values to be 18.3 and 34.1 µg/l, respectively (U.S. EPA, 1979). The chronic toxicity of cyanide in marine species has not been reported.

C. Plant Effects

In the only plant test reported, 90 percent of the blue-green alga, Microcystis aerusinoss, was killed when exposed to a free cyanide concentration of 7,790 µg/l (Fitzgerald, et al. 1952).

There was an inhibition of respiration in the marine alga, Prototheca zopfi, at 3,000 µg/l and enzyme

inhibition in Chlorella sp. at 30,000 µg/l (Webster and Hackett, 1965; Nelson and Tolbert, 1970).

D. Residue

No residue data is available for cyanide toxicity in either salt or freshwater species. The U.S. EPA (1979) has estimated the bioconcentration factor of cyanide to be 2.3.

VI EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA, 1979, which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will change.

A. Human

The U.S. Public Health Service Drinking Water Standards of 1962 established 0.2 mg CN^-/l as the acceptable level for water supplies. A similar criterion has been adopted by the Canadian government (Health and Welfare Canada, 1977). In addition to defining the 0.2 mg CN^-/l criterion, the U.S. Public Health Service (1962) has set forth an "objective" of 0.01 mg CN^-/l in water, "because proper treatment will reduce cyanide levels to 0.01 mg/l or less."

The U.S. Occupational Safety and Health Administration (OSHA) has established a permissible exposure limit for KCN and NaCN at 5 mg/m^3 as an eight-hour, time-weighted average. The National Institute for Occupational Safety and Health (NIOSH) recommends 5 mg/m^3 as a ten minute ceiling for occupational exposure to KCN and NaCN.

The OSHA permissible limit for exposure to HCN is 10 ppm (11 mg/m^3) as an eight-hour time-weighted average. NIOSH recommends 5 mg/m^3 as a ten minute ceiling level for exposure to HCN.

Based upon the results of a two year chronic feeding study in rats, the U.S. EPA (1979) has calculated an acceptable daily intake (ADI) of cyanide for man to be 8.4 mg/kg. This value was derived from the no observable adverse effect level (NOAEL) for rats of 12 mg/kg/day and the application of a safety factor of 100. The corresponding draft water quality criterion derived from these data is 4.11 mg/l. However, the U.S. EPA (1979) has recommended that the U.S. Public Health Service Drinking Water Standard of 200 µg/l be retained as a safe level for man.

B. Aquatic

For free cyanide (expressed as CN), the draft criterion to protect freshwater aquatic life is 1.4 µg/l as a 24-hour average, and the concentration should not exceed 38 µg/l at any time (U.S. EPA, 1979).

Draft saltwater criterion is not available for cyanide toxicity, because of the paucity of valid data (U.S. EPA, 1979).

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No. 57

Cyanogen Chloride

Health and Environmental Effects

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CYANOGEN CHLORIDE

I. INTRODUCTION

Cyanogen chloride is a colorless gas at room temperature with a molecular weight of 61.48, a melting point of -6.5°C, a boiling point of 13.8°C, and a specific gravity of 1.186. It is soluble in alcohol or ether, and slightly soluble in water. (Int. Tch. Inf. Inst., 1978).

Cyanogen chloride is used as a fumigant, metal cleaner, in ore refining, production of synthetic rubber and in chemical synthesis (Arena, 1974). Cyanogen chloride can be used in the military as a poison gas.

II. EXPOSURE

The major sources of exposure to cyanogen chloride are in the above mentioned industrial uses. The potentiality of cyanogen chloride as a water pollutant has not been described in the available literature.

III. PHARMACOKINETICS

The toxicity of cyanogen chloride resides very largely on its pharmacokinetic property of yielding readily to hydrocyanic acid (also called hydrogen cyanide or prussic acid) in vivo. The red cells of whole blood rapidly convert cyanogen chloride to cyanide, while serum destroys cyanogen chloride without forming hydrocyanic acid (Aldridge and Evans, 1946).

Reference should be made to the EPA/ECAO Hazard Profile for cyanides (U.S. EPA, 1979) for a general discussion on absorption, distribution, metabolism and excretion. Cyanogen chloride, like HCN, is metabolically converted to thiocyanate (HCNS) (Aldridge and Evans, 1946).

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity, and Other Reproductive Effects

Pertinent information could not be located in the available literature.

B. Chronic Toxicity

Inhaling small amounts of cyanogen chloride causes dizziness, weakness, congestion of the lungs, hoarseness, conjunctivitis, loss of appetite, weight loss, and mental deterioration. These effects are similar to those found from inhalation of cyanide (Dreisbach, 1977). Cyanogen chloride is an irritant to both eyes and throat (Int. Tech. Inf. Inst., 1978).

Cyanogen chloride acts as a chemical asphyxiant, releasing cyanide which causes internal asphyxia by inhibiting cellular respiration. Cyanohemoglobin may also be formed slowly, but the toxicity is mainly due to the inhibition of cytochrome oxidase, an enzyme which utilizes molecular oxygen for cell respiration (Dreisback, 1977).

C. Acute Toxicity

Ingestion or inhalation of a lethal dose of cyanogen chloride (LD_{50} = 13 mg/kg), as for cyanide or other cyanogenic compounds, causes dizziness, rapid respiration, vomiting, flushing, headache, drowsiness, drop in blood pressure, rapid pulse, unconsciousness, convulsions with death occurring within 4 hours (Dreisbach, 1977).

By subcutaneous route, the LD_{LO} for cyanogen chloride are as follows: mouse, 39 mg/kg; dog, 5 mg/kg; and rabbit, 20 mg/kg. By inhalation, an LC_{LO} in the dog was found to be 79 ppm/8 hours. Also by inhalation, the LC_{50}'s in terms of ppm for 30 minute exposures are: rat, 118; mouse, 177; rabbit, 207; and guinea pig, 207 (Int. Teh. Inf. Inst., 1978).

V. AQUATIC TOXICITY

Pertinent information could not be found in the available literature pertaining to the toxic effects of cyanogen chloride to aquatic organisms. The reader is referred to EPA/ECAO Hazard Profile for cyanides (U.S. EPA, 1979).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Threshold limit values for cyanogen chloride have been set at 0.3 ppm and 0.6 mg/m^3 for an 8-hour workday. (ACGIH, 1979).

CYANOGEN CHLORIDE

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No. 58

DDD

Health and Environmental Effects

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APRIL 30, 1980

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DISCLAIMER

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DDD

Summary

DDD can exist in two forms, the o,p'- or the p,p'-isomers. p,p'-DDD [1,1-(2,2-dichloroethylidlene)-bis-4-chlorobenzene] is a contaminant (~0.3%) of commerical preparations of DDT [1,1'-(2,2,2-trichloroethylidene)-bis-4-chlorobenzene] as well as being a metabolite of DDT. It has also been used as an insecticide in its own right under the names TDE or Rhothane. p,p'-DDD is the first metabolite of p,p'-DDT leading to the eventual elimination of p,p'-DDT from the body as p,p'-DDA [2,2-bis(4-chlorophenyl) acetic acid]. The residency time of DDD in the body is relatively short. There is some evidence that DDD is carcinogenic in mice; however, in other species, it appears to be non-carcinogenic. p,p'-DDD has been shown to be mutagenic in Drosophila, but not in yeast or bacteria. In cell culture, p,p'-DDD causes chromosomal breaks.

The only available p,p'-DDD toxicity data involves saltwater fish and invertebrates and freshwater invertebrates. The 96-hour LC_{50} value for two invertebrates and three fish range from 1.6 to 42.0 µg/l. p,p'-DDD appears to be one-fifth to one-seventh as acutely toxic as p,p'-DDT.

DDD

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for DDT (U.S. EPA, 1979a).

DDD is a contaminant of technical p,p'-DDT [1,1'-(2,2,2-trichloroethylidene)-bis-4-chlorobenzene]. It has also been utilized as an insecticide in its own right under the common names TDE or Rhothane. Its two isomers, p,p'-DDD [1,1'-(2,2-dichloroethylidene)-bis-4-chlorobenzene] and o,p'-DDD, make up approximately 0.3 and 0.1 percent, respectively, of technical DDT. Between 1970 and 1973 (the EPA banned DDT in 1972), a significant drop in residues of DDD and DDT occurred in the U.S.A., constituting decreases of 89 and 86 percent, respectively.

II. EXPOSURE

Little information is available on exposure to DDD, although the general exposure pattern probably follows that of DDT, as outlined in DDT: Hazard Profile (U.S. EPA, 1979b). DDD appears to be disappearing from the U.S. environment at approximately the same rate as DDT as a result of the 1972 ban on DDT (U.S. EPA, 1975). Wessel (1972) calculated the daily intake of p,p'-DDD to be 0.012 mg/man/day; this was about half the daily intake of p,p'-DDT.

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature.

B. Distribution

The distribution of DDD is the same as that described for DDT in DDT: Hazard Profile (U.S. EPA, 1979b). The human adipose storage of DDD is less than that of either DDT or DDE [1,1'-(2,2-dichloroethenylidene)-bis-4-chlorobenzene].

C. Metabolism

p,p'-DDD is the first metabolite in the multistep pathway of converting p,p'-DDT to p,p'-DDA [2,2-bis(4-chlorophenyl)-acetic acid], the metabolite which is eventually excreted by rats and by man (Peterson and Robinson (1964). Urinary p,p'-DDA excretion and serum DDD concentrations showed increases with DDT dosage in man and declined after dosing ended (Morgan and Roan, 1977). The enzymes for converting p,p'-DDT to p,p'-DDD are present in all tissues, while the enzymes for further metabolism of DDD appear to be absent in brain, heart, pancreas, and muscle of rats (Fang, et al. 1977).

D. Excretion

Doses of o,p'-DDD yield o,p'-DDA and ring hydroxylation products of o,p'-DDA in the urine and feces of rats in addition to serine and glycine conjugates in urine (Reif and Sinsheimer, 1975).

DDD is further metabolized to DDA, which is excreted in the urine (U.S. EPA, 1979a).

IV. EFFECTS

A. Carcinogenicity

Only two studies have been performed to assess the carcinogenicity of p,p'-DDD. In a lifespan study, CF1 mice were fed 37.5 mg/kg/day DDD in their diet (Tomatis, et al. 1974). DDD-exposed animals showed slight increases in liver tumors in males only, but lung adenomas were markedly increased in both sexes. In a National Cancer Institute study (1978), Osborne-Mendel rats and B6C3F1 mice were dosed with p,p'-DDD for 78 weeks. In rats, DDD had no carcinogenic effects in the females, (43 or 85 mg/kg/day), but caused a significant increase of follicular cell adenomas in the low dose males (82 mg/kg/day). Carcinomas of the thyroid were also observed. Be-

cause of high variation of thyroid lesions in control male rats, these findings are considered only suggestive of a chemical-related effect. In mice, p,p'-DDD was not carcinogenic.

B. Mutagenicity

p,p'-DDD has been shown to be non-mutagenic in E. coli Pol-A strains (Fluck, et al. 1976) and Escherichia marcescens (Fahrig, 1974). The only positive result found in any of the bacterial test systems was reported by Buselmaier, et al. (1972) upon the administration of p,p'-DDD to mice and assaying for back mutation of Salmonella typhimurium and E. marcescens following incubation in the peritoneum in the host-mediated assay. Yeast host mediated assays using Saccharomyces cerevisiae were negative (Fahrig, 1974), along with an X-linked recessive lethal assay in Drosphila melanogaster (Vogel, 1972). In mammalian systems, the mutagenic activity of p,p'-DDD is relatively weak. This is evidenced by the fact that, depending upon the dose and route of administration and the species sensitivity of the test organism, reported studies are negative or marginally positive (U.S. EPA, 1979a). Some chromosomal aberrations and inhibition of proliferation have been observed with p,p'-DDD in cell culture (Palmer, et al. 1972; Mahr and Miltenburger, 1976). The o,p'-isomer is less active with regard to chromosome damage (Palmer, et al. 1972).

C. Teratogenicity, Other Reproductive Effects, and Chronic Toxicity

Pertinent data could not be located in the available literature.

D. Other Relevant Information

Since DDD is a metabolite of DDT, as well as a contaminant of commercial preparations of DDT, many of the effects of DDT could be mediated through DDD. Information on DDT is presented in DDT: Hazard Profile (U.S. EPA, 1979b).

V. AQUATIC TOXICITY

A. Acute Toxicity

The most insensitive freshwater invertebrate was the scud, Gammarus lacustris, with a 96-hr. LC_{50} static value of 0.60 µg/L (Sanders, 1969). Of the Cladoceran, the Daphnia pulex species was the most sensitive with a static LC_{50} of 3.2 µg/l, while the Simocephalus serrulatus was the least sensitive with a LC_{50} of 5.2 µg/l (Sanders and Cope, 1966). p,p'-DDD toxicity has been investigated for several saltwater species. LC_{50} values for two invertebrates, the Eastern oyster, Crassostrea virginica, and the Korean shrimp, Palaemon macrodactylus (Schoettger, 1970), are 25 µg/l and 1.6 µg/l, respectively, in 96-hr flow-through exposures. In flow-through exposures to three species of saltwater fish, 96-hr LC_{50} values range from 2.5 to 42 µg/l for the stripped bass, Morone saxatilis, Korn and Earnest, 1974). Two species, Morone saxatilis (Korn and Earnest, 1974) and Fundulus similis (U.S. EPA, 1979a), were exposed to both p,p'-DDD and p,p'-DDT under similar conditions. A comparison of the results indicates that p,p'-DDD is one-fifth to one-seventh as acutely toxic to these species as is p,p'-DDT. However, four to five week old tadpoles of the freshwater toad (Bufo woodhuusei fowleri) were much more sensitive, having 96-hr. LC_{50} values of 160 µg/l compared with 1,000 µg/l for p,p'-DDT. The DDT sensitivity increased with age (Sanders, 1970).

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

In 1972, the U.S. EPA banned the agricultural use of DDT in the United States. There are no other specific guidelines or standards for DDD. However, for the protection of human health with respect to DDD, criteria of 0.98, 0.098, and 0.0098 ng/l have been proposed for DDT corresponding to risk levels of 10^{-5}, 10^{-6}, and 10^{-7}, respectively. If water alone is consumed, the water concentration should be less than 0.36 µg/l to keep the lifetime cancer risk below 10^{-5}.

B. Aquatic

The criteria for DDT and its metabolites are proposed for the protection of aquatic life from the effects of DDD. The 24-hour average for the protection of freshwater aquatic life is 0.00023 µg/l, not to exceed 0.41 µg/l at any time. For saltwater aquatic life, the 24-hour average is 0.0067 µg/l, not to exceed 0.021 µg/l at any time.

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No. 59

DDE

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

DDE

Summary

DDE exists as two isomers, o,p'- and p,p'-DDE. [1,1'-(2,2-dichloroethenylidene)-bis-4-chlorobenzene] is the major contaminant (ca. 4 percent) of commercial preparations of p,p'-DDT [1,1'-(2,2,2-trichloroethylidene)- bis-4-chlorobenzene], as well as being a metabolite of p,p'-DDT. p,p'-DDE is a highly lipophilic compound which undergoes no further metabolism. Its residency time in the body is extremely long. p,p'-DDE has been shown to be carcinogenic in mice but not in rats. In cell culture it causes chromosomal breaks.

The only aquatic toxicity data available on p,p'-DDE involve acute toxic flow-through exposures to two saltwater invertebrates. The 48-hr. LC_{50} for a shrimp is 28 µg/l; the 96-hr. LC_{50} for the Eastern oyster is 14 µg/l.

DDE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for DDT and metabolites (U.S. EPA, 1979a).

DDE is a contaminant of technical 1,1'-(2,2,2-trichloroethylidene)-bis-4-chlorobenzene (DDT). Its two isomers, p,p'-DDE [1,1'-(2,2-dichloroethenylidene)-bis-4-chlorobenzene] and o,p'-DDE make up approximately 4.0 and 0.1 percent, respectively, of technical grade DDT. Between 1970 and 1973 (the EPA banned DDT in 1972), a significant drop in the residues of DDT in the U.S. occurred, constituting a decrease of 86 percent. However, during this time period, residues of DDE decreased only 27 percent. In fact, p,p'-DDE residues comprise most of the biological residues (ca. 71 percent) arising from DDT application (U.S. EPA, 1979a; Kveseth, et al. 1979).

II. EXPOSURE

Little information is available on exposure to DDE, although the general exposure pattern probably follows that of DDT, as outlined in DDT: Hazard Profile (U.S. EPA, 1979b). DDE residues appear to be disappearing from the environment at a slower rate than DDT following the 1972 ban on DDT (U.S. EPA, 1975). Wessel (1972) calculated the daily dietary intake of p,p'-DDE to be 0.018 mg/man/day, as compared with a value of 0.027 mg/man/day for DDT. A recent study by de Campos and Olszyne-Marzys (1979) based on studies in Latin American countries still using DDT indicates that human milk contains more p,p'-DDE than p,p'-DDT (up to 3 µg/l whole milk) in every sample taken.

III. PHARMACOKINETICS

A. Absorption

DDE is absorbed from the gastrointestinal tract with high efficiency characteristic of dietary fat. Maximum lipid solubilities reach 100,000 ppm.

B. Distribution

The distribution of DDE is similar to that described for DDT in the EPA/ECAO Hazard Profile on DDT (U.S. EPA, 1979b). Serum and adipose concentrations of p,p'-DDE rise slower than DDT, with the peak some months in following termination of dosing. The human adipose storage of p,p'-DDE is greater than that for DDT, and p,p'-DDE is eliminated from the body very slowly. This is also true for the Rhesus monkey (Durham, et al. 1963). Storage loss data predict that, if dietary intake were eliminated, it would take an entire lifespan to eliminate the average human body burden of p,p'-DDE. It has been shown that tissue storages of p,p'-DDE in the general population originate almost entirely from dietary p,p'-DDE rather than DDT conversion (U.S. EPA, 1979a). However, this may not be the case for p,p'-DDE residues in human milk (de Campos and Olszyne-Marzys, 1979).

C. Metabolism

The end product of the metabolism of DDT which proceeds via reductive dehydrochlorination is p,p'-DDE. In addition, p,p'-DDE is the major storage product of DDT in animals [apart from hamsters (Agthe, et al. 1970)] and humans: The enzymes for metabolizing DDT to p,p'-DDE are present in all tissues (Fang, et al. 1977).

In humans given p,p'-DDT orally, no more than one-fifth of the absorbed DDT ultimately undergoes conversion to p,p'-DDE (Morgan and Roan, 1977). p,p'-DDE does not undergo further metabolism to 2,2-bis(4-chlorophenyl)-acetic acid (DDA), the urinary excretion product of DDT.

D. Excretion

Excretion of p,p'-DDE has not been demonstrated in man. In mice, p,p'-DDE is excreted in the urine (Wallcave, et al. 1974). The o,p'-isomer is more easily excreted than the p,p'-isomer (Morgan and Roan, 1977).

IV. EFFECTS

A. Carcinogenicity

Only two studies have been performed to assess the carcinogenicity of p,p'-DDE. In a lifespan study, CF-1 mice were fed 37.5 mg/kg/day p,p'-DDE in their diet (Tomatis, et al. 1974). p,p'-DDE increased liver tumor incidence from 1 percent in controls to 90 percent in treated female animals, and from 34 to 74 percent in male animals. The combination p,p'-DDE/DDD produced more tumors than either constituent alone at the same concentration in the combination. In a National Cancer Institute study (1978), Osborne-Mendel rats and B6C3F1 mice were dosed with p,p'-DDE for 78 weeks. In rats, p,p'- DDE had no carcinogenic effect on either females (22 mg/kg/day) or males (42 mg/kg/ day), although hepatotoxicity was evident. In mice, hepatocellular carcinomas were significantly increased in the animals fed p,p'-DDE (22 and 39 mg/kg/day for females and males, respectively).

B. Mutagenicity

p,p'-DDE has been shown to be nonmutagenic in E. coli Pol-A strains (Fluck, et al. 1976), Escherichia marcescens (Fahrig, 1974), and in the host mediated assay using Salmonella typhimurium and E. marcescens (Buselmaier, et al. 1972) and Saccharomyces cerevisiae (Fahrig, 1974). Vogel (1972) measured X-linked recessive lethal mutations in Drosophila melanogaster and found no activity for p,p'-DDE. In mammalian systems, the mutagenic activity of p,p'-DDE is relatively weak. This is evidenced by the fact that, de-

pending upon the dose and route of administration and the species sensitivity of the test organism, reported studies are negative or marginally positive (U.S. EPA, 1979a). Some chromosomal aberrations and inhibition of proliferation have been observed with p,p'-DDE in cell culture (Palmer, et al. 1972; Mahr and Miltenburger, 1976). The o,p'-isomer causes fewer chromosomal aberrations (Palmer, et al. 1972).

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent information could not be located in the available literature.

D. Other Relevant Information

Since p,p'-DDE is a metabolite of DDT, as well as a contaminant of commercial preparations of DDT, many of the effects of DDT could be mediated through p,p'-DDE. Information on DDT is presented in DDT: Hazard Profile (U.S. EPA, 1979b). Oral acute LD_{50} values for p,p'-DDE in rat are 380 mg/kg for males but 1,240 mg/kg for females (Hayes, et al. 1965).

V. AQUATIC TOXICITY

A. Acute Toxicity

The 96-hr. LC_{50} value for p,p'-DDE for the comparatively resistant freshwater planarian (Polycelis felina) was 1,050 µg/l (Kouyoumjian and Uglow, 1974). The acute toxicity of p,p'-DDE has also been investigated in two saltwater invertebrates. The 48-hr. LC_{50} for the brown shrimp, Penaeus aztecus, was 28 µg/l; the 96-hr. LC_{50} for the Eastern oyster, Crassostrea virginica, was 14 µg/l (U.S. EPA, 1979a). Both studies were flow-through exposures.

B. Chronic Toxicity and Plant Effects

Pertinent data could not be located in the available literature.

C. Residues

p,p'-DDE is a major metabolite of DDT in aquatic ecosystems. One study involving bird eggshells and DDT showed p,p'-DDE to comprise 62 percent of the DDT metabolites (U.S. EPA, 1979a). Average residues in eggshells of the great black-backed gull ranged from 14 to 68 ng/g of lipid (Cooke, 1979). p,p'-DDE in fat and muscle of the white-faced ibis in 1974/75 were as high as 65 ng/g lipid (Capen and Leiker, 1979). No studies are available, however, involving p,p'-DDE specifically.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

In 1972, the U.S. EPA banned the agricultural use of DDT in the United States. There are no other specific guidelines or standards for DDE. However, for the protection of human health with respect to DDE, criteria of 0.98, 0.098 and 0.0098 ng/l have been proposed for DDT corresponding to risk levels of 10^{-5}, 10^{-6}, and 10^{-7}, respectively. If water alone is consumed, the water concentration should be less than 0.36 µg/l to keep the lifetime cancer risk below 10^{-5}.

B. Aquatic

The criteria for DDT and its metabolites are proposed for the protection of aquatic life from the effects of DDE. The 24-hour average for the protection of freshwater aquatic life is 0.00023 µg/l, not to exceed 0.41 µg/l at any time. For saltwater aquatic life, the 24-hour average is 0.0067 µg/l, not to exceed 0.021 µg/l at any time.

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No. 60

DDT

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated DDT and has found sufficient evidence to indicate that this compound is carcinogenic.

DDT

Summary

The most commonly used DDT was a technical formulation and usually consisted of a mixture of p,p'-DDT (77.1 percent), o,p'-DDT (14 percent), p,p'-DDD (0.3 percent), o,p'-DDD (0.1 percent), p,p'-DDE (4 percent), o,p'-DDE (0.1 percent and 3.5 percent unidentified compounds. Pure DDT is the p,p'-isomer [1,1'-(2,2,2-trichloroethylidene)-bis-4-chlorobenzene]. Unless specifically identified, the term DDT will refer to the pure form. Prior to being banned in the U.S. in 1972, DDT was used extensively as a pesticide.

Due to the high lipid solubility of DDT, it has a long residency time in the body. DDT has produced adverse reproductive effects in rodents and birds, but adverse effects have not been noted in man. The lowest acute oral LD_{50} value was found for the dog (60-75 mg/kg). There is suggestive evidence that DDT might be a carcinogen, and weak evidence that it might be a teratogen. Chromosomal breaks have been observed with DDT exposure *in vitro* and *in vivo*.

DDT is acutely toxic to freshwater fish at concentrations as low as 0.8 µg/l and to invertebrates at 0.18 µg/l. Chronic toxicity has been manifested in the fathead minnow in the range of 0.37 to 1.48 µg/l. A weighted average bioconcentration factor of 39,000 has been estimated for DDT for consumed fish and shellfish. For saltwater fish and invertebrates, DDT concentrations as low as 0.2 µg/l and 0.14 µg/l, respectively, have been reported to be acutely toxic. Chronic toxicity data for saltwater organisms are not available.

DDT

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for DDT (U.S. EPA, 1979a).

DDT has been used extensively world-wide for public health and agricultural programs as a broad spectrum insecticide. It has played a large role in the world-wide control of the malaria mosquito. In 1972, following an extensive review of health and environmental hazards of the use of DDT, the U.S. EPA decided to ban any further use of DDT. Prior to this, technical grade DDT had been widely used in the U.S., with a peak usage in 1959 of 80 million pounds. This amount decreased steadily to less than 12 million pounds by 1972. Since the 1972 ban, the use of DDT in the U.S. has been effectively discontinued. However, technical grade DDT is still used in many other countries and widespread contamination still occurs. Since DDD and DDE are also metabolites of DDT, it is sometimes difficult to separate contamination from metabolic accumulation. The compounds of DDT are extremely persistent and are so widespread that levels as high as 15 ppb have been detected in feed for laboratory animals (Coleman and Tardiff, 1979).

II. EXPOSURE

The primary route of human exposure to DDT is from ingestion of small amounts in the diet. Biological magnification of DDT in the food chains occurs by two routes: (1) direct absorption from contaminated water by aquatic organisms; (2) transfer of residues through sequential predator feeding. Meats, fish, poultry, and dairy products are the primary sources of DDT residues in the human diet. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor of DDT at 39,000 for consumed fish and shellfish. Due to the banned usage of DDT in the U.S., there has been a

continual decline in the DDT residue in food. These decreases are reflected in the changing amounts of estimated dietary intake: 1965 - 0.062 mg/man/day; 1970 - 0.024 mg/man/day; 1973 - 0.008 mg/man/day (U.S. EPA, 1975). Levels of DDT found in the air are far below levels that add significantly to total human intake. Stanley, et al. (1971) sampled air in nine localities, and found DDT in the ranges of 1 ng/m^3 to 2520 ng/m^3 of air. Wolfe and Armstrong (1971) showed that industrial workers not wearing respirators could be exposed to significant levels of DDT in the air (up to 34 mg/man/hour), particularly in the formulating plants. Exposure for agricultural spray operators may be as high as 0.2 mg/man/hour (Wolfe, 1967). Dermal exposure for formulators was estimated to range from 5 to 993 mg/man/hour (Wolfe and Armstrong, 1971). Little DDT was found in the urine, however. Dermal absorption of DDT is minimal.

Dermal toxicity in rats occurs at 3,000 mg/kg (U.S. EPA, 1979a). Hayes (1966) estimated the intake of DDT to be in the following proportions: food - 0.04 mg/man/day; water - 4.6×10^{-6} mg/man/day; and air - 9×10^{-6} mg/man/day. The actual dose for the average man is now estimated to be 0.01 mg/man/day (U.S. EPA, 1979a).

III. PHARMACOKINETICS

A. Absorption

DDT is absorbed from the gastrointestinal tract with efficiency approaching 95 percent when ingested with dietary fat. In humans, Morgan and Roan (1971) showed that absorption of an oral dose of 20 mg DDT proceeded faster than transport out of the vascular compartment into tissue storage. Studies concerning the kinetics of absorption of DDT via inhalation or dermal routes were not found in the available literature.

B. Distribution

DDT has been found in virtually all body tissues, approximately in proportion to respective tissue content of extractable lipid. The adipose/blood ratios of DDT have been recently estimated to be approximately 280:1 (Morgan and Roan, 1977). DDT concentrations in body tissues were highest for fat tissue, followed by reproductive organs, the liver and kidney together, with lowest concentrations found in the brain (Tomatis, et al. 1971). Elimination of very low levels of DDT from storage proceeds much more slowly than that of the large stores of DDT accumulated by occupationally exposed workers or dosed volunteers (Morgan and Roan, 1971). The average North American adult, with 17 kg of body fat, contains approximately 25 mg of DDT. It is predicted from storage loss data that, if dietary intake were eliminated, most of the DDT would be lost within one or two decades (U.S. EPA, 1979a). Trace metals in the diet, particularly cadmium, may affect the mobilization of DDT in tissues (Ando, 1979).

C. Metabolism

The metabolism of DDT in man appears to be the same as the pathways reported by Peterson and Robison (1964) for the mouse. Generally, two separate reductive pathways produce the primary endpoint metabolites, p,p'-DDE and p,p'-DDA. The predominant conversion is of DDT to p,p'-DDD via dechlorination. This is the first product in a series which results in metabolites which are later excreted. The other primary pathway proceeds via reductive dehydrochlorination which results in the formation of p,p'-DDE the major storage product in animals and humans. Fant, et al. (1977) suggest that enzymatic activity for the dehydrochlorination and reductive dechlorination reactions transforming DDT to DDD and DDE is present in all tissues, whereas the enzymes involved in the hydrogenation and hydroxylation steps changing

DDD to DDA are absent in the brain, heart, pancreas, and muscle of the rat. Metabolic conversion of DDT to DDA proceeds more rapidly than conversion to the storage metabolite of DDE. For additional information regarding the DDT metabolites DDD and DDE, the reader is referred to the Hazard Profile for those chemicals (U.S. EPA, 1979b,c).

D. Excretion

The excretion of DDT was investigated in human volunteer studies of Hayes, et al. (1971) and Roan, et al. (1971). Urinary excretion predominated, with 13 to 16 percent of the daily dose being excreted as p,p'-DDA, and was shown to correlate with exposure levels of individuals working in a formulating plant (Ortelee, 1958). p,p'-DDE and DDT are the predominant compounds excreted and p,p'-DDD and p,p'-DDA are excreted in the least amounts (Morgan and Roan, 1977). p,p'-DDE was found in slightly higher concentrations in exposed workers versus the general population. Gut microorganisms have demonstrated a capacity for degradation of DDT to p,p'-DDD and p,p'-DDA.

IV. EFFECTS

A. Carcinogeniity

Lifetime and multigeneration exposures to DDT in the diet of rats, mice, and fish have produced significant increases in the formation of a number of tumor types (U.S. EPA, 1979a). The predominant lesion appears to be hepatoma. Also, Tomatis, et al. (1974) demonstrated that short-term exposure to technical grade DDT (37.5 mg/kg/day for 15 or 30 weeks), using CF-1 mice, resulted in an increased incidence and early appearance of hepatomas, similar to that caused by lifespan exposure. Mice appear much more susceptible than rats (U.S. EPA, 1979a) and the use of the mouse as an animal model for humans has been criticized (Deichmann, 1972). In these studies contaminants p,p'-DDD and p,p'-DDE were present, both of which have pro-

duced liver tumors in CF-1 mice (Tomatis, et al. 1974). Also, the combination of p,p'-DDD/DDE was found to produce more tumors than and equal concentration of either compound alone. Tarjan and Kemeny (1969) noted leukemias and pulmonary carcinomas in Bald-C mice fed 3 ppm DDT in the diet. Hepatomas have been observed in rainbow trout (Halver, et al. 1962).

A number of other studies have shown no significant increase in tumor formation following DDT exposure. Lifetime feeding studies with Syrian Golden Hamsters (Agthe, et al. 1970) and a number of long term feeding studies with various strains of rats have shown no significant increase in tumor incidence (Cameron and Cheng, 1951; Fitzhugh and Nelson, 1947; Radomski, et al. 1965; Deichmann, et al. 1967). In a 78-week National Cancer Institute study (1978), Osborne-Mendel rats given 16 and 32 mg/kg/day (males) or 11 and 21 mg/kg/day (females) showed no tumors. B6C3F1 mice given 3.3 and 6.6 mg/kg/day (males) or 13 and 26 mg/kg/day (females) also showed no tumor development. Durham, et al. (1963) found no liver pathology in Rhesus monkeys fed 100 mg/kg/day or less DDT for up to 7.5 years. At the present time, no evidence of neoplasia has been found in the studies performed in occupationally exposed or dosed volunteer subjects (U.S. EPA, 1979a).

B. Mutagenicity

DDT has not shown mutagenic activity in any of the bacterial test systems thus far studied: Salmonella typhimurium (McCann, et al. 1975; Marshall, et al. 1976); E. coli Pol-A strains (Fluck, et al. 1976); Bacillus subtilis (Shirasu, et al. 1976). Tests on eukaryotic yeast cells have been uniformly negative, with Fahrig (1974) using Saccharomyces cerevisiae and Clark (1974) using Neurospora crassa. Vogel (1972) and Clark (1974) found positive mutagenic activity in Drosophila melanogaster by measuring x-linked recessive lethal mutations. In mammalian systems, the mutagenic activity of

DDT is relatively weak. This is evidenced by the fact that, depending upon the dose and route of administration and the species sensitivity of the test organisms, reported studies are negative or only marginally positive (U.S. EPA, 1979a). In vivo and in vitro cytogenetic studies seem to indicate that DDT is a clastogenic (chromosome breaking) substance. The metabolites p,p'-DDE, p,p'-DDD, p,p'-DDA and p,p'-DDOH were also non-mutagenic except possibly for p,p'-DDD (U.S. EPA, 1979a). Chromosomal aberrations in cell lines of the kangaroo rat occurred more often with p,p'-isomers than o,p'-isomers (Palmer, et al. 1972).

C. Teratogenicity

Only minimal teratogenic effects have been reported following high dosages of DDT. Sprague-Dawley rats receiving 200 ppm DDT in their diet showed a significant increase in ring tail, a constriction of the tail followed by amputation, in the offspring (Ottoboni, 1969).

D. Other Reproductive Effects

Hart, et al. (1971) showed that DDT has an effect on prematurity and causes an increase in the number of fetal resorptions in rabbits given 50 mg/kg on days 7, 8, and 9 of gestation. Chronic exposure (less than 200 mg/kg) of rats and mice produced no adverse effects on survival of the offspring (Ware and Good, 1967; Ottoboni, 1969). Krause, et al. (1975) noted a damaging effect on spermatogenesis in rats following acute exposure to DDT (7,200 mg/kg). Also, DDT has been shown to possess estrogenic activity in rodents and birds (Welch, et al. 1969; Bittman, et al. 1968).

E. Chronic Toxicity

A number of pathological changes have been noted in rodents; the most consistent finding in lifetime feeding studies has been an increase in the size of liver, kidneys, and spleen; extensive degenerative changes in

the liver; and an increased mortality rate (U.S. EPA, 1979a). In contrast to the rodent models, Rhesus monkeys fed diets with up to 200 ppm DDT did not show liver histopathology, decrease in weight gain or food consumption, or clinical signs of illness (Durham, et al. 1963).

F. Other Relevant Information

DDT is a strong inducer of the mixed function oxidase system; this could potentially enhance the biological effects of other chemicals by activation, or diminish their activities through detoxification mechanisms (U.S. EPA, 1979a). Exposure to DDT has caused enhanced tumor incidence in N-fluorenacetamide-treated rats (Weisburger and Weisburger, 1968) and decreased phenobarbital-induced sleeping times (Conney, 1967). Acute oral LD_{50} values in rats typically range from 100 to 400 mg/kg and 40 to 60 mg/kg i.v. The oral LD_{50} values in other animals are: 60 to 75 mg/kg (dogs); 250 to 400 mg/kg (rabbits); approximately 200 mg/kg (mice). For p,p'-DDE, the values are 380 and 1,240 mg/kg in male and female rats, respectively; for p,p'-DDA in rats, the values are 740 and 600 mg/kg, respectively (U.S. EPA, 1979a). Symptoms of DDT poisoning in humans include the following: convulsions, parasthesia of extremities and vomiting (at high doses), convulsions and nausea (less than 16 mg/kg), dizziness, confusion and most characteristically, tremors (Hayes, 1963). In rats, the liver shows changes at dietary doses less than 5 ppm (Laug, et al. 1950). No permanent injury to man from DDT has been recorded (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

A. Acute Toxicity

The acute toxicity of DDT to freshwater organisms has been well documented. Data are available for 25 species of fish. The 96-hour LC_{50} values are available for the following freshwater fish: rainbow trout (Sal-

mo gairdneri), 1.7 to 42 µg/l; fathead minnow (Pimephales promelas), 7.4 to 58 µg/l; channel catfish (Ictalurus punctatus), 16 to 17.5 µg/l; bluegill (Lepomis macrochirus), 1.2 to 210 µg/l. The most sensitive of fish was the yellow perch (Perca flavesceus) with a 96-hour LC_{50} of 0.6 µg/l (Marking, 1966). Invertebrate freshwater species are more sensitive than fish. For Daphnia magna, 48-hour LC_{50} values of 1.48 µg/l have been reported (Priester, 1965). One week old crayfish (Orconectus nais) had a 96-hour LC_{50} value of 0.18 µg/l (Saunders, 1972). LC_{50} values for nine saltwater fish species range from 0.2 to 4.2 µg/l. Saltwater invertebrates were slightly more sensitive, with LC_{50} values ranging from 0.14 to 10.0 µg/l (U.S. EPA, 1979a).

Concentrations as low as 8 µg/l elicited hyperactive locomotor responses in bluegill (Lepomis macrochirus) over 16 days old (Ellgaard, et al. 1977). The acute LD_{50} in adult summer frogs (Rana temporaria) was only 7.6 mg/kg. Though adipose tissues contained most of the DDT, the ovaries of females contained as much of the compound as did bones and spleen (Harri, et al. 1979).

B. Chronic Toxicity

Only one chronic freshwater fish value is available (Pimephales promelas), indicating that the chronic toxicity value is 0.74 µg/l (Jarvinen, et al., 1977). Freshwater invertebrate chronic toxicity data are not available. Concentration of DDT affecting three saltwater invertebrate species in chronic studies are similar in LC_{50} values (U.S. EPA, 1979a).

C. Plant Effects

Four species of freshwater algae (Calovella sp.) have evidenced a wide range of sensitivities, 0.3 to 800 µg/l (Sodergren, 1968). Wurster (1968) investigated the effects of DDT on four species of marine algae. The

data showed reduced rates of photosynthesis at 10 µg/l, indicating that algae are much less sensitive to DDT than are fish and invertebrates.

D. Residues

DDT is bioconcentrated to a very high degree in aquatic organisms. An average bioconcentration factor (BCF) of 640,000 has been calculated from 31 experimental measurements of bioconcentration done on 26 species of freshwater fish. Individual BCF's ranged from 490 to 2,236,666. In the field, BCF factors have been observed which are seven times higher than the average values derived from laboratory data. This discrepancy may be due to the many additional trophic levels involved and the possibly higher lipid content of the organisms in the field. In saltwater species, the BCF for DDT ranges from 800 to 76,300 times for fish and shellfish (U.S. EPA, 1979a). The lowest observed allowable maximum tissue concentration was 0.5 µg/kg for domestic animals in animal feed (U.S. FDA, 1977) and in the brown pelican (Pelecanus occidentalis) for eggshell thinning (Blus, et al. 1972, 1974).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979c), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The existing guidelines and standards for DDT are:

YEAR	AGENCY/ORG.	STANDARD	REMARKS
1971	WHO	0.005 mg/kg body weight	Maximum Acceptable Daily Intake in food
1976	U.S. EPA	0.001 µg/l	Ambient Water Quality Criteria

1977	Natl. Acad. Sci., Natl. Res. Counc.	-	In light of carcinogenic risk projection, suggested strict criteria for DDT and DDE in drinking water
1978	Occup. Safety Health Admin.	1 mg/m^2	Skin exposure
1978	U.S. EPA	0.41 µg/l 0.00023 µg/l	Final acute and chronic values for water quality criteria for protection of aquatic life (freshwater)

The U.S. EPA (1979a) is in the process of establishing ambient water quality criteria. Based on the potential carcinogenicity of DDT, current draft criteria are calculated on the estimate that 0.98 µg/man/day would result in an increased additional lifetime cancer risk of no more than 1/100,000. Since man and the rat appear to be less sensitive than mice, greater levels may be tolerable.

B. Aquatic

For DDT, the proposed draft criterion to protect freshwater aquatic life is 0.00023 µg/l as a 24-hour average; the concentration should not exceed 0.41 µg/l at any time. For saltwater aquatic species, the concentration is 0.0067 µg/l as a 24-hour average and should not exceed 0.021 µg/l at any time (U.S. EPA, 1979a).

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No. 61

Dibromochloromethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

61-1

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

DIBROMOCHLOROMETHANE

SUMMARY

Dibromochloromethane has been detected in drinking water in the United States. It is believed to be formed by the haloform reaction that may occur during water chlorination. Dibromochloromethane can be removed from drinking water via treatment with activated carbon. There is a potential for dibromochloromethane to accumulate in the aquatic evironment because of its resistance to degradation. Volatilization is likely to be an important means of environmental transport.

Very little toxicity information is available. Dibromochloromethane gave positive results in mutagenicity tests with Salmonella typhimurium TA100. It is currently under test by the National Cancer Institute.

I. INTRODUCTION

Dibromochloromethane ($CHBr_2Cl$, molecular weight 208.29) is a clear, colorless liquid. It is insoluble in water, but is soluble in a number of organic solvents. Its boiling point is 119-120°C and its density is 2.45 at 20°C (Weast, 1972). At 10.5°C, its vapor pressure is 15 torr (Dreisbach, 1952).

A review of the production range (includes importation) statistics for dibromochloromethane (CAS No. 124-48-1) which is listed in the initial TSCA Inventory (1979) has shown that

between 0 and 900 pounds of this chemical were produced/imported in 1977.*/

Dibromochloromethane is used as a chemical intermediate in the manufacture of fire extinguishing agents, aerosol propellants, refrigerants, and pesticides (Verschueren, 1977).

II. EXPOSURE

A. Environmental Fate

No information was found pertaining to the rate of oxidation of dibromochloromethane in either the aquatic or atmospheric environments. Dibromochloromethane is probably like other halogenated aliphatics in that it is not easily oxidized in aquatic systems because there are no functional groups which react strongly with HO radical. A maximum hydrolytic half-life of 274 years has been reported for dibromochloromethane at pH 7 and 25°C (Mabey and Mill, 1978).

The vapor pressure of dibromochloromethane, while lower than that for chloroform and other chloroalkanes, is, nonetheless, sufficient to ensure that volatilization will be an important means of environmental transport. The concentration of dibromochloromethane present in water supplies has been reported to

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

decrease as a result of volatilization while flowing through open channels (Rook, 1974).

B. Bioaccumulation

The log of the octanol/water partition coefficient (log P) as calculated by the method of Hansch is 2.09 (Tute, 1971) indicating that dibromochloromethane is somewhat lipophilic. As a result, dibromochloromethane may exhibit a tendency to bioaccumulate in organisms. No experimental data were found to confirm this.

C. Environmental Occurrence

Dibromochloromethane has been detected in finished drinking water (Kleoper and Fairless, 1972; U.S. EPA, 1975), in drinking water supplies (U.S. EPA, 1975), and in wastewater effluents (Glaze and Henderson, 1975). Dibromochloromethane is hypothesized to be present in water supplies as a result of the haloform reaction which takes place during the chlorination of such water (Rook, 1974; U.S. EPA, 1975; Glaze and Henderson 1975).

III. HEALTH EFFECTS

A. Carcinogenicity

Dibromochloromethane is currently under test for carcinogenicity by the National Cancer Institute. No results are available.

B. Mutagenicity

Dibromochloromethane was found mutagenic in Salmonella typhimurium TA100 in the absence of metabolic activation (Simmon 1977).

C. Other Toxicity

A long-term test conducted by administration of high doses of the chemical by gavage in mice showed a dose-dependent decrease in the activity of liver and spleen phagocytes (Munson et al., 1978).

The oral LD_{50} of dibromochloromethane in mice is 800 mg/kg and 1200 mg/kg for males and females respectively. Sedation and anesthesia occurred within 30 minutes of administration of the compound and lasted 4 hours. Necropsies were performed on animals that died. Hemorrhaging was observed in the adrenals, the kidneys were pale, and the liver appeared to have fatty infiltration (Bowman, 1978).

IV. AQUATIC EFFECTS

No information was found.

V. EXISTING GUIDELINES

The Maximum Contaminant Level (MCL) for total trihalomethanes (including dibromochloromethane) in drinking water has been set by the U.S. EPA at 0.10 mg/l (44 FR 68624). The concentration of dibromochloromethane produced by chlorination can be reduced by treatment of drinking water with powdered activated carbon (Rook, 1974). This is the technology that has been proposed by the EPA to meet this standard.

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No. 62

Di-n-butyl Phthalate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

DI-n-BUTYL PHTHALATE

Summary

Teratogenic effects in rats have been reported in testing of di-n-butyl phthalate following i.p. administration, but not after oral administration at high doses (0.600 g/kg/day). Other reproductive effects in rats following i.p. administration include impaired implantation and parturition. Rats fed di-n-butyl phthalate or its monoester metabolite have developed testicular damage and atrophy.

Mutagenic or carcinogenic effects of di-n-butyl phthalate have not been reported.

One clinical study has indicated that workers exposed primarily, but not exclusively, to di-n-butyl phthalate showed a higher incidence of toxic polyneuritis.

The only toxicity data available for review demonstrate that di-n-butyl phthalate is acutely toxic to freshwater organisms at concentrations as low as 730 µg/l.

DI-n-BUTYL PHTHALATE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Phthalate Esters (U.S. EPA, 1979a).

Di-n-Butyl phthalate (DBP) is a diester of the ortho form of benzene dicarboxylic acid. The compound has a molecular weight of 278.34, specific gravity of 1.0465, boiling point of 340°C and a solubility of 0.45 gms per 100 ml of water at 25°C (U.S. EPA, 1979a).

DBP is used as a plasticizer in polyvinyl acetate emulsions and as an insect repellent.

Current Production: 8.3×10^3 tons/year in 1977 (U.S. EPA, 1979a).

Phthalates have been detected in soil, air, and water samples, in animal and human tissues, and in certain vegetation. Evidence from in vitro studies indicates that certain bacterial flora may be capable of metabolizing DBP to the monoester form (Engelhardt, et al. 1975). For additional information regarding the phthalate esters in general, the reader is referred to the EPA/ECAO Hazard Profile on Phthalate Esters (U.S. EPA, 1979b).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of phthalates may occur through leaching of the compound from plastics, volatilization of phthalate from plastics, or the incineration of plastic items. Sources of human exposure to phthalates include contaminated foods and fish, dermal application, and parenteral administration by use of plastic blood bags, tubings, and infusion devices (mainly DEHP release). Relevant factors in the migration of phthalate esters from packaging materials to food and beverages are: temperature, surface area contact, lipoidal nature of the food and length of contact (U.S. EPA, 1979a).

Monitoring studies have indicated that most water phthalate concentrations are in the ppm range, or 1-2 μg/liter (U.S. EPA, 1979a). Industrial air monitoring studies have measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1973). Levels of DBP in foods have ranged from not detectable to 60 ppm (Tomita, et al. 1977). Cheese, milk, fish and shellfish present potential sources of high phthalate intake (U.S. EPA, 1979a). The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for DBP to be 26 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on the octanol/water partition coefficient.

III. PHARMACOKINETICS

A. Absorption

A human study in which subjects ate food containing DBP leached from plastic containers shows significantly higher levels of DBP found in the blood (Tomita, et al. 1977).

B. Distribution

Pertinent data could not be located in the available literature.

C. Metabolism

Monobutyl phthalate has been identified as a urinary metabolite in rabbits administered DBP (Ariyoshi, et al. 1976). This metabolite has also been detected in the urine of rats, hamsters, and guinea pigs, as well as other metabolites with side chain oxidation, and phthalic acid (Tanaka, et al. 1978).

D. Excretion

Pertinent data could not be located in the available literature.

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

Mutagenic effects of DBP were not observed in the Ames Salmonella assay (Rubin, et al. 1979) or in a yeast (Saccharomyces) assay system (Shahin and VonBorstel, 1977).

C. Teratogenicity

Teratogenic effects were not produced by DBP, (0.600 g/kg/day), following oral administration to pregnant rats (Nikonorow, et al. 1973) while Singh, et al. (1972) reported teratogenic effects of DBP following i.p. injection of pregnant rats.

D. Other Reproductive Effects

Intraperitoneal injection of DBP to pregnant rats showed that adverse effects prior to gestation day six were primarily on implantation, while after this day the effect was primarily on parturition (Peters and Cook 1973).

Testicular damage has been reported in rats fed DBP or its monoester metabolite (Carter, et al. 1977).

E. Chronic Toxicity

An increase in toxic polyneuritis has been reported by Milkov, et al. (1973) in workers exposed primarily to dibutyl phthalate. Lesser levels of exposure to dioctyl, diisooctyl, and benzylbutyl phthalates, and to tricresyl phosphate were also noted in these workers.

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity for di-n-butyl phthalate ranged from a 96-hour static LC_{50} of 730 µg/l for the bluegill sunfish (Lepomis macrochirus) to 6,470 µg/l for the rainbow trout (Salmo gairdneri) (Mayer and Sanders, 1973). The freshwater scud (Gammarus pseudolimnaeus) was shown to provide a 48-hour static LC_{50} value of 2,100 ug/l di-n-butyl phthalate. Marine data were not available for review.

B. Chronic

Pertinent data could not be located in the available literature.

C. Plants

Pertinent data could not be located in the available literature.

D. Residues

Bioconcentration factors ranging from 400 to 1400 have been obtained for the aquatic invertebrates Daphnia magna and Gammarus pseudolimnaeus.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of review; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on "no effect" levels observed in chronic feeding studies in rats or dogs, the U.S. EPA (1979a) has calculated an acceptable daily intake (ADI) level of 12.6 mg/day.

The recommended water quality criterion level for protection of human health is 5 mg/liter for DBP (U.S. EPA, 1979a).

B. Aquatic

The data base for toxic effects in both freshwater and marine environments was insufficient for the drafting of a water quality criterion to protect aquatic organisms.

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No. 63

Dibenzo(a,h)anthracene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated dibenzo(a,h)anthracene and has found sufficient evidence to indicate that this compound is carcinogenic.

DIBENZO(a,h)ANTHRACENE

Summary

Dibenzo(a,h)anthracene (DBA) is a member of the polycyclic aromatic hydrocarbon (PAH) class. DBA was the first pure chemical shown to produce tumors in animals. It is carcinogenic by skin application, by injection, and by oral administration to rodents. Since humans are not exposed to only DBA in the environment, it is not possible to attribute human cancers solely to exposure to DBA. Furthermore, it is not known how DBA may interact with other carcinogenic and non-carcinogenic PAH in human systems.

DIBENZO(a,h)ANTHRACENE

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multimedia Health Assessment Document for Polycyclic Organic Matter (U.S. EPA. 1979b).

Dibenzo(a,h)anthracene (DBA; $C_{22}H_{14}$) is one of the family of polycyclic aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Other than a reported melting point of 266-266.5°C (U.S. EPA. 1979b), its physical and chemical properties have not been well-characterized.

PAH, including DBA are ubiquitous in the environment, being found in ambient air, food, water, soils and sediment (U.S. EPA. 1979b). The PAH class contains a number of potent carcinogens (e.g., benzo(a)pyrene), moderately active carcinogens (e.g., benzo(b)fluoranthene), weak carcinogens (benz(a)anthracene), and cocarcinogens (e.g., fluoranthene), as well as numerous non-carcinogens (U.S. EPA. 1979b).

PAH which contain more than three rings (such as DBA) are relatively stable in the environment, and may be transported in air and water by adsorption to particulate matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment.

II. EXPOSURE

A. Water

Levels of DBA in water have not been reported. However, the concentration of six representative PAH (benzo(a)pyrene, fluor-

anthene, benzo(j)fluoranthene, benzo(k)fluoranthene, benzo(ghi)-perylene, indeno(1,2,3-cd-pyrene) in United States drinking water averaged 13.5 nanograms/liter (Basu and Sacena, 1977, 1978).

B. Food

Based on limited monitoring studies, DBA has been detected in various foods, such as, butter and smoked fish. Although, it is not possible to estimate the human dietary intake of DBA, it has been concluded (U.S. EPA. 1979b) that the daily dietary intake of all types of PAH is about 1.6 to 16 μg per day. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor of DBA to be 24,000 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient for DBA.

C. Inhalation

Levels of DBA have not been monitored in ambient air. However, it has been estimated that the average total PAH level in ambient air is about 10.9 nanograms/m^3 (U.S. EPA, 1979a). Thus the total daily intake of PAH by inhalation of ambient air may be about 207 nanograms, assuming that a human breathes 19 m^3 of air per day.

III. PHARMACOKINETICS

There are no data available concerning the pharmacokinetics of DBA, or other PAH, in humans. Nevertheless, it is possible to make limited assumptions based on the results of animal research conducted with several PAH, particularly benzo(a)pyrene.

A. Absorption

The absorption of DBA in humans or other animals has not been thoroughly studied. However, it is known (U.S. EPA, 1979a) that, as a class, PAH are well-absorbed across the respiratory and

gastrointestinal epithelia. The high lipid solubility of compounds in the PAH class supports this observation.

B. Distribution

Only limited work on distribution of DBA in mammals has been performed (Heidelberger and Weiss, 1959). However, it is known (U.S. EPA, 1979a) that other PAH become localized in a wide variety of body tissues following their absorption in experimental rodents. Relative to other tissues, PAH tend to localize in body fat and fatty tissues (e.g., breast).

C. Metabolism

The mammalian metabolism of DBA has been well-characterized (Sims, 1976). DBA, like other PAH, is metabolized by the microsomal mixed function oxidase enzyme system in mammals (U.S. EPA. 1979b). Metabolic attack on one or more of the aromatic rings leads to the formation of phenols, and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed function oxidases to yield diol epoxides, compounds which are known to be ultimate carcinogens for certain PAH. Removal of activated intermediates by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

There is no direct information available concerning the excretion of PAH in man. The excretion of DBA however, by mice was studied by Heidelberger and Weiss (1959). The excretion of DBA was

rapid and occurred mainly via the feces. Elimination in the bile accounts for a significant percentage of all administered PAH (U.S. EPA, 1979a). It is unlikely that PAH will accumulate in the body with chronic low-level exposures.

IV. EFFECTS

A. Carcinogenicity

DBA was the first pure chemical ever shown to produce tumors in animals. DBA has considerable carcinogenic potency when applied to the skin of mice (Iball, 1939; U.S. EPA. 1979b), injected subcutaneously in mice (U.S. EPA. 1979b), injected into newborn mice (Beuning, et al. 1979), injected into Strain A mice (Shimkin and Stoner, 1975) or administered orally to mice (Snell and Stewart, 1962).

B. Mutagenicity

DBA is a mutagenic in the Ames Salmonella assay (Andrews, et al. 1978; Wood, et al. 1978) in cultured hamster cells (Huberman and Sacks, 1974), and is positive in the in vivo sister-chromatid exchange assay in Chinese hamsters (Roszinsky-Kocher, et al. 1979).

C. Teratogenicity

There are no data available concerning the possible teratogenicity of DBA in man. Other related PAH apparently are not significantly teratogenic in mammals (U.S. EPA, 1979a).

D. Other Reprodutive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

As long ago as 1937, investigators knew that carcinogenic PAH, including DBA, could inhibit growth in rats and mice (Haddow, et al. 1937). In early studies, DBA was administered to mice in weekly subcutaneous injections for 40 weeks, which produced increased reticulum (stem) cells, dilation of lymph sinuses, and decreased spleen weights in comparison to controls (Hoch-Ligeti, 1941).

A more detailed study of subchronic effects of DBA on lymph nodes of male rats was reported in 1944 (Lasnitzki and Woodhouse, 1944). Subcutaneous injections given five times weekly for several weeks caused normal lymph nodes to undergo hemolymphatic changes.

V. AQUATIC TOXICITY

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have yet gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

There are no established exposure criteria for DBA. However, PAH as a class are regulated by several authorities. The World Health Organization recommends that the concentration of PAH in drinking water (measured as the total of fluoranthene, benzo-(g,h,i)perylene, benzo(b)fluoranthene, benzo(k)fluoranthene, in

deno(1,2,3-cd)pyrene, and benzo(a)pyrene) not exceed 0.2 µg/l. Occupational exposure criteria have been established for coke oven emissions, coal tar products, and coal tar pitch volatiles, all of which contain large amounts of PAH including DBA (U.S. EPA, 1979a).

The U.S. EPA (1979a) draft recommended criteria for PAH in water are based upon the extrapolation of animal carcinogenicity data for benzo(a)pyrene and DBA. Levels for each compound are derived which will result in specified risk levels of human cancer as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria			
	ng/l			
	0	10^{-7}	10^{-6}	10^{-5}
BaP				
2 liters of drinking water and consumption of 18.7 grams fish and shellfish	0	0.097	0.97	9.7
Consumption of fish and shellfish only		0.44	4.45	44.46
DBA				
2 liters of drinking water and consumption of 18.7 grams fish and shellfish	0	0.43	4.3	43
Consumption of fish and shellfish only.		1.96	19.6	196

B. Aquatic

The criterion for freshwater and marine life have not been derived (U.S. EPA, 1979a).

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No. 64

1,2-Dichlorbenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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1,2-DICHLOROBENZENE

SUMMARY

1,2-Dichlorobenzene is a lipophilic compound which upon absorption into the body, deposits in the fatty tissues. This compound is detoxified by the liver microsomal enzymes. On chronic exposure to 0.1 mg 1,2-dichlorobenzene/kg, rats developed anemia, liver damage, and central nervous system depression. There have not been studies available to determine the carcinogenic or teratogenic potential of 1,2-dichlorobenzene. 1,2-Dichlorobenzene was mutagenic when tested with the mold Aspergillis nidulans and negative when tested with the bacteria Salmonella typhimurium in the Ames assay.

The toxicity of 1,2-dichlorobenzene appears to be similar for freshwater and marine organisms with reported LC_{50} values ranging between 1,970 and 27,000 µg/l.

1,2-DICHLOROBENZENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichlorobenzenes (U.S. EPA, 1979a).

1,2-Dichlorobenzene (1,2-DCB or ODCB; $C_6H_4Cl_2$; molecular weight 147.01) is a liquid at normal environmental temperatures. 1,2-Dichlorobenzene has a melting point of -17.6°C, a boiling point of 179°C, a density of 1.30 g/ml at 20°C, a water solubility of 145,000 µg/l at 25°C, and a vapor pressure of 1 mm Hg at 20°C (Weast, 1975). The major uses of 1,2-dichlorobenzene are as a process solvent in the manufacturing of toluene diisocyanate and as an intermediate in the synthesis of dyestuffs, herbicides, and degreasers (West and Ware, 1977).

II. EXPOSURE

A. Water

1,2-Dichlorobenzene has been detected in rivers, groundwater, municipal and industrial discharges, and drinking water. 1,2-Dichlorobenzene has been reported entering water systems at average levels of 2 mg/l as a result of its use by industrial wastewater treatment plants for odor control (Ware and West, 1977). In 4 out of 110 drinking waters, 1,2-dichlorobenzene was detected at an average concentration of 2.5 µg/l (U.S. EPA, 1979a). ALso, 1,2-dichlorobenzene may be formed during chlorination of water containing organic precursor material (Glaze, et al. 1976).

B. Food

There are not enough data to state quantitatively the degree of 1,2-dichlorobenzene exposure through total diet (U.S. EPA, 1979a). The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor of 1,2-dichlorobenzene to be 200 for the edible portion of aquatic organisms consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegill.

C. Inhalation

1,2-Dichlorobenzene has been detected on airborne particulate matter in California at concentrations between 8 and 53 ng/m^2 (Ware and West, 1977). There is no other available information on the concentration of this compound in ambient air (U.S. EPA, 1979a).

III. PHARMACOKINETICS

A. Absorption

There is little information provided in U.S. EPA (1979a) on the absorption specifically of 1,2-dichlorobenzene. General information on the absorption of dichlorobenzenes can be found in the Hazard Profile for Dichlorobenzenes (U.S. EPA, 1979b). Reidel (1941) has reported absorption of 1,2-dichlorobenzene through the skin of rats in lethal amounts after five dermal applications under severe test conditions (painting twice daily directly on a 10 cm^2 area of abdominal skin). Also, 1,2-dichlorobenzene fed to rats at less than 0.4 to 2 mg/kg/day was absorbed and accu-

mulated in various tissues indicating significant absorption by the gastrointestinal tract even at low levels of exposure (Jacobs, et al. 1974a,b).

B. Distribution

After feeding rats low levels of 1,2-dichlorobenzene, in combination with other trace pollutants found in the Rhine River, tissue accumulation was greater in fat than in the liver, kidney, heart, and blood (Jacobs, et al. 1974a).

C. Metabolism

The metabolism of 1,2-dichlorobenzene was studied by Azouz, et al. (1955) in rabbits. 1,2-Dichlorobenzene was mainly metabolized by oxidation to 3,4-dichlorophenol followed by the formation of conjugates with glucuronic and sulfuric acids. Minor oxidative metabolites and their conjugates were also detected.

D. Excretion

Excretion of the metabolic products of 1,2-dichlorobenzene in the rabbit was mainly through the urine (Azouz, et al. 1955).

IV. EFFECTS

A. Carcinogenicity

Specific positive evidence of the carcinogenicity of DCB's is lacking. However, a sufficient collection of varied data exist to suggest prudent regard of DCB as a potential carcinogen (U.S. EPA, 1979a).

B. Mutagenicity

Treatment of the soil mold Aspergillus nidulans for one hour in an ether solution of 1,2-dichlorobenzene increased the frequency of back-mutations (Prasad, 1970). In the Ames assay, 1,2-dichlorobenzene did not increase the mutational rate of the histidine-requiring strains of Salmonella typhimurium (Andersen, et al. 1972).

C. Teratogenicity

Studies of the teratogenicity of 1,2-dichlorobenzene could not be located in the available literature.

D. Other Reproductive Effects

Information is not available.

E. Chronic Toxicity

In an inhalation study, Hollingsworth, et al. (1958) exposed groups of 20 rats, 8 guinea pigs, 4 rabbits, and 2 monkeys to the vapor of 1,2-dichlorobenzene seven hours per day, five days per week for six to seven months at an average concentration of 560 mg/m^3. No adverse effects were noted in behavior, growth, organ weights, hematology, or upon gross and microscopic examination of tissues. In a nine month chronic toxicity study, Varshavskaya (1967) gave rats 1,2-dichlorobenzene at daily doses of 0.001, 0.01, and 0.1 mg/kg. The toxicological observations in the highest dose group were anemia and other blood changes, liver damage, and central nervous system depression. The highest no-observable-adverse-effect level for 1,2-dichlorobenzene by Varshavskaya (1967) was 0.001 mg/kg/day, whereas the compar-

able level in the rat study by Hollingsworth, et al. (1958) was 18.8 mg/kg/day.

F. Other Relevant Information

1,2-Dichlorobenzene can induce microsomal drug metabolizing enzymes (Ware and West, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

For freshwater fish, two 96-hour static bioassays have produced LC_{50} values of 5,590 and 27,000 µg/l for the bluegill (Lepomis macrochirus) (U.S. EPA, 1978; Dawson, et al. 1977). A single 96-hour static assay for the freshwater invertebrate Daphnia magna provided an LC_{50} value of 2,440 µg/l. In marine fish, LC_{50} values reported were 7,300 µg/l for the tidewater silverside (Menidia beryllina) and 9,660 µg/l for the sheepshead minnow (Cyprinodon variegatus) (U.S. EPA, 1978). An adjusted LC_{50} value of 1,970 µg/l was obtained for the marine invertebrate (Mysidopsis bahia).

B. Chronic

The only freshwater organisms tested were embryo-larval stages of the fathead minnow (Pimephales promelas), which produced a chronic value of 1,000 µg/l for 1,2-dichlorobenzene. No chronic data for marine organisms were available for evaluation.

C. Plants

The freshwater algae Selenastrum capricornutum has been tested for the effects of 1,2-dichlorobenzene on

chlorophyll a and cell numbers. The EC_{50} values were 91,600 and 98,000 µg/l, respectively, while comparable values of 44,200 to 44,100 µg/l were reported for the marine algae Skeletonema costatum (U.S. EPA, 1978).

D. Residues

A bioconcentration of 89 was obtained for the bluegill.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The Occupational Safety and Health Administration (OSHA, 1976), and the American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value is 300 mg/m^3 for 1,2-dichlorobenzene. The U.S. EPA (1979a) draft water quality criterion for total dichlorobenzene (all three isomers) is 160 µg/l.

B. Aquatic

Criteria have been drafted for freshwater organisms as 44 µg/l for the 24-hour average concentration, not to exceed 99 µg/l. The marine draft criterion is 15 µg/l not to exceed 34 µg/l (U.S. EPA, 1979a).

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No. 65

1,3-Dichlorobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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1,3-DICHLOROBENZENE

Summary

1,3-Dichlorobenzene is not used commercially and is produced only as a by-product in the manufacture of chlorinated benzenes. This compound is metabolized by the liver mixed function oxidase system. Little is known of the toxicological, teratogenic, or carcinogenic properties of this compound. 1,3-Dichlorobenzene has been shown to be mutagenic to the soil mold Aspergillus nidulans. Since 1,3-dichlorobenzene may be a contaminant of the other dichlorobenzenes, some of the toxicologic properties ascribed to these isomers may be due to the 1,3-isomer.

For freshwater and marine fish and invertebrates, acute toxicity values ranged from 2,414 to 4,248 µg/l, but the freshwater invertebrate, Daphnia magna, was more resistant to 1,3-dichlorobenzene with an acute value of 23,800 µg/l.

1,3-DICHLOROBENZENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichlorobenzenes (U.S. EPA, 1979a).

1,3-Dichlorobenzene (1,3-DCB; MDCB; $C_6H_4Cl_2$; molecular weight 147.01) is a liquid at normal environmental temperatures, has a melting point of -24.2°C, a boiling point of 172°C, a density of 1.29 g/ml at 20°C, a water solubility of 123,000 µg/l at 25°C, and a vapor pressure of 5 mm Hg at 39°C (Weast, 1975). 1,3-Dichlorobenzene may occur as a contaminant of 1,2- or 1,4-dichlorobenzene formulations (U.S. EPA, 1979a).

II. EXPOSURE

A. Water

1,3-Dichlorobenzene has been detected or quantified in groundwater, raw water, and drinking water. In two of 110 drinking water samples, 1,3-dichlorobenzene was detected at an average concentration of 0.1 µg/l (U.S. EPA, 1979a). Also, 1,3-dichlorobenzene may be formed during chlorination of raw and waste water containing organic precursor material (Glaze, et al. 1976).

B. Food

The data are insufficient to state quantitatively the degree of 1,3-dichlorobenzene exposure through total diet (U.S. EPA, 1979a). 1,3-Dichlorobenzene is reported to be among several metabolites of gamma-pentachloro-1-cyclohexane found in corn and pea seedlings (Mostafa and Moza, 1973). The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor to be 150 for 1,3-dichlorobenzene for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady- state bioconcentration studies in bluegill.

C. Inhalation

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

Specific information on the absorption of 1,3-dichlorobenzene was not found in the available literature. General information on the absorption of the dichlorobenzenes can be found in the Hazard Profile for Dichlorobenzenes (U.S. EPA, 1979b).

B. Distribution

Specific information on the distribution of 1,3-dichlorobenzene was not found in the available literature. Reference may be made to the Hazard Profile for Dichlorobenzene (U.S. EPA, 1979b) and the 1,2-isomer (U.S. EPA, 1979c).

C. Metabolism

The metabolism of 1,3-dichlorobenzene in rabbits was studied by Parke and Williams (1955). 1,3-Dichlorobenzene was mainly metabolized by oxidation to 2,4-dichlorophenol followed by the formation of the glucuronides and ethereal sulfates. Minor oxidative metabolites and their conjugates were also detected.

D. Excretion

Excretion of the metabolic products of 1,3-dichlorobenzene in the rabbit is mainly through the urine with excretion being essentially complete within five days (Parke and Williams, 1955).

IV. EFFECTS

A. Carcinogenicity

Reports of specific carcinogenicity tests of 1,3-dichlorobenzene in animals or of pertinent epidemiologic studies in humans were not found in the available literature (U.S. EPA, 1979a).

B. Mutagenicity

Treatment of the soil mold Aspergillus nidulans for one hour in an ether solution of 1,3-dichlorobenzene increased the frequency of back mutations (Prasad, 1970).

C. Teratogenicity and Other Reproductive Effects

Studies of the teratogenicity and other reproductive effects of 1,3-dichlorobenzene were not found in the available literature.

D. Chronic Toxicity

Specific information on the chronic toxicity of 1,3-dichlorobenzene was not found in the available literature. However, 1,3-dichlorobenzene may have been a contaminant of the 1,2- and 1,4-dichlorobenzenes used in toxicological studies. For further information on the general toxicologic properties of the dichlorobenzenes, refer to the Hazard Profile for Dichlorobenzenes (U.S. EPA, 1979b).

E. Other Relevant Information

1,3-Dichlorobenzene can induce microsomal drug metabolizing enzymes. Changes in the levels of microsomal enzymes can affect the metabolism and biological activity of a wide variety of xenobiotics (Ware and West, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

For the bluegill (Lepomis macrochirus), a 96-hour static LC_{50} of 5,020 µg/l has been obtained. The freshwater invertebrate, Daphnia magna, has a much higher LC_{50} of 28,100 µg/l for a 48-hour static assay. For the sheepshead minnow, an acute LC_{50} of 7,770 µg/l has been obtained. A value of 2,850 µg/l has been obtained for the marine mysid shrimp (Mysidopsis bahia) (U.S. EPA, 1978).

B. Chronic

Chronic studies with either freshwater or marine species are not available.

C. Plant Effects

The freshwater alga Selenastrum caoricornutum was tested for the effects of 1,3-dichlorobenzene on chlorophyll a and cell numbers. The EC_{50} values ranged from 149,000-179,000 µg/l. For the marine alga Skeletonema costatum, the EC_{50} values for cell number and chlorphyll a ranged from 49,600-52,800 µg/l (U.S. EPA, 1979a).

D. Residues

A bioconcentration factor of 66 was obtained for the bluegill (U.S. EPA, 1979a).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

There are no existing standards for 1,3-dichlorobenzene. The U.S. EPA (1979a) draft water quality criterion for total dichlorobenzene (all three isomers) is 160 µg/l.

B. Aquatic

A criterion for the protection of freshwater organisms has been drafted as 310 µg/l for a 24-hour average concentration not to exceed 700 µg/l. For marine life, the criterion has been proposed as 22 µg/l for 24-hour average not to exceed 49 µg/l.

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No. 66

1,4-Dichlorobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

1,4-DICHLOROBENZENE

SUMMARY

1,4-Dichlorobenzene is a lipophilic compound which, upon absorption into the body, deposits in the fatty tissues. This compound is detoxified by the liver microsomal enzymes. Chronic intoxication produces increased liver and kidney weights and abnormal liver pathology. Studies to determine the carcinogenic or teratogenic potential of 1,4-dichlorobenzene could not be located in the available literature. 1,4-Dichlorobenzene produces chromosomal aberrations in root tips and has been shown to increase the mutation rate in the mold Aspergillus nidulans.

Acute values for freshwater and marine organisms ranged from 1,990 to 11,000 µg/l for 1,4-dichlorobenzene. Marine in vertebrates were most sensitive and freshwater invertebrates were most resistant to the effects of 1,4-dichlorobenzene.

1,4-DICHLOROBENZENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichlorobenzene (U.S. EPA, 1979a).

1,4-Dichlorobenzene ($C_6H_4Cl_2$; molecular weight 147.01) is a solid at normal environmental temperatures. 1,4-Dichlorobenzene has a melting point of 53.0°C, a boiling point of 174°C, a density of 1.25 g/ml at 20°C, a water solubility of 80,000 µg/l at 25°C, and a vapor pressure of 0.4 mm Hg at 25°C (Weast, et al. 1975). The primary use of 1,4-dichlorobenzene is as an air deodorant and insecticide. This compound is produced almost entirely as a byproduct during the manufacture of monochlorobenzene (Ware and West, 1977).

For a more general discussion of dichlorobenzene, the reader is referred to the Hazard Profile for Dichlorobenzene (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

1,4-Dichlorobenzene has been detected or quantified in rivers, groundwater, municipal and industrial discharge, and drinking water. 1,4-Dichlorobenzene enters wastewater systems because of its use in toilet blocks (Ware and West, 1977). 1,4-Dichlorobenzene may also be formed during chlorination of raw and waste water containing organic percursor material (Glaze, et al. 1976). In 20 of 113 drinking water samples, 1,4-dichlorobenzene was detected at an average concentration of 0.14 µg/l (U.S. EPA, 1979a).

B. Food

There are not enough data available to quantitatively state the degree of 1,4-dichlorobenzene exposure through total diet (U.S. EPA, 1979a). Schmidt (1971) reported the tainting of pork as a result of the use of an odor control agent containing 1,4-dichlorobenzene in pig stalls. Also, Morita, et al. (1975) reported 0.05 mg/kg 1,4-dichlorobenzene in fish from Japanese coastal waters. The U.S EPA (1979a) has estimated the weighted bioconcentration factor of 1,4-dichlorobenzene to be 140 for the edible portion of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

C. Inhalation

Morita and Chi (1975) measured 1,4-dichlorobenzene in the vapor phase, in and around Tokyo, by use of a cold solvent trap. Urban levels were found to range from 2.7 to 4.2 $\mu g/m^3$, while suburban levels were lower, ranging from 1.5 to 2.4 $\mu g/m^3$; indoor levels were considerably higher, ranging 0.105 to 1.7 mg/m^3. No other information was found regarding the concentration of this compound in ambient air (U.S. EPA, 1979a).

III. PHARMAKINETICS

A. Absorption

In humans, toxic effects following accidentally or deliberately ingested 1,4-dichlorobenzene clearly indicate significant absorption by the gastrointestinal route (Campbell and Davidson, 1970; Frank and Cohen, 1961; Hallowell,

1959). Also, Azouz, et al. (1955) detected no 1,4-dichlorobenzene in the feces of rabbits dosed intragastrically with the compound in oil. This suggests virtually complete absorption under these conditions.

B. Distribution

The studies of Morita and Ohi (1975) and Morita, et al. (1975) have shown 1,4-dichlorobenzene in adipose tissue (mean about 2 mg/kg) and blood (about 0.01 mg/l) of humans exposed to ambient pollution levels in the Tokyo area.

C. Metabolism

The metabolism of 1,4-dichlorobenzene in rabbits was studied by Azouz, et al. (1955). 1,4-Dichlorobenzene was primarily metabolized by oxidation to 2,5-dichlorophenol, followed by the formation of the glucuronides and ethereal sulfates. Minor oxidative metabolites and their conjugates were also detected. Pagnatto and Walkley (1966) indicated that 2,5-dichlorophenol was also the principal metabolite of 1,4- dichlorobenzene in humans.

D. Excretion

Excretion of the metabolic products of 1,4-dichlorobenzene in the rabbit occurs mainly through the urine (Azouz, et al. 1955), with no mention made of fecal excretion.

IV. EFFECTS

A. Carcinogenicity

No reports of specific carcinogenicity tests of 1,4-dichlorobenzene in animals or of pertinent epidemiologic studies in humans were available. A few inconclusive experi-

ments which indicate further investigation of the carcinogenic potential of 1,4-dichlorobenzene is warranted are reviewed in U.S EPA (1979a).

B. Mutagenicity

Various mitotic anomalies were observed in cells and somatic chromosomes of 1,4-dichlorobenzene treated root tips (Carey and McDonough, 1943; Sharma and Sarkar, 1957; Srivastava, 1966). Treatment of Aspergillus nidulans (a soil mold organism) for one hour in an ether solution of 1,4-dichlorobenzene increased the frequency of back-mutations (Prasad, 1970).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Effects observed in rats and guinea pigs exposed to a concentration of 2,050 mg/m^3 1,4-dichlorobenzene for six months included: growth depression (guinea pigs); increased liver and kidney weights (rats); abnormal liver pathology (cloudy swelling, fatty degeneration, focal necrosis, cirrhosis) (Hollingsworth, et al. 1956). In animals exposed to 4,800 mg/m^3 1,4-dichlorobenzene, up to 25 percent deaths were noted; and in survivors, symptoms were noted that were similar to those observed at the lower dose. Similar pathology was also observed in female rats, who received 376 mg/kg dose of 1,4-dichlorobenzene by stomach tube 5 days a week for a total of 138 doses.

E. Other Relevant Information

1,4-Dichlorobenzene can induce microsomal drug-metabolizing enzymes. Changes in the levels of microsomal enzymes can affect the metabolism and biological activity of a wide variety of xenobiotics (Ware and West, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute 96-hour LC_{50} values for all aquatic species tested were relatively similar. For the freshwater fish, the bluegill (Lepomis macrochirus), a LC_{50} of 4,280 µg/l was obtained, while the freshwater invertebrate Daphnia magna was more resistant, with a LC_{50} value of 11,000. An LC_{50} value of 7,400 µg/l was obtained for the marine fish, the sheepshead minnow (Cyprinodon variegatus); and the myrid shrimp (Mysidopsis bahia) had an LC_{50} value of 1,990 µg/l (U.S. EPA, 1978).

B. Chronic

Pertinent data could not be located in the available literature.

C. Plants

The freshwater alga, Selenastrum capricornutum, when tested for the effects of 1,4-dichlorobenzene on chlorophyll a and cell numbers, was shown to have had a range of effective concentration of 96,700 to 98,100 µg/l, while the marine alga Skeletonema costatum was more sensitive, with an effective concentration range of 54,800 to 59,100 µg/l.

D. Residues

A bioconcentration factor of 60 was obtained for the freshwater bluegill.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The Occupational Safety and Health Administration Standard (OSHA, 1976), and the American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value are 450 mg/m^3 for 1,4-dichlorobenzene. The acceptable daily intake (ADI) of 1,4-dichlorobenzene is 0.94 mg/day (Natl. Acad. Sci., 1977). The U.S. EPA (1979a) draft water quality criterion for total dichlorobenzene (all three isomers) is 0.16 mg/l.

B. Aquatic

A criterion for the protection of freshwater aquatic life has been drafted as a 190 µg/l 24-hour average concentration, not to exceed 440 µg/l at any time. For the protection of marine life, the criterion is 15 µg/l as a 24-hour average, not to exceed 34 µg/l at any time.

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No. 67

Dichlorobenzenes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

DICHLOROBENZENES

Summary

Dichlorobenzenes are lipophilic compounds which, upon absorption into the body, deposit in the fatty tissues. These compounds are metabolized by the liver microsomal enzyme system to water soluble compounds. Chronic exposure to any of the three isomers produces effects on the liver, blood, central nervous system and respiratory tract. Studies to determine the carcinogenic or teratogenic potential of the dichlorobenzenes were not located in the available literature. In one study these compounds have increased the mutational rate of soil mold.

The position of the chlorine atoms on the benzene ring appears to have little significant effect on the toxicity of the 1,2-, 1,3-, or 1,4-dichlorobenzene isomers to fish and invertebrates, except for the apparent resistance of the freshwater invertebrate Daphnia magna to 1,3-chlorobenzene. Marine fish tend to be slightly more resistant than freshwater fish, although the inverse is true for freshwater and marine invertebrates.

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DICHLOROBENZENES

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichlorobenzenes (U.S. EPA, 1979).

The dichlorobenzenes ($C_6H_4Cl_2$; molecular weight 147.01) are a class of halogenated aromatic compounds represented by three structurally similar isomers: 1,2-dichloro-, 1,3-dichloro-, and 1,4-dichlorobenzenes (Weast, et al. 1975). 1,2-Dichloro- and 1,3-dichlorobenzene are liquids at normal environmental temperatures while 1,4-dichlorobenzene is a solid. All the dichlorobenzenes boil at approximately 175°C and have a density close to 1.28 g/ml. The solubilities in water of the 1,2-, 1,3-, and 1,,4-dichlorobenzene isomers at 25°C are 145,000 µg/l, 123,000 µg/l, and 80,000 µg/l, respectively (Jacobs, 1957). The vapor pressure of 1,2-dichlorobenzene at 20°C is 1 mm Hg; the vapor pressure of 1,3-dichlorobenzene at 39°C is 5 mm Hg; and the vapor pressure of 1,4-dichlorobenzene at 25°C is 0.4 mm Hg (Jordan, 1954; Kirk and Othmer, 1963).

The major uses of 1,2-dichlorobenzene are as a process solvent in the manufacturing of toluene diisocyanate and as an intermediate in the synthesis of dyestuffs, herbicides, and degreasers. 1,4-Dichlorobenzene is used as an air deodorant and an insecticide. 1,3-Dichlorobenzene is found as a contaminant of the other two isomers. The combined annual production of 1,2-, and 1,4-dichlorobenzene in the United States approaches 50,000 metric tons (Ware and West, 1977).

II. EXPOSURE

A. Water

Dichlorobenzenes have been detected or quantified in rivers, ground water, municipal and industrial discharges, and drinking water. Dichlorobenzenes enter the water systems from the use of 1,2-dichlorobenzene as a deodorant in industrial wastewater treatment and from the use of 1,4-dichlorobenzene toilet blocks (Ware and West, 1977). Chlorinated benzenes may also be formed during chlorination of raw and wastewater containing organic precursor material (Glaze, et al. 1976). In two case studies the concentration of dichlorobenzene in finished water was higher than in the raw water supply (Gaffney, 1976).

B. Food

There are not enough data to state quantitatively the degree of dichlorobenzene exposure through total diet. Tainting of pork has been reported due to the use of an odor control product containing 1,4-dichlorobenzene in pig stalls (Schmidt, 1971). Also, low levels of contamination of plant products have been noted from the metabolism of lindane and gamma-pentachlor-1-cyclohexane (Balba and Saha, 1974; Mostafa and Moza, 1973). Morita, et al. (1975) reported detectable levels of 1,4-dichlorobenzene in fish of the Japanese coastal waters; the concentration was 0.05 mg/kg. The U.S. EPA (1979) has estimated the weighted average bioconcentration factors for the edible portion of fish and shellfish consumed by Americans for 1,2-dichloro-, 1,3-dichloro-, and 1,4-dichlorobenzene to be 200, 150, and 140, respectively. These estimates are based on measured steady-state bioconcentration studies in bluegills.

C. Inhalation

1,2-Dichlorobenzene has been detected in airborne particulate matter in California at concentrations between 8 and 53 ng/m^2 (Ware and West, 1977). Morita and Ohi (1975) measured 1,4-dichlorobenzene in the vapor phase, by the use of a cold solvent trap, in and around Tokyo. Urban levels were 2.7 to 4.2 $\mu g/m^3$; suburban levels were lower at 1.5 to 2.4 $\mu g/m^3$; however, indoor levels were considerably higher at 0.105 to 1.7 mg/m^3.

III. PHARMACOKINETICS

A. Absorption

The dichlorobenzenes may be absorbed through the lungs, gastrointestinal tract, and intact skin (Ware and West, 1977). There is no data on the quantitative efficiency of absorption of dichlorobenzenes; however, as indicated from the appearance of metabolites in the urine, respiratory absorption during inhalation exposure is rapid (Pagnatto and Walkley, 1966). In humans, toxic effects following accidentally or deliberately ingested 1,4-dichlorobenzene clearly indicate significant absorption by the gastrointestinal route (Campbell and Davidson, 1970; Frank and Cohen, 1961; Hallowell, 1959). Also, 1,2-dichlorobenzene fed to rats at less than 0.4 to 2 mg/kg/day was absorbed and accumulated in various tissues, indicating significant absorption by the gastrointestinal tract even at low levels of exposure by ingestion (Jacobs, et al. 1974a,b).

B. Distribution

After feeding rats low levels of 1,2-dichlorobenzene in combination with other trace pollutants found in the Rhine River, tissue accumulation was greater in fat than in the liver, kidney, heart, and blood (Jacobs, et al. 1974a). Studies of Morita and Ohi (1975) and Morita, et al. (1975) have

shown 1,4-dichlorobenzene in adipose tissue (mean about 2 mg/kg) and blood (about 0.01 mg/l) of humans exposed to ambient pollution levels in the Tokyo area.

C. Metabolism

Metabolism of the 1,2- and 1,4-dichlorobenzenes was studied by Azouz, et al. (1955), and 1,3-dichlorobenzene was studied by Parke and Williams (1955) in rabbits. These compounds are mainly metabolized by oxidation to 3,4-dichlorophenol, 2,5-dichlorophenol, and 2,4-dichlorophenol respectively, which are subsequently conjugated. Other oxidation products are formed to a lesser extent, followed again by conjugation. Pagnatto and Walkley (1966) indicated that 2,5-dichlorophenol was also the principal metabolite of 1,4-dichlorobenzene in humans.

D. Excretion

In studies of rabbits, Azouz, et al. (1955) and Parke and Williams (1955) reported the excretion of metabolic products of the dichlorobenzenes in the urine.

IV. EFFECTS

A. Carcinogenicity

No reports of carcinogenicity testing of specific dichlorobenzenes could be located in the available literature. Inconclusive experiments reviewed in U.S. EPA (1979) indicate that further investigation of the carcinogenic potential of the dichlorobenzenes is warranted.

B. Mutagenicity

Various mitotic anomalies were observed in cells and somatic chromosomes of 1,4-dichlorobenzene-treated root tips (Srivastava, 1966; Sharma and Sarkar, 1957; Carey and McDonough, 1943). Treatment of Aspergillus nidulans (a soil mold organism) for one hour in an ether

solution of any of the three isomers of dichlorobenzene increased the frequency of back-mutations (Prasad, 1970). In the Ames assay, 1,2-dichlorobenzene did not increase the mutational rate of the histidine-requiring strains of Salmonella typhimurium (Andersen, et al. 1972).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

Campbell and Davidson (1970) reported the history of a woman who was eating p-DCB during her pregnancy, and which had no apparent effect on the offspring.

D. Chronic Toxicity

In humans, chronic occupational exposure by inhalation has occurred mainly from 1,4-dichlorobenzene and to a lesser extent 1,2-dichlorobenzene. Toxicity has involved the following organs and tissues: liver, blood (or reticulcendothelial system, including bone marrow and/or immune components), central nervous system, respiratory tract, and integument (U.S. EPA, 1979). In an inhalation study, Hollingsworth, et al. (1958) exposed groups of 20 rats, eight guinea pigs, four rabbits, and two monkeys to vapor of 1,2-dichlorobenzene for seven hours per day, five days per week for six to seven months at an average concentration of 360 mg/m^3. No adverse effects were noted in behavior, growth, organ weights, hematology, or gross and microscopic examination of tissues. In a nine-month chronic toxicity study Varshavskaya (1967), gave rats 1,2-dichlorobenzene at daily doses of 0.001, 0.01, and 0.1 mg/kg. The toxicological observations in the highest dose group was anemia and other blood changes, liver damage, and central nervous system depression. Liver damage has also been observed with rats and guinea pigs exposed to 1,4-dichlorobenzene at a concentration of 2,050 mg/m^3 for

six months (Hollingsworth, et al. 1956). There have been no specific studies on the chronic effects of 1,3-dichlorobenzene, although this compound may have been a contaminant in the preparations of the other two isomers used for toxicological testing (U.S. EPA, 1979).

E. Other Relevant Information

Dichlorobenzenes can induce the microsomal drug metabolizing enzymes. Changes in the levels of microsomal enzymes can affect the metabolism and biological activity of a wide variety of xenobiotics (Ware and West, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute studies have indicated that the position of the chlorine atoms on the benzene ring do not dramatically influence the toxicity of dichlorobenzenes for freshwater fish. In 96-hour static bioassays with bluegills, Lepomis macrohirus, LC_{50} values were 4,280, 5,590 and 5,020 µg/l for 1,4-, 1,2, and 1,3-dichlorobenzene, respectively (U.S. EPA, 1978). However, Dawson, et al. (1977) has provided a 96-hour static LC_{50} value of 27,000 µg/l for 1,2-dichlorobenzene for the same species. A greater range of toxicities was obtained for the freshwater invertebrate Daphnia magna tested in 96-hour static bioassays. LC_{50} values were: 2,440; 11,000; and 28,100 µg/l for the 1,2-, 1,4-, and 1,3-dichlorobenzene isomers, respectively (U.S. EPA, 1978). Marine fish were slightly more resistant than freshwater fish in 96-hour static assays with LC_{50} values ranging from 17,400 to 9,660 µg/l for 1,4- and 1,2-dichlorobenzene, respectively, for the sheepshead minnow. Marine invertebrates were the most sensitive organisms

tested with LC_{50} values of 1,970, 1,990, and 2,850 µg/l obtained for 1,2-, 1,4-, and 1,3- dichlorobenzenes respectively in mysid shrimp (Mysidopsis bahia) (U.S. EPA, 1978).

B. Chronic Toxicity

The only chronic study performed was an embryo-larval test of the freshwater fish, the fathead minnow (Pimephales promelas), that produced a chronic value of 1,000 µg/l. No other chronic studies were available.

C. Plant Effects

The freshwater algae Selenastrum capricornutum, when tested for the effects of dichlorobenzenes on chlorophyll a and cell numbers, had effective concentrations ranging from 91,600 to 98,000; 149,000 to 179,000; and 96,700 to 98,100 µg/l for 1,2-, 1,3-, and 1,4-dichlorobenzene, respectively. Similar studies in the marine algae Skeletonema costatum revealed effective concentrations of 44,100 to 44,200; 49,600 to 52,800; and 54,800 to 59,100 for 1,2-, 1,3-, and 1,4-dichlorobenzenes.

D. Residues

Bioconcentration factors of 89, 66, and 60 were obtained for 1,2-, 1,3-, and 1,4-dichlorobenzenes in the bluegill. Data on marine bioconcentration factors are not available.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The Occupational Safety and Health Administration, (OSHA, 1976), and the American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value is 300 mg/m^3 for 1,2-dichlorobenzene and 450 mg/m^3 for 1,4-dichlorobenzene. The acceptable daily intake (ADI) of 1,2- or 1,4-dichlorobenzene is 1.316 mg/day (Natl. Acad. Sci., 1977). There are

no standards for 1,3-dichlorobenzene. The U.S. EPA (1979) draft water quality criterion for total dichlorobenzene (all three isomers) is 0.16 mg/l.

B. Aquatic

The draft criteria for the protection of freshwater organisms are 44 µg/l not to exceed 99 µg/l for 1,2-dichlorobenzene; 310 µg/l not to exceed 700 ug/l for 1,3-dichlorobenzene; and 190 µg/l not to exceed 440 µg/l for 1,4-dichlorobenzene. For marine organisms criteria have been drafted as 15 µg/l not to exceed 34 µg/l for 1,2-dichlorobenzene; 22 µg/l not to exceed 49 µg/l for 1,3-dichlorobenzene; and 15 µg/l not to exceed 34 µg/l for 1,4-dichlorobenzene.

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No. 68

3,3'-Dichlorobenzidine

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 3,3'-dichlorobenzidine and has found sufficient evidence to indicate that this compound is carcinogenic.

3,3'-DICHLOROBENZIDINE

SUMMARY

The adverse health effects associated with 3,3'-dichlorobenzidine include the elevated risk of carcinogenicity based upon data from several experimental bioassays. Animals exposed to dust containing dichlorobenzidine were found to have a slight to moderate pulmonary congestion.

One aquatic toxicity test has been performed for dichlorobenzidine, yielding results indicating that concentrations of 0.5 µg/l were acutely toxic to a freshwater fish species.

3,3'-DICHLOROBENZIDINE

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Dichlorobenzidine (U.S. EPA, 1979). The molecular formula of 3,3'-dichlorobenzidine (4,4'-diamino-3,3'-dichlorobiphenyl) is $C_{12}H_{10}Cl_2N_2$, and has a molecular weight of 253.13. The chemical is sparingly soluble in water (0.7 g/l at 15°C), but readily soluble in organic solvents. Because of the fact that 3,3'-dichlorobenzidine is an organic base, it may be fairly tightly bound to humic materials, causing long-term storage in soils.

3,3'-Dichlorobenzidine has been demonstrated to be a carcinogen in experimental animals. Various types of sarcomas and adenocarcinomas have been induced at injection sites, and in specific organ systems upon dosage by gavage. No evidence is available implicating 3,3'-dichlorobenzidine as a human carcinogen.

II. EXPOSURE

A. Water

3,3'-Dichlorodibenzidine has been detected in water near a waste disposal lagoon ranging from 0.13 to 0.27 mg/l, as have benzidine concentrations up to 2.5 mg/l (Sikka, et al. 1978). In water of the Sumida River in Tokyo receiving effluents of dye and pigment factories (Takemura, et al. 1965) total aromatic amines including 3,3'-dichlorobenzidine were reported as high as 0.562 mg/l. The literature tends to support the possibility that the use of storage lagoons to handle 3,3'-dichlorobenzidine wastes may pose a threat to persons relying on nearby wells for drinking water.

B. Food

Data quantifying levels of 3,3'-dichlorobenzidine in foods have not been reported. It was suggested that consumption of fish would serve as the major dietary intake of 3,3'-dichlorobenzidine. No measurable levels of 3,3'-dichlorobenzidine were detected (<10 µg/l) in fish sampled near a contaminated waste-lagoon (Diachenko, 1978).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor to be 1,150 for 3,3'-dichlorobenzidine for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

C. Inhalation

The low volatility and large crystal structure of 3,3'-dichlorobenzidine would tend to minimize the risk of exposure to the chemical in ambient air. However, inhalation may be a major source of exposure to those individuals occupationally exposed to 3,3'-dichlorobenzidine. Concentrations as high as 2.5 mg/100 m^3 have been reported in one Japanese pigment factory (Akiyama, 1970).

D. Dermal

Under specific conditions of moist skin and high atmospheric humidity and temperature dermal absorption of 3,3'-dichlorobenzidine may be possible.

III. PHARMACOKINETICS

A. Absorption

Data concerning the rates and degree of absorption of dichlorobenzidine have not be quantitated.

B. Distribution

One study administering (^{14}C)-3,3'-dichlorobenzidine at doses of 0.2 mg/kg intravenously in rats, monkeys, and dogs revealed a general distribution of radioactivity after 14 days. The highest (^{14}C)-3,3'-dichlorobenzidine levels were found in the livers of all three species, in the bile of monkeys and in lungs of dogs (Kellner, et al. 1973).

C. Metabolism

Following the intravenous injection of 0.2 mg/kg (^{14}C)-3,3'-dichlorobenzidine, the total urinary radioactivity was recovered as one-third unchanged (^{14}C)-3,3'-dichlorobenzidine, one-third as the mono-N-acetyl derivative of the parent compound, and the remainder not recoverable (Kellner, et al., 1973). Chronic ingestion of small doses of 3,3'-dichlorobenzidine lead to the appearance of four metabolic products including benzidine (U.S. EPA, 1979), however, the results may be questionable due to the analytical methods employed in the study. No metabolites of 3,3'-dichlorobenzidine have been detected in the excreta of dogs experimentally administered the parent compound (U.S. EPA, 1979), nor the urine of human subjects experimentally administered the chemical (Gerarde and Gerarde, 1974).

E. Excretion

Several studies have indicated that fecal elimination may be a major route of excretion in animals and humans (U.S. EPA, 1979). One study (Meigs, et al. 1954) detected unspecified amounts of 3,3'-dichlorobenzidine in the urine of occupationally exposed workers.

IV. EFFECTS ON MAMMALS

A. Carcinogenicity

A number of investigations have reported the carcinogenic potential of 3,3'-dichlorobenzidine. Dietary 3,3'-dichlorobenzidine at 1,000 mg/kg have been associated with the significant occurrence of mammary adenocarcinomas, granulocytic leukemia, and zymbal gland carcinomas in male rats and mammary adenocarcinomas in female rats (Stula, et al. 1975). In dogs, oral doses of 100 mg/kg were associated with the significant occurrence of hepatic and urinary bladder carcinomas (Stula, et al. 1975). Levels of 0.5 and 1.0 mls of a 4.4 percent suspension of 3,3'-dichlorobenzidine in rat feed, resulting in a 4.53 g total dose of the chemical, produced an increase of cancers of the mammary gland, Zymbal gland, urinary bladder, skin, small intestine, liver, thyroid gland, kidney, hematopoietic system and salivary glands (Pliss, 1959). Hepatic tumors and sebaceous gland carcinoma were observed in mice exposed to a total dose of 127.5 to 135 mg over a ten month period of time (Pliss, 1959). 3,3'-Dichlorobenzidine was administered at levels of 30 mg every 3 days for 30 days by gavage. Observations over nine months demonstrated that DCB is ineffective as a mammary carcinogen (Griswold, et al. 1968). A diet of 0.3 percent 3,3'-dichlorobenzidine was marginally carcinogenetic and tumorigenic to hamsters (U.S. EPA, 1979). 3,3'-Dichlorobenzidine has also found to produce transformation in cultured rat embryo cells (Freeman, et al. 1973). Epidemiology studies in the United States, Great Britian, and Japan have not provided evidence

that 3,3'-dichlorobenzidine by itself induces bladder cancer in workers occupationally exposed to the chemical. For some studies, though, the latent period for tumor formation might not have elapsed.

B. Mutagenicity

3,3'-Dichlorobenzidine has been shown to induce frame shift mutations in Salmonella typhimurium tester strain TA1598 in the presence of the S9 NADPH-fortified rat liver enzyme preparation (Garner, et al. 1975). Similar results with tester strain TA98 indicating frame shift mutations and tester strain 1000 indicating base-pair substitutions were observed by prior metabolic activation with a male mouse enzyme system (Lazear and Louis, 1977).

C. Teratogenicity

Information relative to the teratogenic effects of 3,3'-dichlorobenzidine was not found in the available literature. Document (U.S. EPA, 1979). The chemical has been shown to cross the placental barrier and increase the incidence of leukemia in the offspring of pregnant mice given doses of 8-10 mg of 3,3'-dichlorobenzidine subcutaneously during the last week of pregnancy, but these results may represent toxic effects on neonates through suckling milk from dosed mothers (Golub, et al. 1969, 1974). Altered growth and morphology of cultured kidney tissue obtained from prenatally exposed mouse embryos has been observed (Shabad, et al. 1972; Golub, et al. 1969).

D. Toxicity

An acute oral LD_{50} for DCB in mice, given to mice for seven consecutive days was 352 mg/kg/day for females and 386 mg/kg/day for males. Single-dose LD_{50} values were reported as 488 and 676 mg/kg for female and male mice, respectively. Rats exposed to atmospheric dust containing unspecified amounts of 3,3'-dichlorobenzidine for 14 days showed no increased mortalities. Upon autopsy slight to moderate pulmonary congestion and one pulmonary abcess were observed.

V. AQUATIC TOXICITY

The only aquatic species tested for the toxic effects of 3,3'-dichlorobenzidine was the bluegill, Lepomis macrochirus. It was found to be acutely toxic at concentrations of 0.5 mg/l or greater (Sikka, et al. 1978).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The American Conference of Governmental Industrial Hygienists has recommended that exposure to 3,3'-dichlorobenzidine be reduced to zero, based on the demonstrated carcinogenicity of the chemical in experimental animals. Occupational standards have not been placed on 3,3'-dichlorobenzidine and standards regulating levels of the chemical in the environment or in food have not been proposed.

A recommended draft criterion of 1.69×10^{-2} µg/l has been established, corresponding to a lifetime cancer risk of 10^{-5}. This value was derived from data relating 3,3'-dichlorobenzidine to the daily consumption of two liters of water and 18.7 g of fish and shellfish.

B. Aquatic

Data were insufficient to draft criteria for either freshwater or marine life.

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No. 69

1,1-Dichloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

69-1

DISCLAIMER

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1,1-DICHLOROETHANE

Summary

There is no available evidence to indicate that 1,1-dichloroethane produces carcinogenic or mutagenic effects. A single study in rats failed to show teratogenic effects following inhalation exposure.

Symptoms produced by human poisoning include respiratory tract irritation, central nervous system depression, and marked cardiac excitation. Animal studies indicate that 1,1-dichloroethane may produce liver damage.

Sufficient toxicological data are not available to calculate aquatic exposure criteria.

1,1-DICHLOROETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms have been replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. 1,1-Dichloroethane (ethylidene dichloride; ethylidene chloride; molecular weight 98.96) is a liquid at room temperature with a boiling point of 57.3°C, a melting point of -98°C, a specific gravity of 1.1776, and a solubility in water of 5 g/liter (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds. No commercial production of 1,1-dichloroethane has been reported in the United States (NIOSH, 1978).

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes are present in raw and finished waters due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water or treatment of sewage. Air levels of these volatile compounds are produced by evaporation during use as degreasing agents and in dry-cleaning operations (U.S. EPA, 1979a).

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976).

No information on levels of 1,1-dichloroethane in foods was found in the available literature. Sufficient data is not available to estimate a steady-state bioconcentration factor for 1,1-dichloroethane.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature on 1,1-dichloroethane for absorption, distribution, metabolism and excretion. However, the reader is referred to a more general treatment of chloroethanes (U.S. EPA, 1979b) which indicates rapid absorption of chloroethanes following oral or inhalation exposure; widespread distribution of the chloroethanes throughout the body; enzymatic dechlorination and oxidation to the alcohol and ester forms; and excretion of the chloroethanes primarily in the urine and in expired air.

Additionally, it has been indicated that the absorption of 1,1-dichloroethane is most similar to that of the 1,2-isomer (indicating significant dermal absorption as well as rapid oral or inhalation absorption).

IV. EFFECTS

A. Carcinogenicity and Mutagenicity

Pertinent data could not be located in the available literature.

B. Teratogenicity

An inhalation study in rats has indicated no major teratogenic effects of 1,1-dichloroethane (Schwetz, et al. 1974).

C. Other Reproductive Effects

Inhalation of 1,1-dichloroethane by pregnant rats produced delayed ossification of sternebrae in fetuses, indicating an effect of the compound in retarding fetal development (Schwetz, et al. 1974).

D. Chronic Toxicity

Use of 1,1-dichloroethane as an anesthetic was discontinued because of marked excitation of the heart (Browning, 1965). Poisoning cases have shown respiratory tract irritation and central nervous system depression (U.S. EPA, 1979a). Animal studies indicate that inhalation of 1,1-dichloroethane may produce liver damage (Sax, 1975).

V. AQUATIC TOXICITY

Pertinent aquatic toxicity data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The current promulgated Occupational Safety and Health Administration exposure standard for 1,1-dichloroethane is 100 ppm, time-weighted average for up to a 10-hour work day, 40-hour work week.

Sufficient data are not available to derive a criterion to protect human health from exposure to 1,1-dichloroethane from ambient water.

B. Aquatic

Sufficient toxicologic data are not available to calculate aquatic exposure criteria.

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No. 70

1,2-Dichloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 1,2-dichloroethane and has found sufficient evidence to indicate that this compound is carcinogenic.

1,2-DICHLOROETHANE

Summary

Results of an NCI carcinogenesis bioassay in rats and mice have shown that 1,2-dichloroethane may produce a wide variety of tumors, including squamous cell carcinomas, hemangiosarcomas, mammary adenocarcinomas, and hepatocellular carcinomas. Mutagenic effects have been shown in the Ames Salmonella system and in E. coli; metabolites of 1,2-dichloroethane have also shown mutagenic effects in the Ames assay.

One study has failed to indicate teratogenic effects following inhalation exposure to 1,2-dichloroethane although reproductive toxicity was demonstrated. Chronic human exposure to 1,2-dichloroethane has produced neurological symptoms and liver and kidney damage. Poisoning victims have shown diffuse dystrophic changes in the brain and spinal cord.

Acute toxicity values for freshwater organisms ranged from 431,000 to 550,000 µg/l. Marine invertebrates appeared to be somewhat more sensitive to 1,2-dichloroethane with an LC_{50} value of 113,000 µg/l reported.

1,2-DICHLOROETHANE

I. INTRODUCTION

This profile is based on the draft Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms of ethane are replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. 1,2-Dichloroethane (molecular weight 98.96) is a liquid at room temperature with a boiling point of 83.4^{o}C, a melting point of -35.4^{o}C, a specific gravity of 1.253, and a solubility of 8.1 g/l in water (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds. A large portion of 1,2-dichloroethane is used in the production of vinyl chloride and chlorinated chemicals, and as an ingredient, along with tetraethyl lead, in antiknock mixtures (U.S. EPA, 1979a).

1,2-Dichloroethane production in 1976 was 4,000 x 10^{3} tons (U.S. EPA, 1979a). The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes present in raw and finished waters are due primarily to industrial discharges. Small amounts of the chloroethanes may be formed

by chlorination of drinking water or treatment of sewage. Of 80 water samples tested, 27 contained 1,2-dichloroethane at concentrations of 0.2 to 8 µg/l (U.S. EPA, 1974).

Sources of human exposure to chloroethanes not only include water, but also air, contaminated foods and fish, and dermal absorption. For example, 1,2-dichloroethane has been detected in 11 of 17 spices in concentrations ranging from 2 to 23 µg/g of spice (Page and Kennedy, 1975). In fish and shellfish, levels of chloroethanes in the nanogram range have been found (Dickson and Riley, 1976).

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for 1,2-dichloroethane to be 4.6 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on the measured steady-state bioconcentration studies in bluegills.

III. PHARMACOKINETICS

A. Absorption

The chloroethanes are absorbed rapidly following oral or inhalation routes of exposure (U.S. EPA, 1979a). Animal studies indicate that significant absorption of 1,2-dichloroethane may occur following dermal application (Smyth, et al. 1969).

B. Distribution

Pertinent information could not be located in the available literature on 1,2-dichloroethane. The reader is referred to more general treatment of the chloroethanes (U.S. EPA, 1979b) which indicates a widespread distribution of chloroethanes through the body.

C. Metabolism

In general, the metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation to corresponding alcohols (U.S. EPA, 1979a). Metabolism of 1,2-dichloroethane produces a variety of metabolites in the urine. The main two are: s-carboxymethylcysteine and thiodiacetic acid (Yllner, 1971a,b,c,d). Yllner (1971a,b,c,d) also stated that the percentage of 1, 2-dichloroethane metabolized decreased with increasing dose, suggesting saturation of metabolic pathways.

D. Excretion

The chloroethanes are excreted primarily in the urine and in expired air (U.S. EPA, 1979a). Animal studies conducted by Yllner (1971a,b, c,d) indicate that large amounts of chlorinated ethanes administered by i.p. injection are excreted in the urine, with very little excretion in the feces. Excretion appears to be rapid, since 90 percent of an i.p. administered dose of 1,2-dichloroethane was eliminated in the first 24 hours (U.S. EPA, 1979a).

IV. EFFECTS

A. Carcinogenicity

Results of the NCI bioassay for carcinogenicity (NCI, 1978) have indicated that 1,2-dichloroethane administration produced an increase in several types of tumors. Squamous cell carcinomas and hemangiosarcomas were produced in male rats, and mammary adenocarcinomas in female rats, following feeding of 1,2-dichloroethane. In mice, hepatocellular carcinomas in males and mammary adenocarcinomas in females were both increased after oral treatment with 1,2-dichloroethane.

B. Mutagenicity

Testing of 1,2-dichloroethane in the Ames Salmonella assay and an E. coli assay system have indicated mutagenic activity of this compound (Brem, et al. 1974). Metabolites of 1,2-dichloroethane (S-chloroethyl cysteine, chloroethanol, and chloroacetaldehyde) have shown positive mutagenic effects in the Ames system (U.S. EPA, 1979a). 1,2-Dichloroethane has also been reported to increase mutation frequencies in pea plants (Kiricheck, 1974) and Drosophila (Nylander, et al. 1978).

C. Teratogenicity

Inhalation studies with 1,2-dichloroethane in pregnant rats did not indicate teratogenic effects (Vozovaya, 1974).

D. Other Reproductive Effects

Rats exposed to 1,2-dichloroethane by inhalation showed reduced litter sizes, decreased live births, and decreased fetal weights (Vozovaya, 1974).

E. Chronic Toxicity

Patients suffering from 1,2-dichloroethane poisoning have shown diffuse dystrophic changes in the brain and spinal cord (Akimov, et al. 1978). Chronic exposures have produced neurologic changes and liver and kidney impairment (NIOSH, 1978a).

Animal studies with 1,2-dichloroethane toxicity have shown liver and kidney damage and fatty infiltration, and some bone marrow effects (U.S. EPA, 1979a).

F. Acute Toxicity

Oral human LD_{Lo} (lowest dose which has caused death) values have been estimated at 500 and 810 mg/kg in two studies (NIOSH, 1978b). Other species show a similar sensitivity to 1,2-dichloroethane, except for the

rat. An LD_{50} value for this species has been estimated to be 12 µg/kg (NIOSH, 1978b).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute 96-hour static LC_{50} values ranged from 431,000 to 550,000 µg/l for the bluegill (Lepomis macrochirus), while a single 48- hour static LC_{50} value of 218,000 µg/l was obtained for the freshwater cladoceran Daphnia magna (U.S. EPA, 1978). A single acute marine invertebrate study was available, reporting a 96-hour static LC_{50} value of 113,000 µg/l for the mysid shrimp (Mysidopsis bahia) (U.S. EPA, 1978).

B. Chronic Toxicity and Plant Effects

Pertinent information could not be located in the available literature on chronic toxicity and plant effects.

C. Residues

A bioconcentration factor of 2 has been reported for the bluegill (U.S. EPA, 1979a).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on the NCI carcinogenesis bioassay data, and using a linear, nonthreshold model, the U.S. EPA (1979a) has estimated a level of 1,2-dichloroethane in ambient water that will result in an additional cancer risk of 10^{-5} to be 7 µg/l.

The 8-hour TWA exposure standard developed by OSHA for 1,2-dichloroethane is 50 ppm.

B. Aquatic

In freshwater environment a criterion has been drafted for 1,2-dichloroethane as 3,900 µg/l as a 24-hour average, not to exceed 8800 µg/l. For marine life, the criterion has been drafted as 880 µg/l, not to exceed 2000 µg/l.

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