H E A L T H A N D E N V I R O N M E N T A L

E F F E C T P R O F I L E S

APRIL 30, 1980
U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF SOLID WASTE

BACKGROUND DOCUMENT

RESOURCE CONSERVATION AND RECOVERY ACT

SUBTITLE C - IDENTIFICATION AND LISTING OF HAZARDOUS WASTE

APPENDIX A - HEALTH AND ENVIRONMENTAL EFFECT PROFILES

APRIL 30, 1980

U.S. ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF SOLID WASTE

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

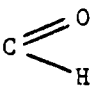
Summary

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

DISCLAIMER

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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

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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

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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.

ACROLEIN

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No. 7

Acrylonitrile

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 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).

ACRYLONITRILE

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No. 8

Aldrin

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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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.

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 saltwater 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 µg/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)

ANTIMONY

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No. 11

Arsenic

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 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	

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).

ARSENIC

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No. 12

Asbestos

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 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

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BARIUM

18

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 ($\approx$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

DISCLAIMER

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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

U.S. ENVIRONMENTAL PROTECTION AGENCY
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

B. 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.

BENZENE

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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 intrapertioneally 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).

BENZIDINE

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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.

BENZ(a)ANTHRACENE

REFERENCES

Basu, D.K., and J. Saxena. 1977. Analysis of raw and drinking water samples for polynuclear aromatic hydrocarbons. EPA PO No. CA-7-2999-A, and CA-8-2275-B. Expo. Evalu. Branch, HERL, Cincinnati, Ohio.

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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

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(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).

BENZO(b)FLUORANTHENE

REFERENCES

Basu, D.K. and J. Saxena. 1977. Analysis of raw and drinking water samples for polynuclear aromatic hydrocarbons. U.S. Environ. Prot. Agency, P.O. No. CA-7-2999-A. Exposure Evaluation Branch, HERL, Cincinnati, Ohio.

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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

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.

BENZO(A)PYRENE

REFERENCES

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No. 20

Benzotrichloride

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.

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^oC
Boiling Point:	220.8^oC
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 quidelines 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
WASHINGTON, D.C. 20460

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.

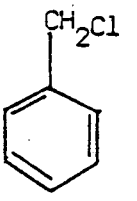
Weak mutagenic activity of the compound has been demonstrated in the Ames *Salmonella* assay and in *E. coli*.

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

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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 $\mu g/m^3$, while in rural areas beryllium concentrations have been measured at 0.00013 $\mu g/m^3$ (Tabor and Warren, 1958; National Air Sampling Network, 1968). At a beryllium extraction plant in Ohio, beryllium concentrations were generally around 2 $\mu g/m^3$ 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/l. 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/l. Acute toxicity for aquatic invertebrates provides two 48-hour LC_{50} values of 7,900 and 2,500 µg/l, with water hardness values of 180 and 200 µg/l 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-weighted 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 re-evaluation 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).

BERYLLIUM

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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.

BIS(2-CHLOROETHOXY)METHANE

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No. 24

Bis(2-chloroethyl)ether

Health and Environmental Effects

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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.

B. Aquatic

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

BIS(2-CHLOROETHYL)ETHER

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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).

BIS(2-CHLOROISOPROPYL)ETHER (BCIE)

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No. 26

Bis(Chloromethyl)ether

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 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.

BIS(CHLOROMETHYL)ETHER

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No. 27

Bis(2-ethylexyl)phthalate

Health a[illegible]nvironmental Effects

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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.