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

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U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF SOLID WASTE

BIS-(2-ETHYLHEXYL)PHTHALATE

I. INTRODUCTION

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

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

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

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

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

II. EXPOSURE

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

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

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

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

III. PHARMACOKINETICS

A. Absorption

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

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

B. Distribution

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

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

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

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

C. Metabolism

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

D. Excretion

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

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

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

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

C. Teratogenicity

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

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

D. Other Reproductive Effects

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

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

E. Chronic Toxicity

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

F. Other Relevant Information

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

V. AQUATIC TOXICITY

A. Acute Toxicity

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

B. Chronic Toxicity

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

C. Plant Effects

Pertinent information could not be located in the available literature.

D. Residues

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

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

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

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

B. Aquatic

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

BIS-(2-ETHYLHEXYL) PHTHALATE

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No. 28

Bromoform

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

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

BROMOFORM

SUMMARY

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

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

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

I. INTRODUCTION

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

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

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

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

Bromoform is used as a chemical intermediate; solvent for waxes, greases, and oils; ingredient in fire-resistant chemicals and gauge fluids (U.S. EPA 1978a; Hawley, 1977).

II. EXPOSURE

A. Environmental Fate

Bromoform gradually decomposes on standing; air and light accelerate decomposition (Windholz, 1976). The vapor pressure of bromoform, while lower than that for chloroform and other chloroalkanes, is, nonetheless, sufficient to ensure that volatilization will be an important means of environmental transport. The

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

half-life for hydrolysis of bromoform is estimated at 686 years. Bromoform should be much more reactive in the atmosphere. Oxidation by HO radical will result in a half-life of a few months in the troposphere (U.S. EPA, 1977).

B. Bioconcentration

The bioconcentration factor for bromoform in aquatic organisms that contain about 8% lipid is estimated to be 48. The weighted average bioconcentration factor for bromoform in the edible portion of all aquatic organisms consumed by Americans is estimated to be 14 (U.S. EPA, 1979b).

C. Environmental Occurence

The National Organics Reconnaissance Survey detected bromoform in the finished drinking water of 26 of 80 cities, with a maximum concentration of 92 ug/l. Over 90% of the samples contained 5 ug/l or less. No bromoform was found in raw water samples (Symons et al., 1975). Similarly, the EPA Region V Organics Survey found bromoform in 14% of the finished drinking water samples and none in raw water (U.S. EPA, 1975). Using a variety of sampling and analysis methods, the National Organic Monitoring Survey found bromoform in 3 of 111, 6 of 118, 38 of 113, 19 of 106, and 30 of 105 samples with mean concentrations ranging from 12-28 ug/l (U.S. EPA, 1978b). A Canadian survey of drinking water found 0-0.2 ug/l with a median concentration of 0.01 ug/l (Health and Welfare Can., 1977).

The National Academy of Sciences (1978) concluded that water chlorination, via the haloform reaction, results in the production of trihalomethanes (including bromoform) from the organic precursors present in raw water.

Significant quantities of bromoform are also produced from natural sources, especially red algae. For example, the essential oil of Asparagopsis taxiformis (a red marine algae eaten by Hawaiians) contains approximately 80% bromoform (Burreson et al., 1975).

III. PHARMACOKINETICS

Bromoform is absorbed through the lungs, gastrointestinal tract, and skin. Some of the absorbed bromoform is metabolized in the liver to inorganic bromide ion. Bromide is found in tissues and urine following inhalation or rectal administration of bromoform (Lucas, 1929). Metabolism of bromoform to carbon monoxide has also been reported (Ahmed, 1977). Recent studies show that phenobarbital-induced rats metabolize bromoform to carbonyl bromide ($COBr_2$), the brominated analog of phosgene (COCl) ~~(Pohl~~ et al., 1979).

IV. HEALTH EFFECTS

A. Carcinogenicity

Bromoform caused a significant increase in tumor incidence at one dose level in a short-term in vivo oncogenicity assay known as the strain A mouse lung adenoma test. The increase was observed at a dose of 48 mg/kg/injection with a total dose of 1100 mg/kg. The tumor incidence was not increased significantly at doses of 4 mg/kg (total dose of 72 mg/kg) or 100 mg/kg (total dose of 2400 mg/kg) (Theiss et al., 1977.

B. Mutagenicity

Bromoform was mutagenic in S. typhimurium strain TA 100 (without metabolic activation) (Simmon, 1977).

C. Other Toxicity

Rats inhaling 250 mg/m^3 bromoform for 4 hr/day for 2 months developed impaired liver and kidney function (Dykan, 1962).

In humans, inhalation of bromoform causes irritation to the respiratory tract. Mild cases of bromoform poisoning may cause only headache, listlessness, and vertigo. Unconsciousness, loss of reflexes, and convulsions occur in severe cases. The primary cause of death from a lethal dose of bromoform is respiratory failure. Pathology indicates that the chemical causes fatty degenerative and centrolobular necrotic changes in the liver (U.S. PHS, 1955).

Acute animal studies indicate impaired function and pathological changes in the liver and kidneys of animals exposed to bromoform (Kutob and Plaa, 1962; Dykan, 1962).

V. AQUATIC EFFECTS

A. Fresh Water Organisms

The 96-hr LC_{50} (static) in bluegill sunfish is 29.3 mg/l. The 48-hr LC_{50} (static) for Daphnia magna is 46.5 mg/l. The 96-hr EC_{50}s for chlorophyll A production and cell number in S. capricornutum are 112 mg/l and 116 mg/l, respectively (U.S. EPA, 1978a). (See also Section II.B.)

B. Marine Organisms

The 96-hr LC_{50} (static) in sheepshead minnow is 17.9 mg/l. The 96-hr LC_{50} (static) in mysid shrimp is 20.7 mg/l. The EC_{50}s for chlorophyll A production and cell number in S. costatum are, respectively, 12.3 mg/l and 11.5 mg/l (U.S. EPA, 1978a).

VI. EXISTING GUIDELINES

A. Human

The OSHA standard for bromoform in air is a time weighted average (TWA) of 0.5 ppm (39CFR23540).

The Maximum Contaminant Level (MCL) for total trihalomethanes (including bromoform) in drinking water has been set by the U.S. EPA at 100 ug/l (44FR68624). The concentration of bromoform produced by chlorination can be reduced by treatment of drinking water with powdered activated carbon (Rook, 1974). This is the technology that has been proposed by the EPA to meet this standard.

B. Aquatic

The proposed ambient water criterion for the protection of fresh water aquatic life from excessive bromoform exposure is 840 ug/l as a 24-hour average. Bromoform levels are not to exceed 1900 ug/l at any time. The criterion for the protection of marine life is 180 ug/l (24 hr avg), not to exceed 1900 ug/l (U.S. EPA, 1979b).

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No. 29

Bromomethane

Health and Environmental Effects

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DISCLAIMER

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BROMOMETHANE

Summary

On acute exposure to bromomethane, neurologic and psychiatric abnormalities may develop and persist for months or years. There is no information on the chronic toxicity, carcinogenicity, or teratogenicity of bromomethane. Bromomethane has been shown to be mutagenic in the Ames *S. typhimurium* test system.

Acute LC_{50} values have been reported in two tests as 12,000 and 11,000 µg/l for a marine and freshwater fish, respectively.

BROMOMETHANE

I. INTRODUCTION

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

Bromomethane (CH_3Br, methyl bromide, monobromomethane, and embafume; molecular weight 94.94) is a colorless gas. Bromomethane has a melting point of -93.6°C, a boiling point of 3.56°C, a specific gravity of 1.676 g/ml at -20°C, and a water solubility of 17.5 g/l at 20°C (Natl. Acad. Sci., 1978). Bromomethane has been widely used as a fumigant, fire extinguisher, refrigerant, and insecticide (Kantarjian and Shaheen, 1963). Today the major use of bromomethane is as a fumigating agent. Bromomethane is believed to be formed in nature, with the oceans as a primary source (Lovelock, 1975). The other major environmental source of bromomethane is from its agricultural use as a soil, seed, feed and space fumigant. For additional information regarding Halomethanes as a class the reader is referred to the Hazard Profile on Halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

The U.S. EPA (1975) has identified bromomethane qualitatively in finished drinking waters in the U.S. There are, however, no data on its concentration in drinking water, raw water, or waste water (U.S. EPA, 1979a).

B. Food

There is no information on the concentration of bromomethane in food. Bromomethane residues from fumigation decrease rapidly through loss to the atmosphere and reaction with protein to form

inorganic bromide residues. With proper aeration and product processing, most residual bromomethane will rapidly disappear due to methylation reactions and volatilization (Natl. Acad. Sci., 1978; Davis, et al. 1977). There are no bioconcentration data for bromomethane (U.S. EPA, 1979a).

C. Inhalation

Saltwater atmospheric background concentrations of bromomethane averaging about 0.00036 mg/m^3 have been reported (Grimsrud and Rasmussen, 1975; Singh, et al. 1977). This is higher than reported average continental background and urban levels and suggests that the oceans are a major source of global bromomethane (Natl. Acad. Sci., 1978). Bromomethane concentrations of up to 0.00085 mg/m^3 may occur outdoors locally with light traffic, as a result of exhaust containing bromomethane as a breakdown product of ethylene dibromide, which is used in leaded gasoline (Natl. Acad. Sci., 1978).

III. PHARMACOKINETICS

A. Absorption

Absorption of bromomethane most commonly occurs via the lungs, although it can also occur through the gastrointestinal tract and the skin (Davis, et al. 1977; von Oettingen, 1964).

B. Distribution

Upon absorption, blood levels of residual non-volatile bromide increase, indicating rapid uptake of bromomethane or its metabolites (Miller and Haggard, 1943). Bromomethane is rapidly distributed to various tissues and is broken down to inorganic bromide. Storage, only as bromides, occurs mainly in lipid-rich tissues.

C. Metabolism

Evidently the toxicity of bromomethane is mediated by the bromomethane molecule itself. Its reaction with tissue (methylation of sulfhydryl groups in critical cellular proteins and enzymes) results in disturbance of intracellular metabolic functions, with irritative, irreversible, or paralytic consequences (Natl. Acad. Sci., 1978; Davis, et al. 1977; Miller and Haggard, 1943).

D. Excretion

Elimination of bromomethane is rapid initially, largely through the lungs. The kidneys eliminate much of the remainder as bromide in the urine (Natl. Acad. Sci., 1978).

IV. EFFECTS

Pertinent information relative to the carcinogenicity, teratogenicity or other reproductive effects, or chronic toxcity of bromomethane were not found in the available literature.

A. Mutagenicity

Simmon and coworkers (1977) reported that bromomethane was mutagenic to Salmonella typhimurium strain TA100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required, and the number of revertants per plate was directly dose-related.

B. Other Relevant Information

In several species, acute fatal poisoning has involved marked central nervous system disturbances with a variety of manifestations: ataxia, twitching, convulsions, coma, as well as changes in lung, liver,

heart, and kidney tissues (Sayer, et al. 1930; Irish, et al. 1940; Gorbachev, et al. 1962; von Oettingen, 1964). Also, residual bromide in fumigated food has produced some adverse effects in dogs (Rosenblum, et al. 1960).

V. AQUATIC TOXICITY

Two acute toxicity studies on one freshwater and one marine fish species were reported with LC_{50} values of 11,000 µg/l for freshwater bluegill (*Lepomis macrochirus*) and an LC_{50} value of 12,000 µg/l for the marine tidewater silversides (*Menidia beryllina*) (U.S. EPA, 1979a). Pertinent information relative to aquatic chronic toxicity or plant effects for bromomethane were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

The current OSHA standard for occupational exposure to bromomethane (1976) is 80 mg/m^3; the American Conference of Governmental Industrial Hygienist's (ACGIH, 1971) threshold limit value is 78 mg/m^3. The U.S. EPA (1979a) draft water quality criteria for bromomethane is 2 µg/l. Refer to the Halomethane Hazard Profile for discussion of criteria derivation (U.S. EPA, 1979b).

B. Aquatic Toxicity

The draft criterion for protecting freshwater life is a 24-hour average concentration of 140 µg/l, not to exceed 320 µg/l. The marine criterion is 170 µg/l as a 24-hour average, not to exceed 380 µg/l.

BROMOMETHANE

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No. 30

4-Bromophenyl Phenyl Ether

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.

4-Bromophenyl phenyl ether

SUMMARY

Very little information on 4-bromophenyl phenyl ether exists. 4-Bromophenyl phenyl ether has been identified in raw water, in drinking water and in river water. 4-Bromophenyl phenyl ether has been tested in the pulmonary adenoma assay, a short-term carcinogenicity assay. Although the results were negative, several known carcinogens also gave negative results. No other health effects were available. 4-Bromophenyl phenyl ether appears to be relatively toxic to freshwater aquatic life: a 24-hour average criterion of 6.2 ug/L has been proposed.

I. INTRODUCTION

4-Bromophenyl phenyl ether ($BrC_6H_4OC_6H_5$; molecular weight 249.11) is a liquid at room temperature; it has the following physical/chemical properties (Weast 1972):

Melting point:	18.72°C
Boiling point:	310.14°C (760 mm Hg) 163°C (10 mm Hg)
Density:	1.4208^{20}
Solubility:	Insoluble in water; soluble in ether

No information could be found on the uses of this substance.

A review of the production range (includes importation) statistics for 4-bromophenyl phenyl ether (CAS Nol 101-55-3) which is listed in the initial TSCA Inventory (1979) has shown that between 0 and 900 pounds of this chemical were produced/imported in 1977.*

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

II. EXPOSURE

No specific information relevant to the environmental fate of 4-bromophenyl phenyl ether was found in the literature. A U.S. EPA report (1975a) included this substance in a category with several other drinking water contaminants considered to be refractory to biodegradation (i.e., lifetime greater than two years in unadapted soil; point sources unable to be treated biologically). However, the authors did not present or reference experimental data to support the inclusion of 4-bromopheny phenyl ether in this category. U.S. EPA (1975a) estimated that three tons of 4-bromophenyl phenyl ether are discharged annually.

4-Bromophenyl phenyl ether has been identified as a contaminant in finished drinking water on three occasions, in raw water on one occasion and in river water on one occasion. No quantitative data were supplied (U.S. EPA, 1976). Friloux (1971) and U.S. EPA (1972) have also reported the presence of 4-bromophenyl phenyl ether in raw and finished water of the lower Mississippi River (New Orleans area). Again, no quantitative data were supplied. U.S. EPA (1975) suggest that 4-bromophenyl phenyl ether may be formed during the chlorination of treated sewage and drinking water.

III. PHARMACOKINETICS

No information was located.

IV. HEALTH EFFECTS

A. Carcinogenicity

Three groups of 20 male mice were administered intraperitoneal doses (23, 17 or 18 doses, respectively) of 4-bromophenyl phenyl ether in tricaprylin vehicle three times a week for 8 weeks (Theiss et al. 1977). The total doses were 920, 1700, or 3600 mg/kg, respectively. Animals were sacrificed at 24 weeks from the start of the experiment. Incidences of lung adenomas were not significantly increased, as compared with vehicle controls. However, this short-term assay should not be considered indicative of the nononcogenicity of 4-bromophenyl phenyl ether as several known oncogens tested negative in this assay.

V. AQUATIC TOXICITY

A. Acute

An unadjusted 96 hour LC_{50} of 4,940 ug/L was determined by exposing bluegills to 4-bromophenyl phenyl ether (Table 1). Adjusting this value for test conditions and species sensitivity, a Final Fish Acute Value of 690 ug/L is obtained (U.S. EPA, undated).

Exposure of *Daphnia magna*, yielded an unadjusted 48 hour LC_{50} of 360 ug/L (Table 2). The Final Invertebrate Acute Value (and the Final Acute Value) for 4-bromophenyl phenyl ether is 14 ug/L (U.S. EPA, undated).

B. Chronic

In an embryo-larval test using the fathead minnow (in which survival and growth were observed), a chronic value of 61 ug/L was obtained for 4-bromophenyl phenyl ether exposure (Table 3). Dividing by the species sensitivity factor (6.7), a Final Fish Chronic Value of 9.1 ug/L is derived. Since no other information is available, this value is also the Final Chronic Value (U.S. EPA, undated).

VI. EXISTING GUIDELINES

A. Aquatic

A 24 hour average concentration of 6.2 ug/L (6.2 ug/L = 0.44 x 14 ug/L (Final Acute Value)) is the recommended criterion to protect freshwater aquatic life. The maximum allowable concentration should not exceed 14 ug/L at any time (U.S. EPA, undated).

Table 1. Freshwater fish acute values

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC_{50} (ug/L)	Adjusted LC50 (ug/L)
Bluegill, *Lepomis macrochirus*	S	U	4-Bromophenyl-phenyl ether	96	4,940	2,700

* S = static

** U = unmeasured

Geometric mean of adjusted values: 4-Bromophenylphenyl ether = 2,700 ug/L

$\frac{2,700}{3.9}$ = 690 ug/L

Table 2. Freshwater invertebrate acute values

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC_{50} (ug/L)	Adjusted LC_{50} (ug/L)
Cladoceran, *Daphnia magna*	S	U	4-Bromophenyl-phenyl ether	48	360	300

* S = static

** U = unmeasured

Geometric mean of adjusted values: 4-Bromophenyl phenyl ether = 300 ug/L

$\frac{300}{21}$ = 14 ug/L

Table 3. Freshwater fish chronic values, 4-Bromophenyl phenyl ether

Organism	Test*	Limits (ug/L)	Chronic Value (ug/L)
Fathead minnow, *Pimephales promelas*	E-L	89-167	61

* E-L = embryo-larva

Geometric mean of chronic values = 61 ug/L $\frac{61}{6.7}$ = 9.1 ug/L

Lowest chronic value = 61 ug/L

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No. 31

Cadmium

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 cadmium and has found sufficient evidence to indicate that this compound is carcinogenic.

CADMIUM

Summary

The major non-occupational routes of human cadmium exposure are through food and tobacco smoke. Drinking water also contributes relatively little to the average daily intake.

Epidemiological studies indicate that cadmium exposure may increase the mortality level for cancer of the prostate. Long-term feeding and inhalation studies in animals have not produced tumors, while intravenous administration of cadmium has produced only injection site tumors. Mutagenic effects of cadmium exposure have been seen in animal studies, bacterial systems, *in vitro* tests, and in the chromosomes of occupationally exposed workers.

Cadmium has produced teratogenic effects in several species of animals, possibly through interference with zinc metabolism. Testicular necrosis and neurobehavioral alterations in animals following exposure during pregnancy have been produced by cadmium in animals.

Chronic exposure to cadmium has produced emphysema and a characteristic syndrome (Itai-Itai disease) following renal damage and osteomalacia. A causal relationship between chronic cadmium exposure and hypertension in humans has been suggested but not confirmed.

Cadmium is acutely toxic to freshwater fish at levels as low as 0.55 µg/l. Freshwater fish embryo/larval stages tended to be the most sensitive to cadmium. Marine fish were generally more resistant than freshwater fish. The long half-life of cadmium in aquatic organisms has been postulated, and severe restrictions to gill-tissue respiration have been observed at concentrations as low as 0.5 µg/l.

CADMIUM

I. INTRODUCTION

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

Cadmium is a soft, bluish-silver-white metal, harder than tin but softer than zinc. The metal melts at 321°C and shows a boiling point of 765°C (U.S. EPA, 1978b). Cadmium dissolves readily in mineral acids. Some of the physical/chemical properties of cadmium and its compounds are summarized in Table 1 (U.S. EPA, 1978b).

Cadmium is currently used in electroplating, paint and pigment manufacture, and as a stabilizer for plastics (Fulkerson and Goeller, 1973).

Current production: 6000 metric tons (1968) (U.S. EPA, 1978b)

Projected production: 12,000 metric tons (2000) (U.S. EPA, 1978b)

Since cadmium is an element, it will persist in some form in the environment. Cadmium is precipitated from solution by carbonate, hydroxide, and sulfide ions (Baes, 1973); this is dependent on pH and on cadmium concentration. Complexing of cadmium with other anions will produce soluble forms (Samuelson, 1963). Cadmium is strongly adsorbed to clays, muds, humic and organic materials and some hydrous oxides (Watson, 1973), all of which lead to precipitation from aqueous media. Cadmium corrodes slightly in air, but forms a protective surface film which prevents further corrosion (U.S. EPA, 1978b).

II. EXPOSURE

Cadmium is universally associated with zinc and appears with it in natural deposits (Hem, 1972). Major sources of cadmium release into the environment include emissions from metal refining and smelting plants, incineration of polyvinyl chloride plastics, emissions from use of fossil

Table 1. Some Properties of Cadmium and its Important Compounds

Compound	Primary use or occurrence	Formula	Molecular weight (g/mole)	Density (g/ml)	Physical state, 20°C	Melting point (°C)	Boiling point (°C)	Solubility in water 20°C (g/liter)	Solubility in other solvents	Acute Lethal dose[a]
Cadmium metal	Cadmium nickel batteries	Cd	112.4	8.6	Silver metal	321	765	Insoluble	Soluble in acid and NH_4NO_3	9 mg/m^3 is the approximate lethal concentration in man, inhaled as fume
Cadmium oxide	Smelting plant or coal combustion emission	CdO	128.4	7.0	Brown powder	Decomposes at 900		0.00015[b]	Soluble in acid and NH_3 salts	50 mg/m^3 is the approximate lethal concentration in man, inhaled; 72 mg/kg, rat, LD_{50} (oral)
Cadmium sulfide	Pigment for plastics and enamels; phosphors	CdS	144.5	4.8	Yellow crystal	1750	Decomposes	0.0013	Soluble in acid, very slightly soluble in NH_4OH	
Cadmium sulfate	Fruit tree fumicide	$CdSO_4$	208.5	4.7	White crystalline	1000		755	Insoluble in acid and alochol	27 mg/kg dog, LD_{50} (subcutaneous)
Cadmium carbonate	Turf treatment	$CdCO_3$	172.4	4.3	White powder or crystalline	Decomposes below 500		0.001	Soluble in acid and KCN, NH_4 salts	

Table 1. Some Properties of Cadmium and its Important Compounds (Cont'd)

Compound	Primary use or occurrence	Formula	Molecular weight (g/mole)	Density (g/ml)	Physical state, 20°C	Melting point (°C)	Boiling point (°C)	Solubility in water 20°C (g/liter)	Solubility in other solvents	Acute Lethal dose[a]
Cadmium chloride	Turf grass fungicide	$CdCl_2$	183.3	4.0	Colorless crystal	568	960	1400	15.2 g/liter in alcohol	88 mg/kg rat, LD_{50} (oral)
Cadmium potassium cyanide	Electroplating	$K_2Cd(CN)_4$	294.7	1.85	Colorless, glass crystal			333	Insoluble in alcohol	
Cadmium cyanide	Electroplating	$Cd(CN)_2$	164.4		Colorless crystal	Decomposes at 200		17, soluble in hot water	Soluble in acid and KCN	

Sources:

[a]Fulkerson and Goeller, 1973
[b]Hahne and Kroontje, 1973
Other data compiled from Weast, 1971

fuels, use of certain phosphate fertilizers, and leaching of galvanized iron pipes (U.S. EPA, 1978b). The major non-occupational routes of human exposure to cadmium are through foods and tobacco smoke (U.S. EPA, 1979).

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

Source	Adult µg/day
	Maximum conditions
Air-ambient	.008 mg/day
Air-smoking	9.0
Foods	75.0
Drinking water	20.0
Total	304.008
	Minimum conditions
Air-ambient	0.00002
Air-smoking	0
Food	12.0
Drinking water	1.0
Total	13.00002

The variation of cadmium levels in air, food, and water is quite extensive as indicated above. Leafy vegetables, contaminated water, and air near smelting plants all present sources of high potential exposure. The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of cadmium to be 17 in the edible portions of fish and shellfish consumed by Americans.

III. PHARMACOKINETICS

A. Absorption

The main routes by which cadmium can enter the body are inhalation and ingestion. Particle size and solubility greatly influence the biological fate of inhaled cadmium. When a large proportion of particles are in

the respirable range, up to 25% of the inhaled amount may be absorbed (EPA, 1979). Cadmium fumes may have an absorption of up to 50%, and it is estimated that up to 50% of cadmium in cigarette smoke may be absorbed (WHO, 1977; Elinder, et al. 1976). Large particles are trapped by the mucous membranes and may eventually be swallowed, resulting in gastrointestinal absorption (EPA, 1979).

Only a small proportion of ingested cadmium is absorbed. Two human studies using radiolabelled cadmium have indicated mean cadmium absorption from the gastrointestinal tract of 6% and 4.6% (Rahola, et al. 1973; McLellan, et al. 1978). Various dietary factors interact with cadmium absorption; these include calcium levels (Washko and Cousins, 1976), vitamin D levels (Worker and Migicovsky, 1961), zinc, iron, and copper levels (Banis, et al. 1969). and ascorbic acid levels (Fox and Fry, 1970). Low protein diets enhance the uptake of cadmium from the gastrointestinal tract (Suzuki, et al. 1969).

Dermal absorption of cadmium appears to occur to a small extent; Wahlberg (1965) has determined that up to 1.8 percent of high levels of cadmium chloride were absorbed by guinea pig skin.

Cadmium levels have been determined in human embryos (Chaube, et al. 1973) and in the blood of newborns (Lauwerys, 1978), indicating passage of cadmium occurs across the placental membranes.

B. Distribution

Cadmium is principally stored in the liver, kidneys, and pancreas with higher levels initially found in the liver (WHO Task Group, 1977). continued exposure leads to accumulation in all of these organs; levels as

high as 200-300 mg/kg wet weight may be found in the renal cortex. This storage appears to be dependent on the association of cadmium with the cadmium binding protein, metallothionen (Nordberg et al., 1975).

Animal studies indicate that following intraperitoneal or intravenous administration of cadmium most of the compound is found in the blood plasma. After 12-24 hours the plasma is cleared and most of the compound is associated with red blood cells (U.S. EPA, 1978b).

The cadmium body burden of humans increases with age (Friberg, et al. 1974) from very minimal levels at birth to an average of up to 30-40 mg by the age of 50 in non-occupationally exposed individuals. Liver accumulation continues through the last decades of life, while kidney concentrations increase until the fourth decade and then decline (Gross, et al. 1976). The pancreas and salivary glands also contain considerable concentrations of cadmium (Nordberg, 1975). Smoking effects the body burden of cadmium; levels in the renal cortex of smokers may be double those found in non-smokers (Elinder, et al. 1976; Hammer, et al. 1971).

C. Metabolism

Pertinent data were not found in the available literature.

D. Excretion

Since only about 6 percent of ingested cadmium is absorbed, a large proportion of the compound is eliminated by the feces (U.S. EPA, a or b). Some biliary excretion of cadmium has been demonstrated in rats (Stowe, 1976); this represented less than 0.1 percent of a subcutaneously administered dose.

Urinary excretion of cadmium is approximately 1-2 mg/day in the general population (Imbus, et al. 1963; Szadkowski, et al. 1969). Occupationally exposed individuals may show markedly higher urinary excretion

levels (Friberg, et al. 1974). A modest increase in human urinary excretion of cadmium has been noted with increasing age (Katagiri, et al. 1971).

Additional sources of cadmium loss are through salivary excretion and shedding of hair (U.S. EPA, 1979).

Biological half-life calculations for exposed workers have given values of up to 200 days (urine). Direct comparisons of urinary excretion levels and estimated body burden using Japanese, American, and German data, suggest a half-time of 13-47 years. Using more complex metabolic models, Frieberg, et al. 1974 concluded that the biologic half-time is probably 10-30 years. The most recent estimate of biologic half-time is 15.7 years by Ellis (1979).

IV. EFFECTS

A. Carcinogenicity

The results of several epidemiology studies of the relationship of cancer to occupational exposure to cadmium are summarized in Table 3 (U.S. EPA, 1978a). The only consistent trend seen in these studies is an increased incidence of prostate cancer in cadmium-exposed workers. A recent study by Kjellstrom, et al. (1979) of 269 cadmium-nickel battery factory workers found increased cancer mortality from nasopharyngeal cancer (significant) and increased mortality trends for prostate, lung, and colon-rectum cancers (not significant). After reviewing these studies, EPA (1979) has concluded that cadmium cannot be definitely implicated as a human carcinogen with the available data.

Animal experiments with the administration of cadmium by subcutaneous or intravenous injection have demonstrated that cadmium produces

injection site sarcomas and testicular tumors (Leydigiomas) (see Table 2; U.S. EPA, 1978a). A large number of metals and irritants produced comparable injection site sarcomas. Long term feeding and inhalation studies with cadmium have not produced tumors (Schroeder, et al. 1964, Levy, et al. 1973; Decker, et al. 1958; Anwar, et al. 1961; Paterson, 1947; Malcolm, 1972)

At the present time, the draft ambient water quality criterion for protection of human health is based on the toxicity of cadmium rather than on any carcinogenic effects. Though the studies summarized above qualitatively indicate a carcinogenic potential for cadmium, quantitatively, the issue has not been resolved.

B. Mutagenicity

An increased incidence of chromosomal aberrations has been noted in workers occupationally exposed to cadmium and in Japanese patients suffering cadmium toxicity (Itai-Itai disease) (Bauchinger, et al. 1976; Bui, et al. 1975; Deknudt and Leonard, 1976; Shiraishi and Yoshida, 1972).

Cadmium has been shown to produce mutagenic effects in vitro and in vivo in several systems (see Table 4; U.S. EPA, 1978 a or b). These effects include induction of point mutations in bacterial systems, chromosome aberrations in cultured cells and cytogenetic damage in vivo, and promotion of error prone base incorporation in DNA in vitro. Several investigators have been unable to show dominant lethal effects of cadmium in mice (Epstein, et al. 1972; Gillivod and Leonard, 1975; Suter, 1975). Point mutation studies with cadmium in Drosophila have also produced negative findings (Shabalina, 1968; Friberg et al., 1974; Sorsa and Pfeiffer, 1973).

C. Teratogenicity

Damage to the reproductive tract resulting from a single dose of parenterally administered cadmium chloride (2 mg/kg) have been observed in

TABLE 2

STUDIES ON CADMIUM CARCINOGENESIS IN EXPERIMENTAL ANIMALS[a]

Authors	Animals	Compounds and routes	Tumors
Heath *et al.*, 1962; Heath and Daniel, 1964	Rats	Cd powder in fowl serum (im)[b]	Sarcomas
Kazantzis, 1963; Kazantzis and Hanbury, 1966	Rats	CdS, Cdo (sc)[b]	Sarcomas
Haddow *et al.*, 1964; Roe *et al.*, 1964	Rats	$CdSO_4$, $CdCl_2$ (sc)	Sarcoms and Leydigiomas
Guthrie, 1964	Chickens	$CdCl_2$ (intratesticular)	Teratoma
Gunn *et al.*, 1963; 1964; 1965; 1967	Rats, Mice	$CdCl_2$ (im)	Sarcomas and Leydigiomas
Schroeder *et al.*, 1965; Kanisawa and Schroeder, 1969	Rats, Mice	Cd-acetate (drinking water)	No Tumorigenic Effect
Nazari *et al.*, 1967; Favion *et al.*, 1968	Rats	$CdCl_2$ (sc)	Sarcomas and Leydigiomas
Knorre, 1970; 1971	Rats	$CdCl_2$ (sc)	Sarcomas and Leydigiomas
Lucis *et al.*, 1972; 1973	Rats	$CdCl_2$ (sc, intrahepatic)	Sarcomas and Leydigiomas
Reddy *et al.*, 1973	Rats	$CdCl_2$ (sc)	Leydigiomas
Levy *et al.*, 1973	Rats	$CdSO_4$ (sc)	Sarcomas
Levy and Clark, 1975; Levy *et al.*, 1975	Rats, Mice	$CdSO_4$ (gastric intubation)	No Tumorigenic Effect

[a]Adapted from Sunderman, 1977.

[b]Intramuscular: im; subcutaneous: sc.

TABLE 3

SUMMARY OF RESULTS OF HUMAN EPIDEMIOLOGY STUDIES OF CANCER EFFECTS ASSOCIATED WITH OCCUPATIONAL EXPOSURES TO CADMIUM

Population Group Studied	Cadmium Compound Exposed To	Incidences of All Cancers	Incidences of Lung Cancer	Incidences of Prostrate Cancer	Reference
Battery factory workers	Cadmium oxide	High	Normal	High	Potts (1965)
Battery factory workers	Cadmium oxide	Normal	Normal	High	Kipling and Waterhouse (1967)
Cadmium smelter workers	Cadmium oxide, others	High	High	High	Lemon *et al.* (1976)
Rubber industry workers	Cadmium oxide	High	Normal	High	McMichael *et al.* (1976)

rats, rabbits, guinea pigs, hamsters, and mice (Parizek and Zahor, 1956; Parizek, 1957; Meek, 1959). This susceptibility appears to be genetically regulated since different strains of mice show differential susceptibility (Wolkowski, 1975).

Teratogenic effects of cadmium compounds administered parenterally have been reported in mice (Eto, et al. 1975), hamsters (Ferm and Carpenter, 1968; Mulvihill, et al. 1970; Ferm, 1971; Gale and Ferm, 1973) and rats (Chernoff, 1973; Barr, 1973). Oral administration of cadmium (10 ppm) has demonstrated teratogenic effects in rats (Schroeder and Mitchener, 1971), but no teratogenicity has been reported in rats and monkeys (Cuetkova, 1970; Pond and Walker, 1975; Willis, et al. 1976; Campbell and Mills, 1974).

D. Other Reproductive Effects

Rats in late pregnancy are apparently more sensitive to cadmium than non-gravid animals or those immediately post-partum. A single dose of 2-3 mg/kg of body weight given during the last 4 days of pregnancy resulted in high mortality (76 percent).

In addition to the embryotoxic effects of cadmium indicated in Section C, persisting effects of cadmium exposure during pregnancy on postulated development and growth of offspring have been observed. This includes neurobehavioral alteration in newborn rats (Chowdbury and Lauria, 1976) and growth deficiencies in lambs (U.S. EPA, 1978a).

E. Chronic Toxicity

Friberg (1948, 1950) observed emphysema in workmen exposed to cadmium dust in an alkaline battery factory. This finding has subsequently been well documented (U.S. EPA, 1979).

TABLE 4

SUMMARY OF MUTAGENICITY TEST RESULTS

Test System	Genetic Effect	Reported Mutagenicity	References
	Systems in vitro		
Human cells	Chromosomal damage	+	Shiraishi *et al.*, 1972
Chinese Hamster Cells	Point mutation	+	Costa *et al.*, 1976
S. cerevisiae	Point mutation	+	Takahoshi, 1972
B. subtilis recombinant assay	Gene mutation	+	Nishioka, 1975
Polynucleotides	Base mispairing	+	Sirover and Loeb, 1976
	Systems in vivo		
Human leukocytes	Chromosomal damage	+	Shirashi and Yoshida, 1972
Human leukocytes	Chromosomal damage	-	Bui *et al.*, 1975
Human leukocytes	Chromosomal damage	+	Deknudt and Leonard, 1975
Human leukocytes	Chromosomal damage	+	Bauchinger *et al.*, 1976
Rat spermatogonia	Altered spermatogenesis	+	Lee and Dixon, 1973
Mouse oocytes	Cytogenetic damage	+	Shimada *et al.*, 1976
Mouse breeding	Dominant lethal mutations	-	Epstein *et al.*, 1972
Mouse breeding	Dominant lethal mutations	-	Gilliavod and Leonard, 1975
Mouse breeding	Dominant lethal mutations	-	Suter, 1975
Mammals	Chromosomal abnormalities	-	Shimada *et al.*, 1976
D. melanogaster	Sex-linked recessive lethal	-	Sorsa and Pfeifer, 1973

Chronic cadmium exposure produces renal tabular damage that is characterized by the appearance of a characteristic protein $9B_2$-microglobulin) in the urine. Renal damage has been estimated to occur when cadmium levels in the renal cortex reach 200 mg/kg (Kjellstron, 1977). Itai-Itai disease is the result of cadmium induced renal damage plus osteomalacia (U.S. EPA, 1978a).

Exposure to high ambient cadmium levels may contribute to the etiology of hypertension (U.S. EPA, 1979). Several studies, however, have been unable to show a correlation between renal levels of cadmium and hypertension (Morgan 1972; Lewis, et al. 1972; Beevers, et al. 1976).

Friberg (1950) and Blejer (1971) have noted abnormal liver function tests in workers exposed to cadmium; however, these workers were occupationally exposed to a variety of agents.

The immunosuppressive effects of cadmium exposure, including an increased susceptibility to various infections, have been reported in several animal studies (Cook, et al. 1975; Koller, 1973; Exon, et al. 1975).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity in freshwater fish has been studied in a number of 96-hour bioassays consisting of one static renewal, 22 static, and 19 flow-through tests. LC_{50} values ranged from 1 µg/l for stripped bass larvae (*Roccus saxatilus*) (Hughes, 1973) to 73,500 for the fathead minnow (*Pimephales promelas*) (Pickering and Henderson, 1966). Increased resistance to the toxic action of cadmium in hard waters was observed. The LC_{50} values for freshwater invertebrates ranged from 3.5 for Cladoceran (*Simoephalus serrulatus*) to 28,000 µg/l for the mayfly (*Ephemerella grandis grandis*). Acute LC_{50} values for marine fish ranged from 1,600 µg/l for

larval Atlantic silversides (Menidia menida) (Middaugh and Dean, 1977) to 114,000 μg/l for juvenile mummichog (Fundulus heteroclitus) (Voyer, 1975). Intraspecific and life stage differences have shown that larval stages of the Atlantic silversides and mummichog are four times more sensitive than adults under the same test conditions (Middaugh and Dean, 1977). Marine invertebrates are more sensitive to cadmium than are marine fishes. LC_{50} values ranged from 15.5 μg/l for the mysid shrimp (Nimmo, et al. 1977a) to 46,600 for the fiddler crab (Uca pugilator) (O'Hara, 1973).

B. Chronic Toxicity

Chronic values for freshwater fish ranged from 0.9 μg/l in a brook trout (Salvelinus fontinalis) embryo larval assay (Sauter, et al. 1976) to 50 μg/l in a life cycle (or partial life cycle) assay for the bluegill (Lepomis marcochirus) in hard water (Eaton, 1974). Salmonids were in general the most sensitive species examined. Data for freshwater invertebrates depend on a single μg/l obtained for Daphnia magna (Biesinger and Christensen, 1972). No chronic studies were available for cadmium effects in marine fishes. The only marine invertebrates data reported was the chronic value of 5.5 μg/l for the mysid shrimp, Mysidopsis bahia. In this animal no measurable effects on brood appearance in the pouch, release, average number per female, or survival were observed at concentrations of 4.8 μg/l.

C. Plant Effects

Effective concentrations for freshwater plants ranged from 2 μg/l, which causes a 10 fold growth rate decrease in the diatom, Asterionella formosa (Conway, 1978), to 7,400 μg/l, which causes a 50% root weight inhibition in Eurasian water-milfoil (Myriophyllum spicatum). In marine algae,

96-hour EC_{50} growth rate assays yielded values of 160 and 175 μg/l for Cyclotella nana and Skeletonema costatum respectively (Gentile and Johnson, 1974).

D. Residues

Bioconcentration factors ranged from 151 for brook trout to 1,988 for the flagfish (Jordanella floridae). One characteristic of cadmium toxicity in aquatic organisms was the possible long half-life of the chemical in certain tissues of exposed brook trout even after being placed in clean water for several weeks. Testicular damage to adult mallards was observed when fed 20 mg/kg cadmium in the diet for 90 days. In marine organisms bioconcentration values ranged from 37 for the shrimp Crangon crangon to 1,230 for the American oyster, Crassostrea virginica (Schuster and Pringle, 1969).

E. Miscellaneous

Several studies on marine organisms have demonstrated significant reduction in gill-tissues respiratory rates in the cunner, Tautogolabrus adepersus, the winter flounder, Pseudopleuronectes americanus, and the stripped bass, Morone saxatilis, at concentrations as low as 0.5 μg/l.

VI. EXISTING GUIDELINES

A. Human

It is not recommended that cadmium be considered a suspect human carcinogen for purposes of calculating a water quality criterion (U.S. EPA, 1979).

The EPA Primary Drinking Water Standard for protection of human health is 10 μg/l. This level was also adopted as the draft ambient water quality criterion (U.S. EPA, 1979).

The OSHA time-weighted average exposure criterion for cadmium is 100 $\mu g/m^3$.

B. Aquatic

The draft criterion proposed for freshwater organisms to cadmium has been prepared following the Guidelines, and is listed according to the following equation:

$$e^{(0.867 \text{ In-(hardness)} - 4.38)}$$

for a 24-hour average and not to exceed the level described by the following equation:

$$e^{(1.30 \text{ In-(hardness)} - 3.92)}$$

The proposed marine criterion derived following the Guidelines is 1.0 µg as a 24-hour average not to exceed 16 µg/l at any time (U.S. EPA, 1979).

CADMIUM

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No. 32

Carbon Disulfide

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.

CARBON DISULFIDE

I. PHYSICAL AND CHEMICAL PROPERTIES

It is soluble in water at 0.294% at 20°C. It can chelate trace metals, especially Cu and Zn. Its formula weight is 76.14 and it is a colorless, volatile, and extremely flammable liquid at Rt. No odor when pure. At 27°C, its vapor pressure is 200 mm Hg.

II. PRODUCTION AND USE

It is produced in pretroleum and coal tar refining. Its principal uses are in the manufacture of rayon, rubber, chemicals, solvents, and pesticides.[1] In 1974, 782 million pounds of CS_2 were produced in the United States.[2] In 1971, 53% was used in production of viscose rayon and cellphane and 25% for manufacture of CC_{14}.

III. EXPOSURE

It was detected in 5 of 10 water supplies surveyed by the EPA.[3] NIOSH[25] estimates that 20,000 employees are potentially exposed to CS_2 fulltime in the United States.

III. PHARMACOKINETICS

A. Absorption: Absorption differs with species and route of administration.[4]

B. Distribution: Large concentrations of both free and bound CS_2 are found in brain (guinea pig) and peripheral nerves (rats) of exposed animals. The ratio of bound to free CS_2 in brain is 3:1. Blood and fatty tissues contain mainly bound CS_2 while liver contains mainly free.[4]

C. Metabolism: It is 90% metabolized by the P-450 system to inorganic sulfate.[5] A portion of the S released by CS_2 is thought to react with SH groups of cysteine residues in the microsomal protein to form hydro-sulfide.[6]

M. Greenberg
ECAO/RTP NC

D. Excretion: Small amounts are excreted (0.5%) as thiourea, 5-mercapto-thioazolidone, and inorganic constituents in urine.[7] Some portion (8-10%) is also excreted unchanged in the breath. Inhalation studies have shown that 18% of the CS_2 inhaled is exhaled unchanged. Of the remaining inhaled dose, 70% is excreted as free or bound CS_2 and urinary sulfates and 30% is stored in the body and slowly excreted as CS_2 and its metabolites.

V. EFFECTS ON MAMMALS

A. Carcinogenicity: No available data.[4]

B. Mutagenicity: No available data.[4]

C. Teratogenicity: Bariliah et al.[8] showed that inhalation of 10 mg/m^3 was lethal to embryos before and after implantation. CS_2 at 2.2 gm/m^3 for 4 hr/day was embryotoxic if given to female rats during gestation and had no effect on male rats.[9] Inhalation of lower concentrations (0.34 mg/l for 210 days) caused disturbances of estrus.[10] In a dominant lethal test, inhalation of 10 mg/m^3 by male rats before copulation proved lethal to embryos.[8]

D.

E. Toxicity

1. Humans

The lowest lethal concentration has been reported as 4,000 ppm in 30 minutes.[11] In the same study, a person subjected to a concentration of 50 mg/m^3 for 7 years had CNS effects. Moderate chronic exposure of humans at less than 65 mg/m^3 for several years has been reported by Cooper[12] to cause polyneuropathy. In a study by Baranowska et al.[13] humans have been shown to absorb 8.8-37.2 mg from an aqueous solution containing 0.33-1.67 q/l. This was over a period of 1 hour of hand-soaking.

The most thoroughly documented studies on health effects of CS_2 exposure have been on cardiovascular system.[26-29] Heinberg et al.[26,27] reported significantly

elevated rates of coronary heart disease mortality, angina, and high blood pressure. In a 5-year followup of these vicose rayon workers, he reported again increased coronary heart disease mortality and higher than expected incidences of total infarctions, nonfatal infarctions, angina. In an 8-year followup in 1976, Heinberg[30] found no excess coronary heart disease mortality during the last 3 years of the followup.

2. Other species.

IP injection of 400 mg/hg was the lowest lethal dose in guinea pigs.[14] An IV LD50 of 694 mg/kg in mice was reported by Hylen and Chin.[15]

With SC injection, LD50 was 300 mg/kg in rabbits.[16] Toxic effects have been observed at 1.7 mg/kg in rabbits.[17] Rats showed toxic SC effects at 1 mg/kg.[17] Oral doses in rats produce toxic effects at 1 mg/kg.[18,19] Vinogradov[20] showed that 1 ppm in drinking water was nontoxic to rabbits; 70 ppm was fatal.

In a chronic study, Paterni et al.[21] found that 6 mg/kg/day produced toxic effects in rabbits. The lowest lethal chronic dose for rabbits was shown to be 0.1 ml 3 times a week for 7 months.[22]

Applied topically, it produced a higher incidence of anemia in female than in male rats and teratogenic effects were observed.[23] When rats inhaled CS_2 at 10 mg/m^3, abnormalities of genitourinary and skeletal systems were found. Disturbances of ossification and blood formation and dystrophic changes in liver and kidney were noted.[8]

VI. EXISTING GUIDELINES AND STANDARDS

The NAS[4] did not recommend limits for drinking water because estimates of effects of chronic oral exposure cannot be made with any confidence.

The NIOSH[24] recommended standard IS 3 mg/m^3.

Human studies have shown that exposure effects the cardiovascular system, the nervous system, the eyes, the reproductive organs, and other systems.[24]

The current federal standard[25] is 20 ppm (62 mg/m^3) with a ceiling concentration of 30 ppm (93 mg/m^3) for an 8-hour day, 5 day work week.

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No. 33

Carbon Tetrachloride (Tetrachloromethane)

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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

SPECIAL NOTATION

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

CARBON TETRACHLORIDE

Summary

Carbon tetrachloride (CCl_4) is a haloalkane with a wide range of industrial and chemical applications. Toxicological data for non-human mammals are extensive and show that CCl_4 causes liver and kidney damage, biochemical changes in liver function, and neurological damage. CCl_4 has been found to induce liver cancer in rats and mice. Mutagenic effects have not been observed and teratogenic effects have not been conclusively demonstrated.

The data base on aquatic toxicity is limited. LC_{50} (96-hour) values for bluegill range from 27,300 to 125,000 µg/l in static tests. For *Daphnia magna*, the reported 48-hour EC_{50} is 35,200 µg/l. The 96-hour LC_{50} for the tidewater silverside is 150,000 µg/l. An embryo-larval test with the fathead minnow showed no adverse effect from carbon tetrachloride concentrations up to 3,400 µg/l. No plant effect data are available. The bluegill bioconcentrated carbon tetrachloride to a factor of 30 times within 21 days exposure. The biological half-life in the bluegill was less than 1 day.

CARBON TETRACHLORIDE

I. INTRODUCTION

Carbon tetrachloride (CCl_4) is a haloalkane with a wide range of industrial and chemical applications. Approximately 932.7 million pounds are produced at 11 plant sites in the U.S. (U.S. EPA, 1977b; Johns, 1976). The bulk of CCl_4 is used in the manufacture of fluorocarbons for aerosol propellants. Other uses include grain fumigation, a component in fire extinguisher solutions, chemical solvent, and a degreaser in the dry cleaning industry (Johns, 1976).

Carbon tetrachloride is a heavy, colorless liquid at room temperature. Its physical/chemical properties include: molecular weight, 153.82; melting point, -22.99^{o}C; solubility in water, 800,000 µg/l at 25°C; and vapor pressure, 55.65 mm Hg at 10°C. CCl_4 is relatively non-polar and miscible with alcohol, acetone and most organic solvents.

Carbon tetrachloride may be quite stable under certain environmental conditions. The hydrolytic breakdown of CCl_4 in water is estimated to require 70,000 years for 50 percent decomposition (Johns, 1976). This decomposition is accelerated in the presence of metals such as iron (Pearson and McConnell, 1975). Hydrolytic decomposition as a means of removal from water is insignificant when compared with evaporation. In one experiment the evaporative half-life of CCl_4 in water at ambient temperatures was found to be 29 minutes (Dilling, et al. 1975), but this is highly dependent on experimental conditions, such as surface area to bulk volume ratios. For additional information regarding Halomethanes as a class, the reader is referred to the Hazard Profile on Halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

CCl_4 has been found in many water samples including rain, surface, potable, and sea, in the sub-part per billion range (McConnell, et al. 1975). The National Organics Monitoring Survey (NOMS) found CCl_4 in 10 percent of 113 public water systems sampled, with mean values ranging from 2.4-6.4 µg/l (U.S. EPA, 1977a).

Although CCl_4 is a chlorinated hydrocarbon, it is not produced in finished drinking water as a result of the chlorination process (Natl. Res. Coun., 1977,1978).

B. Food

Carbon tetrachloride has been detected in a variety of foodstuffs other than fish and shellfish in levels ranging from 1 to 20 µg/kg (McConnell, et al. 1975).

Results of various studies on CCl_4 fumigant residues in food indicate that the amount of residue is dependent upon fumigant dosage, storage conditions, length of aeration and the extent of processing (U.S. EPA, 1979a). Usually, proper storage and aeration reduce CCl_4 residues to trace amounts.

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for carbon tetrachloride to be 69 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

C. Inhalation

The occurrence of CCl_4 in the atmosphere is due largely to the volatile nature of the compound. Concentrations of CCl_4 in continental and marine air masses range from .00078 - .00091 mg/m^3. Although some

higher quantities (.0091 mg/m^3) have been measured in urban areas, concentrations of CCl_4 are universally widespread with little geographic variation (U.S. EPA, 1979a).

III. PHARMACOKINETICS

A. Absorption

CCl_4 is readily absorbed through the lungs, and more slowly through the gastrointestinal tract (Nielsen and Larsen, 1965). It can also be absorbed through the skin. The rate and amount of absorption are enhanced with the ingestion of fat and alcohol (Nielson and Larson, 1965; Moon, 1950). Robbins (1929) found that considerable amounts of CCl_4 are absorbed from the small intestine, less from the colon, and little from the stomach. Absorption from the gastorintestinal tract appears to vary by species, i.e., it occurs more rapidly in rabbits than dogs.

B. Distribution

The organ distribution of CCl_4 varies with the route of administration, its concentration, and the duration of exposure (U.S. EPA, 1979a).

After oral administration to dogs, Robbins (1929) found the highest concentrations of CCl_4 in the bone marrow. The liver, pancreas and spleen had one-fifth the amount found in the bone marrow. The highest concentrations of CCl_4 after inhalation, however, were found in the brain (Von Oettingen, et al. 1949,1950). After inhalation of CCl_4 by monkeys, the highest levels were detected in fat, followed by liver and bone marrow (McCollister, et al. 1950). McConnell, et al. (1975) found human tissue levels of CCl_4 to range as follows: kidney, 1-3 mg/l; liver, 1-5 mg/l and fat, 1-13 mg/l.

On the cellular level, McClean, et al. (1965) found CCl_4 in all cell fractions with higher concentrations in ribosomes.

C. Metabolism

When CCl_4 is administered to mammals, it is metabolized to a small extent, the majority being excreted through the lungs. The metabolites include chloroform, hexachloroethane, and carbon dioxide. These metabolites play an important role in the overall toxicity of CCl_4 (U.S. EPA, 1979a). Some of the CCl_4 metabolic products are also incorporated into fatty acids by the liver and into liver microsomal proteins and lipids (Gordis, 1969).

The chemical pathology of liver injury induced by CCl_4 is a result of the initial homolytic cleavage of the C-Cl bond which liberates trichloromethyl- and chlorine-free radicals (Fishbein, 1976). The next step may be one of two conflicting reactions: direct attack via alkylation on cellular constituents (especially sulfhydryl groups), or peroxidative decomposition of lipids of the endoplasmic reticulum as a key link between the initial bond cleavage and the pathological phenomena characteristic of CCl_4 (Butler, 1961; Tracey and Sherlock, 1968).

D. Excretion

The largest portion of absorbed CCl_4 is rapidly excreted. Approximately 50-79 percent of absorbed radioactive CCl_4 is eliminated through the lungs, and the remainder is excreted in the urine and feces. No CCl_4 was detected in the blood or in the expired air, 48 hours and 6 days, respectively, after CCl_4 inhalation (Beamer, et al. 1950). CCl_4 is excreted as 85 percent parent compound, 10 percent carbon dioxide, and smaller quantities of other products including chloroform (NRC, 1977).

IV. EFFECTS

A. Carcinogenicity

CCl_4 has been shown to be carcinogenic in rats, mice, and hamsters via subcutaneous injection, intubation, and rectal instillation (U.S.

EPA, 1979). Current knowledge lead to the conclusion that carcinogenesis is a non-threshold, non-reversible process. However, some scientists do argue that a threshold may occur.

Rueber and Glover (1970) administered injections of 1.3 ml/kg of body weight of a 50 percent solution of CCl_4 in corn oil to rats, two times per week until death. Carcinoma of the liver were present in 12/15 (80 percent) Japanese male rats, 4/12 (33 percent) Wistar rats, and 8/13 (62 percent) Osborne-Mendel rats, whereas Black Rats or Sprague-Dawley rats did not develop carcinomas. The incidence of cirrhosis of the liver also differed with the strain of the rat. Carcinoma of the liver tended to develop along with mild or moderate, rather than severe cirrhosis of the liver. When administered with CCl_4, methylcholanthrene (a potent enzyme inducer) was found to increase the incidence of hyperplastic hepatic nodules and early carcinomas in rats (Rueber, 1970). Females were found to be more susceptible to the development of hyperplastic nodules and carcinomas.

The National Cancer Institute (1976) studied the carcinogenic effect of CCl_4 in male and female mice (1,250 mg/kg or 2,500 mg/kg of body weight, oral gavage 5 times/week/78 weeks). Hepatocellular carcinomas were found in almost all of the mice receiving CCl_4. Andervant and Dunn (1955) transplanted 30 CCl_4-induced tumors into mice. They observed growth in 28 of the hepatomas, through 4 to 6 transplant generations.

B. Mutagenicity

Conclusive evidence on the mutageniciity of CCl_4 has not been reported. Kraemer, et al. (1976) found negative results using the Ames bacterial reversion tests. However, they explain that halogenated hydrocarbons are usually negative in the Ames test.

C. Teratogenicity

Very little data are available concerning the teratogenic effects of CCl_4. Schwetz, et al. (1974) found CCl_4 to be slightly embryotoxic, and to a certain degree retarded fetal development, when administered to rats at 300 or 1,000 mg/l for 7 hr/day on days 6 through 15 of gestation. Bhattacharyya (1965) found that subcutaneous injection occasionally gave rise to changes in fetal liver.

D. Other Reproductive Effects

Pertinent data concerning other reproductive effects of CCl_4 were not encountered in the available literature.

E. Chronic Toxicity

Cases of chronic poisoning have been reported by Butsch (1932), Wirtschafter (1933), Strauss (1954), Von Oettingen (1964), and others. The clinical picture of chronic CCl_4 poisoning is much less characteristic than that of acute poisoning. Von Oettingen (1964) has done an excellent job of reviewing the symptoms. Patients suffering from this condition may complain of fatigue, lassitude, giddiness, anxiety, and headache. They suffer from paresthesias and muscular twitchings, and show increased reflex excitability. They may be moderately jaundiced, have a tendency to hypoglycemia, and biopsy specimens of the liver may show fatty infiltration. Patients may complain of a lack of appetite, nausea, and occasionally of diarrhea. In some instances, the blood pressure is lowered and is accompanied by pain in the cardiac region and mild anemia. Other patients have developed pain in the kidney region, dysuria, and slight nocturia, and have had urine containing small amounts of albumin and a few red blood cells. Burning of the eyes and, in a few instances, blurred vision are frequent complaints of those exposed. If these symptoms are not pronounced, or of long

standing, recovery usually takes place upon discontinuation of the exposure if the proper treatment is received (Von Oettingen, 1964).

Reports on pathological changes in fatalities from CCl_4 poisonings are generally limited to findings in the liver and kidneys. The brain and lungs may be edematous. The intestines may be hyperemic and covered with numerous petechial hemorrhages and the spleen may be enlarged and hyperemic. Occasionally the adrenal glands may show degenerative changes of the cortex and the heart may undergo toxic myocarditis (Von Oettingen, 1964).

F. Other Relevant Information

The toxic effects of CCl_4 are potentiated by both the habitual and occasional ingestion of alcohol (U.S. EPA, 1979a). Pretreatment of laboratory animals with ethanol, methanol, or isopropanol increases the susceptibility of the liver to CCl_4 (Wei, et al. 1971; Traiger and Plaa, 1971).

Hafeman and Hoekstra (1977) reported that protective effects against CCl_4-induced lipid peroxidation are exhibited by vitamin E, selenium, and methionine.

According to Davis (1934), very obese or undernourished persons or those suffering from pulmonary diseases, gastric ulcers or a tendency to vomiting, liver or kidney diseases, diabetes or glandular disturbances, are especially sensitive to the toxic effect of CCl_4 (Von Oettingen, 1964).

V. AQUATIC TOXICITY

A. Acute Toxicity

Two studies have investigated the acute toxicity of carbon tetrachloride to bluegills (Lepomis macrochirus) in static tests. The determined LC_{50} varied from 27,300 µg/l to 125,000 µg/l (Dawson, et al. 1977; U.S. EPA, 1978). With Daphnia magna, the reported 48-hr. EC_{50} is 35,200 µg/l (U.S. EPA, 1978). The 96-hr. LC_{50} for the tidewater silversides (Menidia beryllina) is 150,000 µg/l (Dawson, et al. 1977).

B. Chronic Toxicity

An embryo-larval test with the fathead minnow (Pimephales promelas) showed no adverse effect from carbon tetrachloride concentrations up to 3,400 µg/l (U.S. EPA, 1978). Other chronic data are not available.

C. Plant Effects

There are no data in the available literature describing the effects of carbon tetrachloride on freshwater or saltwater plants.

D. Residues

The bluegill bioconcentrated carbon tetrachloride to a factor of 30 times within 21 days. The biological half-life in these tissues was less than 1 day.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

The American Conference of Governmental Industrial Hygienists (1971) recommends a threshold limit value (TLV) of 10 mg/m^3 for CCl_4, with peak values not to exceed 25 mg/m^3 even for short periods of time. The Occupational Safety and Health Administration adopted the American National Standards Institute (ANSI, 1967) standard Z37.17 - 1967 as the Federal standard for CCl_4 (29 CFR 1910.1000). This standard is 10 mg/m^3 for an 8-hour TWA, with an acceptable ceiling of 25 mg/m^3 and a maximum peak for 5 minutes in any 4-hour period of 200 mg/m^3.

The draft ambient water quality criteria for carbon tetrachloride has been set to reduce the human carcinogenic risk levels to 10^{-5}, 10^{-6} or 10^{-7} (U.S. EPA, 1979a). The corresponding criteria are 2.6 µg/l, 0.26

µg/l, and 0.026 µg/l, respectively. Refer to the Halomethane Hazard Profile for discussion of criteria derivation (U.S. EPA, 1979b).

B. Aquatic

For carbon tetrachloride, the drafted criteria to protect freshwater aquatic life is 620 µg/l as a 24-hour average and the concentration should never exceed 1,400 µg/l at any time. To protect saltwater aquatic life, the drafted criterion is 2,000 µg/l as 24-hour average and the concentration should not exceed 4,600 µg/l at any time (U.S. EPA, 1979a).

No. 34

Chloral

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CHLORAL

Summary

Chloral (trichloroacetaldehyde) is used as an intermediate in the manufacture of DDT, methoxychlor, DDVP, naled, trichlorfon, and TCA. Chloral is readily soluble in water, forming chloral hydrate. Chloral hydrate decomposes to chloroform with a half-life of two days. Chloral hydrate has been used as a therapeutic agent due to its hypnotic and sedative properties.

Chloral (as chloral hydrate) has been identified in chlorinated water samples at concentrations as high as 5.0 μg/l. Chloral hydrate is formed through the chlorination of natural humic substances in the raw water. Atmospheric chloral concentrations up to 273.5 mg/m^3 have been reported from spraying and pouring of polyurethanes in Soviet factories. Similar data on exposure levels in U.S. plants were not found in the available literature.

Specific information on the pharmacokinetic behavior, carcinogenicity, mutagenicity, teratogenicity, and other reproductive effects of chloral was not found in the available literature. However, the pharmacokinetic behavior of chloral may be similar to chloral hydrate where metabolism to trichloroethanol and trichloroacetic acid and excretion via the urine (and possibly bile) have been observed. Chloral hydrate produced skin tumors in 4 of 20 mice dermally exposed. Information on the chronic or acute effects of chloral in humans was not found in the available literature. Chronic effects from respiratory exposure to chloral as indicated in laboratory animals include reduction of kidney function and serum transaminase activity, change in central nervous system function (unspecified), decrease in

antitoxic and enzyme-synthesizing function of the liver, and alteration of morphological characteristics of peripheral blood. Slowed growth rate, leukocytosis and changes in arterial blood pressure were also observed. Acute oral LD_{50} values in rats ranged from 0.05 to 1.34 g/kg.

U.S. standards and guidelines for chloral were not found in the available literature.

CHLORAL

ENVIRONMENTAL FATE

Chloral (trichloroacetaldehyde) is freely soluble in water, forming chloral hydrate (Windholz, et al. 1976). Chloral hydrate was identified in drinking water from 6 of 10 cities sampled (Keith, 1976). The author postulated that chloral hydrate was formed by the chlorination of other compounds during the addition of chlorine to the water supplies. Chloral hydrate was not identified prior to chlorination. Chloral hydrate may be formed by the chlorination of ethanol or acetaldehyde and may occur as an intermediate in the reaction involving the conversion of ethanol to chloroform as follows:

Ethanol - Acetaldehyde - Chloral - Chloral hydrate - Chloroform

Chloral hydrate decomposes to chloroform with a half-life of 2 days at pH 8 and 35°C (Luknitskii, 1975). Rook (1974) demonstrated the formation of haloforms from the chlorination of natural humic substances in raw water.

Chloral polymerizes under the influence of light and in the presence of sulfuric acid, forming a white solid trimer called metachloral (Windholz, 1976). Dilling, et al. (1976) studied the effects of chloral on the decomposition rates of trichloroethylene, NO, and NO_2 in the atmosphere and observed that chloral increases the photodecomposition rate of trichloroethylene to a greater extent than it does NO or NO_2.

CHLORAL

I. INTRODUCTION

This profile is based on literature searches in Biological Abstracts, Chemical Abstracts, MEDLINE, and TOXLINE.

Chloral [Cl_3CCHO], also referred to as trichloroacetaldehyde, anhydrous chloral, and trichloroethanol, is an oily liquid with a pungent, irritating odor. The physical properties of chloral are: molecular weight, 147.39; melting point, -57.5°C; boiling point, 97.75°C at 760 mm Hg; density, 1.5121 at 20/4°C (Weast, 1976). The compound is very soluble in water, forming chloral hydrate, and is soluble in alcohol and ether.

Industrial production of chloral involves direct chlorination of ethyl alcohol followed by treatment with concentrated sulfuric acid (Stanford Research Institute, 1976). Production may also occur by direct chlorination of either acetaldehyde or paraldehyde in the presence of antimony chloride. Prior to 1972, essentially all chloral produced was used in the manufacture of DDT. Production of chloral was greatest in 1963 at 79.8 million pounds, decreasing to 62.4 million pounds in 1969. Production data after 1969 were not reported. Consumption of chloral for DDT manufacture was estimated at 25 million pounds in 1975, with an additional 500,000 pounds used in the manufacture of other pesticides, including methoxychlor, DDVP, naled, trichlorfon, and TCA (trichloroacetic acid). Mel'nikov, et al. (1975) identified chloral as an impurity in chlorofos.

Chloral is also used in the production of chloral hydrate, a therapeutic agent with hypnotic and sedative effects used prior to the introduction of barbituates. Production of U.S.P. (pharmaceutical) grade chloral hydrate was estimated to be 300,000 pounds per year in 1975 (Stanford Research Institute, 1976).

II. EXPOSURE

Boitsov, et al. (1970) noted that chloral is evolved in spraying and pouring of polyurethane. The authors reported chloral concentrations as high as 273.5 mg/m^3 in Soviet factories. Similar information on atmospheric occupational exposure to chloral in Western countries was not found in the available literature.

Chloral exposure from water occurs as chloral hydrate. Keith (1976) reported chloral hydrate concentrations ranging from 0.01 µg/l to 5.0 µg/l in chlorinated drinking water supplies of six of ten U.S. cities studied. The mean concentration of chloral hydrate in drinking water for the six cities was 1.92 µg/l.

Chloral hydrate has been used as a hypnotic and sedative agent. Alcohol synergistically increases the depressant effect of the compound, creating a potent depressant commonly referred to as "Mickey Finn" or "knockout drops". Addiction to chloral hydrate through intentional abuse of the compound has been reported (Goodman and Gilman, 1970).

III. PHARMACOKINETICS

A. Absorption

Specific information on the absorption of chloral was not found in the available literature. Goodman and Gilman (1970) reported that chloral hydrate readily penetrates diffusion barriers in the body.

B. Distribution

Specific information on the distribution of chloral was not found in the available literature. Goodman and Gilman (1970), reporting on the distribution of chloral hydrate from oral administration, noted its presence in cerebrospinal fluid, milk, amniotic fluid, and fetal blood. The authors

noted that other investigators were unable to detect significant amounts of chloral hydrate in the blood after oral administration (owing probably to its rapid reduction).

C. Metabolism

Information on the metabolic reaction of chloral is obtained indirectly through a metabolic study of trichloroethylene (Henschler, 1977). The author reported that trichloroethylene oxidizes to a chlorinated epoxide which undergoes molecular rearrangement to chloral, which is further metabolized to either trichloroethanol or trichloroacetic acid. The rearrangement, detected by in vivo studies, is hypothesized to occur by a catalytic action of the trivalent iron of P-450.

Goodman and Gilman (1970) noted that chloral hydrate is reduced to trichloroethanol in the liver and other tissues, including whole blood, with the reaction catalyzed by alcohol dehydrogenase. Additional trichloroethanol is converted to trichloroacetic acid. Chloral hydrate may be directly oxidized to trichloroacetic acid in the liver and kidney.

D. Excretion

Both chloral and chloral hydrate are metabolized to trichloroethanol or trichloroacetic acid (Goodman and Gilman, 1970; Henschler, 1977). Trichloroethanol is then conjugated and excreted in the urine as a glucuronide (urochloralic acid) or is converted to trichloroacetic acid and slowly excreted in the urine. The glucuronide may also be concentrated and excreted in the bile. The fraction of the total dose excreted as trichloroethanol, glucuronide, and trichloroacetic acid is quite variable, indicating other possible routes of elimination.

IV. EFFECTS

A. Carcinogenicity

Specific information on the carcinogenicity of chloral was not found in the available literature. However, Keith (1976) reported skin tumors in 4 of 20 mice dermally exposed to chloral hydrate (4 to 5 percent solution in acetone). Further interpretation of the results and discussion of the study methodology were not given.

B. Mutagenicity, Teratogenicity, and Other Reproductive Effects

Specific information on the mutagenicity, teratogenicity, and reproductive effects of chloral was not found in the available literature.

C. Chronic Effects

Rats receiving 0.1 mg/kg chloral exhibited a reduction of kidney function and serum transaminase after seven months' exposure (Kryatov, 1970). No physiological effects were observed in rats receiving 0.01 mg/kg chloral for periods of seven months. The route of exposure was not reported.

Chronic respiratory exposure of rats and rabbits to chloral at 0.1 mg/l (100 mg/m^3) produced changes in central nervous system function, decreased antitoxic and enzyme synthesizing function of the liver, and altered morphological characteristics of peripheral blood (Pavlova, 1975). Boitsov, et al. (1970) reported slowed growth rate, leukocytosis, decreased albumin-globulin ratio, and changes in arterial blood pressure and central nervous system responses (unspecified) following prolonged respiratory exposure of mice to chloral at 60 mg/m^3.

Goodman and Gilman (1970) reported gastritis, skin eruptions, and parenchymatous renal injury in patients suffering from chronic chloral hydrate intoxication. Habitual use of chloral hydrate may result in the

development of tolerance, physical dependence, and addiction. Death may occur either as a result of an overdose or a failure of the detoxification mechanism due to hepatic damage.

F. Acute Toxicity

According to Hann and Jensen (1974), the human acute oral LD_{50} of chloral is between 50 and 500 mg/kg.

Kryatov (1970) reported the following LD_{50} values for chloral: mice, 0.850 g/kg; rats, 0.725 g/kg; and guinea pigs, 0.940 g/kg. The routes of exposure were not stated. Verschueren (1977) reported an oral LD_{50} for rats of 0.05 to 0.4 g/kg, while Pavlov (1975) reported an acute oral LD_{50} of 0.94 and 1.34 g/kg for mice and rats, respectively. Pavlov (1975) also reported inhalation LC_{50} values of 25.5 g/m^3 and 44.5 g/m^3 for mice and rats, respectively. Boitsov, et al. (1970) reported an LD_{50} of 0.710 g/kg in mice. The route of exposure was not stated. Hawley (1971) reported that chloral is a highly toxic, strong irritant and noted ingestion or inhalation may be fatal. Information on acute toxic effects from occupational exposure to chloral was not found in the available literature.

G. Other Relevant Information

Verschueren (1977) reported an odor threshold concentration of chloral in water of 0.047 ppm. The author also reported an inhibition of cell multiplication in Pseudomonas sp. at a chloral hydrate concentration of 1.6 mg/l.

V. AQUATIC TOXICITY

A. Acute Toxicity

Verschueren (1977) reported inhibition of cell multiplication in Microcystis sp. at 78 mg/l chloral hydrate. Hann and Jensen (1974) ranked the 96-hour TL_m aquatic toxicity of chloral in the range from 1 to 10 ppm.

B. Chronic Toxicity

Information on the chronic aquatic toxicity of chloral was not found in the available literature.

C. Plant Effects

Shimizu, et al. (1974) reported chloral inhibited the growth of rice stems by 63.4 percent relative to controls, but slightly stimulated root growth. The concentration of chloral in water culture was not reported.

D. Residue

Keith (1976) identified chloral hydrate in chlorinated drinking water in six of ten cities sampled. The sample locations and concentrations of chloral hydrate identified were: Philadelphia, PA, 5.0 µg/l; Seattle, WA, 3.5 µg/l; Cincinnati, OH, 2.0 µg/l; Terrebonne Parish, LA, 1.0 µg/l; New York City, NY, 0.02 µg/l; Grand Forks, ND, 0.01 µg/l.

E. Other Relevant Information

Hann and Jensen (1974) ranked the aesthetic effect of chloral on water as very low (zero), noting that the chemical neither pollutes waters nor causes aesthetic problems.

VI. EXISTING GUIDELINES AND STANDARDS

Boitsov, et al. (1970) reported a maximum recommended chloral concentration in workroom air of 0.22 mg/l (220 mg/m^3) (USSR). Kryatov (1970) reported a maximum recommended permissible concentration in bodies of water as 0.2 mg/l (USSR). Verschueren (1977) reported a maximum allowable chloral concentration of 0.2 mg/l in Class I waters used for drinking, but the nation applying this standard was not identified.

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No. 35

Chlordane

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CHLORDANE

Summary

Chlordane is an organochlorinated cyclodiene insecticide commonly used as a formulation consisting of 24% trans-, 19% cis-chlordane, 10% heptachlor, 21.5% chlordenes, 7% nonachlor, and 18.5% of other organochlorinated material. Since heptachlor is also an insecticide and is more toxic than chlordane, technical chlordane is generally more toxic than pure chlordane.

Pure chlordane, which is a cis/trans mixture of isomers, induces liver cancer in mice and is mutagenic in some assays. Chlordane has not been shown to be teratogenic. Little information is available on chronic mammalian toxicity. Repeated doses of chlordane produced alterations in brain potentials and changes in some blood parameters. Chlordane is a convulsant. Chlordane and its toxic metabolite oxychlordane accumulate in adipose tissue.

Ten species of freshwater fish have reported 96-hr LC_{50} values ranging from 8 to 1160 µg/l. Freshwater invertebrates appear to be more resistant to chlordane, with observed 96-hr LC_{50} values ranging from 4 to 40 µg/l. Five species of saltwater fish have LC_{50} values of 5.5 to 160 µg/l, and marine invertebrate LC_{50} values range between 0.4 and 480 µg/l. Chronic studies involving the bluegill *Daphnia magna* gave an LC_{50} of 1.6 µg/l.

CHLORDANE

INTRODUCTION

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

Chlordane is a broad spectrum insecticide of the group of organochlorinated polycyclic hydrocarbons called cyclodiene insecticides. Chlordane has been used extensively over the past 30 years for termite control in homes and gardens, and as a control for soil insects.

Pure chlordane (1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene) is a pale yellow liquid having the empirical formula $C_{10}H_6Cl_8$ and a molecular weight of 409.8. It is composed of a mixture of stereoisomers, with the cis- and trans- forms predominating, commonly referred to as alpha- and gamma-isomers, respectively.) The solubility of pure chlordane in water is approximately 9 µg/l at 25°C (U.S. EPA, 1979).

Technical grade chlordane is a mixture of chlorinated hydrocarbons with a typical composition of approximately 24 percent trans(gamma)-chlordane, 19 percent cis(alpha)-chlordane, 10 percent heptachlor (another insecticidal ingredient), 21.5 percent chlordene isomers, 7 percent nonachlor, and 18.5 percent closely related chlorinated hydrocarbon compounds. Technical chlordane is a viscous, amber-colored liquid with a cedar-like odor. It has a vapor pressure of 1×10^{-5} mm Hg at 25°C. The solubility of technical chlordane in water is 150 to 220 µg/l at 22°C (U.S. EPA, 1979).

Production of chlordane was 10,000 metric tons in 1974 (41 FR 7559; February 19, 1976). Both uses and production volume have declined extensively since the issuance of a registration suspension notice by the U.S. EPA (40 FR34456; December 24, 1975) for all food, crop, home, and garden

uses of chlordane. However, use of chlordane for termite control and limited usage (through 1980) as an agricultural insecticide are still permitted (43 FR 12372; March, 1978).

Chlordane persists for prolonged periods in the environment (U.S. EPA, 1979). Photo-cis-chlordane can be produced in water and on plant surfaces by the action of sunlight (Benson, et al. 1971) and has been found to be twice as toxic as chlordane to fish and mammals (Ivie, et al. 1972; Podowski, et al. 1979). Photo-cis-chlordane (5 ng/l) is accumulated more (ca. 20%) by goldfish (Carassius auratus) than chlordane (5 ng/l) itself (Ducat and Khan, 1979).

Air transport of chlordane has been hypothesized to account for residues in Sweden (Jansson, et al. 1979). Residues in agricultural soils may be as high as 195 ng/g dry weight of soil (Requejo, et al. 1979).

II EXPOSURE

A. Water

Chlordane has been detected in finished waters at a maximum concentration of 8 µg/l (Schafer, et al. 1969) and in rainwater (Bevenue, et al. 1972; U.S. EPA, 1976). There have been reports of individual household wells becoming contaminated after a house is treated with chlordane for termite control (U.S. EPA, 1979). A recent contamination of a municipal water system has been discussed by Harrington, et al. (1978). Chlordane has also been detected in rainwater (U.S. EPA, 1976).

B. Food

Chlordane has been found infrequently in food supplies since 1965, when the FDA began systematic monitoring for chlordane (Nisbet, 1976). The only quantifiable sample collected was 0.059 mg chlordane/kg measured in a sample of grain in 1972 (Manske and Johnson, 1975). In the most recently

published results (for 1975), chlordane was not detected (Johnson and Manske, 1977). Fish are thought to represent the most significant dietary exposure. The average daily uptake from fish is estimated at 1 µg (Nisbet, 1976).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for chlordane to be 5,500 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on measured steady-state bioconcentration studies in the sheepshead minnow (Cyprinodon variegatus).

Eighty-seven percent of 200 samples of milk collected in Illinois from 1971 to 1973 were positive for chlordane. The average concentration was 50 µg/l (Moore, 1975 as reviewed by Nat. Acad. Sci., 1977). Cyclodienes, such as chlordane, apparently are ingested with forage and tend to concentrate in lipids. Oxychlordane, a metabolite of chlordane and heptachlor, was found in 46 percent of 57 human milk samples collected during 1973-74 in Arkansas and Mississippi. The mean value was 5 µg/l, and the maximum was 20 µg/l (Strassman and Kutz, 1977).

C. Inhalation

In a survey of the extent of atmospheric contamination by pesticides, air was sampled at nine localities representative of both urban and agricultural areas. Chlordane was not detected in any samples (Stanley, et al. 1971). In a larger survey, 2,479 samples were collected at 45 sites in 16 states. Chlordane was detected in only two samples, with concentrations of 84 and 204 ng/m^3 (Nisbet, 1976). The vapor concentrations to which spray operators are exposed have not been estimated.

D. Dermal Effects

Chlordane can be absorbed through the skin to produce toxic effects (Gosselin, et al. 1976). Spray operators, chlordane formulators and farmers may be exposed. Chlordane has been known to persist for as long as two years on the hands (Kazen, et al. 1974). Dermal LD_{50} values in rats range from 530 to 700 mg/kg (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Gastrointestinal absorption of chlordane in rats ranged from 6 percent with a single dose to 10-15 percent with smaller daily doses (Barnett and Dorough, 1974).

B. Distribution

In a study of the distribution of chlordane and its metabolites using radioactive carbon, the levels of residues in the tissues were low, except in the fat (Barnett and Dorough, 1974). Rats were fed 1, 5, and 25 mg chlordane/g in food for 56 days. Concentrations of chlordane residues in fat, liver, kidney, brain, and muscle were 300, 12, 10, 4, and 2 percent, respectively, of the concentration in the diet. All residues declined steadily for 4 weeks, at which time concentrations were reduced about 60 percent. During the next four weeks, residues declined only slightly.

C. Metabolism

Mammals metabolize chlordane to oxychlordane, via 1,2-dichlorochlordene which is about twenty times more toxic than the parent compound and persists in adipose tissue (Polen, et al. 1971; Tashiro and Matsumura, 1978; Street and Blau, 1972). Oxychlordane can degrade to form 1-hydroxy-2-cyclochlordenes, and 1-hydroxy-2-chloro-2,3-epoxy-chlordenes (Tashiro and Matsumura, 1978). In general, the metabolism of chlordane takes place via a

series of oxidative enzyme reactions. None of the metabolic intermediates (except for oxychlordane) and end products are more toxic than chlordane (Barnett and Dorough, 1974; Tashiro and Matsumura, 1977; Mastri, et al. 1969). Trans-nonachlor, a major impurity in technical chlordene, is converted to trans-chlordane in rats, but this is not important in humans. This explains the fact that trans-nonachlor accumulates in humans but not in rats (Tashiro and Matsumura, 1978). A very small amount of cis- or trans-chlordane can be converted to heptachlor in rat liver (Tashiro and Matsumura, 1977).

D. Excretion

Chlordane is primarily excreted in the feces of rats, only about six percent of the total intake being eliminated in the urine. Urinary excretion of chlordane in rabbits is greater than excretion in the feces (Nye and Dorough, 1976).

The half-life of chlordane in a young boy was reported to be approximately 21 days (Curley and Garrettson, 1969), while for rats it was 23 days (Barnett and Dorough, 1974). The half-life of chlordane in the serum of a young girl was 88 days (Aldrich and Holmes, 1969).

IV. EFFECTS

A. Carcinogenicity

Hepatocellular carcinomas were induced in both sexes of two strains of mice fed pure (95%) chlordane (56.2 mg/kg) in the diet for 80 weeks (National Cancer Institute, 1977; Epstein, 1976). In contrast to findings with mice, a significantly increased incidence of hepatocellular carcinomas did not appear in rats administered chlordane. Dosages were near the maximum permissible (National Cancer Institute, 1977).

B. Mutagenicity

Pure or technical chlordane induced unscheduled DNA synthesis in the SV-40 transformed human fibroblast cell line VA-4. Metabolic activation eliminated this effect (Ahmed, et al. 1977). Chlordane did not induce mutations in the dominant lethal assay in mice (Arnold, et al. 1977).

While neither pure cis-chlordane nor pure trans-chlordane was mutagenic in the Ames Salmonella microsome assay, technical grade chlordane was mutagenic. Microsomal activation did not enhance the mutagenic activity (Simmon, et al. 1977).

C. Teratogenicity

Chlordane was found not to be teratogenic in rats when fed at concentrations of 150 to 300 mg/kg during gestation (Ingle, 1952).

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

There appears to be little information on chronic mammalian toxicity. Daily injections of 0.15 to 25 mg chlordane/kg in adult rats resulted in dose-dependent alterations of brain potentials (Hyde and Falkenberg, 1976). As changes were directly related to length of exposure, it was concluded that chlordane may be a cumulative neurotoxin. Length of exposure was not specified. Repeated doses of chlordane given to gerbils produced changes in serum proteins, blood glucose, and alkaline and acid phosphatase activities (Karel and Saxena, 1976). Again, duration of treatment was not specified.

F. Other Relevant Information

Carbon tetrachloride produced more extensive hepatocellular necrosis in chlordane-pretreated rats than in rats which were not pretreated (Stenger, et al. 1975). Rats suffered greater cirrhosis when chlordane (50

µg/kg/day) exposure for ten weeks followed prior exposures of ten weeks for carbon tetrachloride above (110 mg/l) or with chlordane (Mahon and Oloffs, 1979). Quail treated with chlordane followed by endrin had considerably more chlordane residues in their brains than did quail treated with chlordane alone (Ludke, 1976). Quail pretreated with 10 mg/kg chlordane exhibited decreased susceptibility to parathion (Ludke, 1977). Chlordane is a convulsant and emetic. It induces twitching, seizures and electroencephalographic dysrhythmia in humans. Acute symptoms can be alleviated with phenobarbital. Acute oral LD_{50} values for the rat range from 100 to 112 mg/kg (U.S. EPA, 1979). The no observable effect level was found to be 2.5 mg/kg/day over 15 days (Natl. Acad. Sci., 1977).

Chlordane inhibits growth of human viridans streptococci of the buccal cavity. Complete inhibition of growth occurred at 3 ppm, and about 20 percent inhibition was seen at 1 ppm (Goes, et al. 1978).

V. AQUATIC TOXICITY

A. Acute Toxicity

Ten species of freshwater fish have reported 96-hr LC_{50} values ranging from 8 to 1160 µg/l resulting from technical and pure chlordane exposure with a geometric mean of 16 µg/l. Rainbow trout, Salmo gairdneri (Mehrle, et al. 1974) was the most sensitive species tested, the channel catfish (Ictalurus punctatus) the least sensitive. The freshwater invertebrates were more sensitive to chlordane, with a reported LC_{50} value ranging from 4.0 for freshwater shrimp Palaemonetes kadiakensis (Sanders, 1972) to 40 µg/l (Gammarus fasciatus), with a geometric mean of 0.36 µg/l. In goldfish (Carassius auratus), only 0.13 percent of cis-chlordane is metabolized in 24 hours. Only 0.61 percent is converted after 25 days. Some metabolites were chlordene chlorohydrin and monohydroxy derivatives (Feroz and Khan, 1979).

The LC_{50}'s for four species of saltwater fish, sheepshead minnows (Cyprinodon variegatus), striped bass (Morone saxatilis), pinfish (Lagodon rhomboides), and white mullet (Mugil curema), ranged from 5.5 to 24.5 µg/l. The three-spine stickleback (Gasterosteus aculeatus) yielded 96-hr LC_{50} values which ranged from 90-160 µg/l (Katz, 1961). Invertebrate LC_{50} values ranged from 0.4 for the pink shrimp, Penaeus duorarum (Parrish, et al. 1976) to 480 µg/l. The geometric mean of the adjusted LC_{50} values for invertebrates was 0.18 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

In a life cycle bioassay involving freshwater organisms, the chronic values for the bluegill Lepomis macrochirus (Cardwell, et al. 1977) was 1.6 µg/l. In two tests involving the sheepshead minnow, Cyprinodon variegatus, the chronic values were 0.63 µg/l for the life cycle test (Parrish, et al. 1978) and 5.49 µg/l for an embryo-level test (Parrish, et al. 1976).

Many blood parameters (clotting time, mean corpuscular hemoglobin and cholesterol level) are lowered after the teleost, Sacco-branchus fossilus, is exposed to 120 µg/l of chlordane for 15 to 60 days (Verma, et al. 1979). Similar results were obtained in Labeo rohita at doses $\geq$ 23 µg/l after 30 to 60 day exposures (Bansal, et al. 1979).

C. Plant Effects

A natural saltwater phytoplankton community suffered a 94 percent decrease in productivity during a 4-hour exposure at 1,000 µg/l (Butler, 1963).

D. Residues

In Daphnia magna, chlordane was bioconcentrated 6,000-fold after seven days' exposure and 7,400-fold by scuds (Hyallela azteca) after 65 days of exposure (Cardwell, et al. 1977). After 33 days' exposure, the fresh-

water alga (Oedegonium sp.) bioconcentrated chlordane 98,000-fold; Physa sp., a snail, concentrated it 133,000-fold (Sanborn, et al. 1976). Equilibrium bioconcentration factors for the sheepshead minnow ranged from 6,580 to 16,035 (Goodman, et al. 1978; Parrish, et al. 1976).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The issue of the carcinogenicity of chlordane in humans is being reconsidered; thus, there is a possibility that the criterion for human health will be changed. Based on the data for carcinogenicity in mice (Epstein, 1976), and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of chlordane in ambient water which will result in risk levels of human cancer as specified in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.012 ng/l	0.12 ng/l	1.2 ng/l
Consumption of fish and shellfish only.	0	0.013 ng/l	0.13 ng/l	1.3 ng/l

The ACGIH (1977) adopted a time-weighted average value of 0.5 mg/m^3 for chlordane, with a short-term exposure limit (15 minutes) of 2 mg/m^3.

A limit of 3 µg/l for chlordane in drinking water is suggested under the proposed Interim Primary Drinking Water Standards (40 FR 11990, March 14, 1975).

Canadian Drinking Water Standards (Dept. Natl. Health Welfare, 1968) limit chlordane to 3 µg/l in raw water supplies.

B. Aquatic

For chlordane, the proposed criterion to protect freshwater aquatic life is 0.024 µg/l for a 24-hour average, not to exceed 0.36 µg/l at any time (U.S. EPA, 1979). For saltwater aquatic species, the draft criterion is 0.0091 µg/l for a 24-hour average, not to exceed 0.18 µg/l at any time (U.S. EPA, 1979).

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No. 36

Chlorinated Benzenes

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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

CHLORINATED BENZENES

Summary

The chlorinated benzenes are a group of compounds with a wide variety of physical and chemical characteristics depending on the degree of chlorination. As chlorination increases, the persistance of the compound in the environment increases. On chronic exposure liver and kidney changes are noted, while the degree of toxicity increases with the degree of chlorination. The chlorinated benzenes have not been shown to be teratogens or mutagens. Only hexachlorobenzene has been demonstrated to be carcinogenic in laboratory animals.

Aquatic toxicity data indicate a trend to increasing toxicity with increasing chlorination for all species tested. The bluegill for example, has the following 96-hour LC_{50} values; chlorobenzene, 15,900 µg/l; 1,2,4-trichlorobenzene 3,360 µg; 1,2,3,5-tetrachlorobenzene, 6,420 micrograms/l; 1,2,4,5-tetrachlorbenzene 1,550 µg/l and pentachlorobenzene, 200 µg/l. Other freshwater and saltwater fish, invertebrates and plants were generally less sensitive to chlorobenzenes toxicity than the bluegill. The sheepshead minnow yielded a chronic value of 14.5 µg/l for 1,2,4,5-tetrachlorobenzene in an embryo-level test. After 28 days exposure, the bioconcentration factor for the bluegill for pentachlorobenzene and 1,2,4,5-tetrachlorobenzene were 3,400 and 1,800, respectively.

CHLORINATED BENZENES

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Benzenes (U.S. EPA, 1979). This document will summarize the general properties of the chlorinated benzenes. For further information on monochlorobenzene, 1,2,4-trichlorobenzene, or hexachlorobenzene, refer to the specific EPA/ECAO Hazard Profiles for these compounds. For detailed information on the other chlorinated benzenes refer to the Ambient Water Quality Document (U.S. EPA, 1979).

The chlorinated benzenes, excluding dichlorobenzenes, are monochlorobenzene (C_6H_3Cl), 1,2,4-trichlorobenzene ($C_6H_3Cl_3$), 1,3,5-trichlorobenzene ($C_6H_3Cl_3$), 1,2,3,4-tetrachlorobenzene ($C_6H_2Cl_4$), 1,2,3,5-tetrachlorobenzene ($C_6H_2Cl_4$), 1,2,4,5-Tetrachlorobenzene ($C_6H_2Cl_4$), pentachlorobenzene (C_6HCl_5), and hexachlorobenzene (C_6Cl_6). All chlorinated benzenes are colorless liquids or solids with a pleasant aroma. The most important properties imparted by chlorine to these compounds are solvent power, viscosity, and moderate chemical reactivity. Viscosity and nonflammability tend to increase from chlorobenzene to the more highly chlorinated benzenes. Vapor pressures and water solubility decrease progressively with the degree of chlorination (U.S. EPA, 1979).

The current production, based on annual production in the U.S., was 139,105 kkg of monochlorobenzene in 1975, 12,849 kkg of 1,2,4-trichlorobenzene, 8,182 kkg of 1,2,4,5-

tetrachlorobenzene and 318 kkg of hexachlorobenzene in 1973 (West and Ware, 1977; EPA, 1975a). The remaining chlorinated benzenes are produced mainly as by-products from the production processes for the above four chemicals. Chlorinated benzenes have many and diverse uses in industry depending upon the individual properties of the specific compound. Some uses are as solvents, chemical intermediates, flame retardants, and plasticizers.

II. EXPOSURE

A. Water

Mono-, tri-, and hexachlorobenzene have been detected in ambient water. Because of its high volatility, monochlorobenzene has a short half-life of only 5.8 hours (Mackay and Leinonen, 1975). However, hexachlorobenzene has an extremely long residue time in water, appearing to be ubiquitous in the aqueous environment. Monochlorobenzene has been detected in "uncontaminated" water at levels of 4.7 μg/l. Both trichlorobenzene and hexachlorobenzene have been detected in drinking waters at concentrations of 1.0 μg/l and 4 to 6 ng/l respectively (U.S. EPA, 1979). There is no information available on the concentration of the other chlorinated benzenes in water.

B. Food

There is little data on the consumption of chlorinated benzenes in food. All the chlorinated benzenes appear to concentrate in fat, and are capable of being absorbed

by the plants from contaminated soil. Both pentachlorobenzene and hexachlorobenzene have been detected in meat fat (e.g. Stijve, 1971; Ushio and Doguchi, 1977). Hexachlorobenzene, the most extensively studied compound, has been found in a wide variety of foods from cereals to milk (including human breast milk), eggs, and meat. The U.S. EPA (1979) has estimated the weighted bioconcentration factor of the following chlorinated benzenes:

Chemical	Weighted bioconcentration factor
monochlorobenzene	13
1,2,4-trichlorobenzene	290
1,2,4,5-tetrachlorobenzene	1,000
pentachlorobenzene	7,800
hexachlorobenzene	12,000

These estimates were based on the octanol/water partition coefficient of the chlorinated benzenes.

C. Inhalation

There is no available data on the concentration of chlorinated benzenes in ambient air with the exception of measurements of aerial fallout of particulate bound 1,2,4-trichlorobenzene in southern California. Five sampling sites showed median levels of 1,2,4-trichlorobenzene of less than 11 $ng/m^2/day$ (U.S. EPA, 1979). The primary site of inhalation exposure to chlorinated benzenes is the workplace in industries utilizing and/or producing these compounds.

III. PHARMACOKINETICS

A. Absorption

There is little data on the absorption of orally administered chlorinated benzenes. It is apparent from

the toxicity of orally administered compounds that absorption does take place, and tetrachlorobenzene has been shown to be absorbed relatively efficiently by rabbits (Jondorf, et al. 1958). Pentachlorobenzene was absorbed poorly after subcutaneous injection (Parke and Williams, 1960). Hexachlorobenzene was absorbed poorly from an orally administered aqueous solution (Koss and Kornasky, 1975), but with high efficiency when administered in oil (Albro and Thomas, 1974). The more highly chlorinated compounds in food products will selectively partition into the lipid portion and be absorbed far better than that in an aqueous medium (U.S. EPA, 1979).

A. Distribution

The chlorinated benzenes are lipophilic, compounds with greater lipophilic tendencies in the more highly chlorinated compounds. The predominant disposition site is either suspected to be, or shown to be, in the lipid tissues of the body (Lee and Metcalf, 1975; U.S. EPA, 1979).

C. Metabolism

The chlorinated benzenes are metabolized in the liver by the NADPH-cytochrome P-448 dependent microsomal enzyme system (Ariyoshi, et al. 1975; Koss, et al. 1976). At least for monochlorobenzene, there is evidence that toxic intermediates are formed during metabolism (Kohli, et al. 1976). Various conjugates and phenolic derivatives are the primary excretory end products of chlorinated benzene metabolism. In the more highly chlorinated compounds, such as hexachlorobenzene, conjugates are formed to only a limited extent, and metabolism is relatively slow.

D. Excretion

The less-chlorinated benzenes are excreted as polar metabolites or conjugates in the urine. An exception occurs with monochlorobenzene where 27 percent of an administered dose appeared as unchanged compounds in the expired air of a rabbit (Williams, 1959). The two highly chlorinated compounds, pentachlorobenzene and hexachlorobenzene, are eliminated predominately by fecal excretion as unchanged compounds (Koss and Koransky, 1975; Rozman, et al. press). The biological half-lives of these two compounds are extremely long in comparison to that of the less-chlorinated compounds (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogencity

Mono- and tetrachlorobenzene have not been investigated for carcinogenic potential (U.S. EPA, 1979). In one study, trichlorobenzene was not shown to produce any significant increase in liver tumors (Gotto, et al. 1972). There is one report, which was not critically evaluated by U.S. EPA (1979), which alludes to the carcinogencity of pentachlorobenzene in mice and the absence of this activity in rats and dogs (Preussman, 1975). Life-time feeding studies in hamsters (Cabral, et al. 1977) and mice (Cabral, et al. 1978) have demonstrated the carcinogenic activity of hexachlorobenzene. However, shorter term studies failed to demonstrate an increasd tumor incidence in strain A mice or ICR mice (Theiss, et al. 1977; Shirai, et al. 1978).

B. Mutagenicity

There are no available studies conducted to evaluate the mutagenic potential of mono-, tri-, tetra-, and pentachlorobenzene (U.S. EPA, 1979). Hexachlorobenzene was assayed for mutagenic activity in the dominant lethal assay, and shown to be inactive (Khera, 1974).

C. Teratogenicity

There are no available studies conducted to evaluate the teratogenic potential of mono-, tri-, tetra-, and pentachlorobenzene (U.S. EPA, 1979). Khera (1974) concluded hexachlorobenzene was not a teratogen when given to CD-1 mice at 50 mg/kg/day on gestation days from 7 to 11.

D. Other Reproductive Effects

Hexachlorobenzene can pass through the placenta and cause fetal toxicity in rats (Grant, et al. 1977). The distribution of hexachlorobenzene in the fetus appears to be the same in the adult, with the highest concentration in fatty tissue.

E. Chronic Toxicity

There is no available data on the chronic effects of pentachlorobenzene (U.S. EPA, 1979). Mono- and trichlorobenzene produce histological changes in the liver and kidney (Irish, 1963; Coate, et al. 1977). There is also some evidence for liver damage occurring with prolonged exposure of rats and dogs to tetrachlorobenzene (Fomenko, 1965; Braun, et al. 1978). Hexachlorobenzene has caused histological changes in the livers of rats (Koss, et al. 1978). In humans

exposed to undefined amounts of hexachlorobenzene for an undetermined time, porphyrinuria has been shown to occur (Cam and Nigogosyan, 1963).

F. Other Relevant Information

Chlorinated benzenes appear to increase the activity of microsomal NADPH-cytochrome P-450 dependent enzyme systems. Induction of microsomal enzyme activity has been shown to enhance the metabolism of a wide variety of drugs, pesticides and other xenobiotics (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

The dichlorobenzenes are covered in a separate EPA/ECAO hazard profile and will not be covered in this discussion on chlorobenzenes.

All data reported for freshwater fish are from 96-hour static toxicity tests. Pickering and Henderson (1966) reported 96-hour LC_{50} values for goldfish, guppys and bluegills to be 51,620, 45,530, and 24,000 µg/l, respectively, for chlorobenzene. Two 96 hour LC_{50} values for chlorobenzene and fathead minnows are 33,930 µg/l in saltwater and 29,120 µg/l in hard water. Reported 96-hour values for the bluegill exposed to chlorobenzene, 1,2,4-trichlorobenzene, 1,2,3,5-tetrachlorobenzene, 1,2,4,5-tetrachlorobenzene and pentachlorobenzene are 15,900, 3,360, 6,420, 1,550 and 250 µg/l, respectively (U.S. EPA, 1978). These data indicate a trend to increasing toxicity with chlorination, except for 1,2,3,5-tetrachlorobenzene (U.S. EPA, 1978).

EC_{50} (48 hour) values reported for Daphnia magna are: chlorobenzene 86,000 µg/l, 1,2,4-trichlorobenzene 50,200 µg/l, 1,2,3,5-tetrachlorobenzene 9,710 µg/l, and pentachlorobenzene 5,280 µg/l (U.S. EPA, 1978).

Toxicity tests with the sheepshead minnow, Cyprinodon variegatus, performed with five chlorinated benzenes under static conditions and yielded the following 96-hour LC_{50} values: chlorobenzene 10,500 µg/l, 1,2,4-trichlorobenzene 21,400 µg/l, 1,2,3,5-tetrachlorobenzene 3,670 µg/l, 1,2,4,5 tetrachlorobenzene 840 µg/l, and pentrachlorobenzene 835 µg/l (U.S. EPA, 1978). As with sheepshead minnows, sensitivity of the mysid shrimp, Mysidopsis bahia, to chlorinated benzenes generally increases with increasing chlorination. The reported 96-hour LC_{50} values are as follows: chlorobenzene 16,400 µg/l, 1,2,4-trichlorobenzene 450 µg/l, 1,2,3,5-tetrachlorobenzene 340 µg/l, 1,2,4,5-tetrachlorobenzene 1,480 µg/l, and 160 µg/l for pentachlorobenzene (U.S. EPA, 1979).

B. Chronic Toxicity

Chronic toxicity data are not available for freshwater fish or invertebrate species. Only one saltwater species, Cyprinodon veriegatus, has been chronically exposed to any of the chlorinated benzenes. In an embryo-level test, the limits for 1,2,4,5-tetrachlorobenzene are 92 to 180 µg/l, with a final chronic value of 64.5 µg/l (U.S. EPA, 1978).

C. Plant Effects

The green freshwater algae Selenastrum capricornutum has been exposed to five chlorinated benzenes. Based on cell number, the 96-hour EC_{50} values are as follows: chlorobenzene 220,000 µg/l, 1,2,4-trichlorobenzene 36,700 µg/l, 1,2,3,5-tetrachlorobenzene 17,700 µg/l, 1,2,4,5-tetrachlorobenzene 46,800 µg/l, and pentachlorobenzene 6,780 µg/l.

D. Residues

No measured bioconcentration factor (BCF) is available for chlorobenzenes. However, the average weighted BCF of 13 was calculated from octanol-water partition coefficient and other factors. (U.S. EPA, 1979).

VI. EXISTING GUIDLINES 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

Monochlorobenzene: The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) threshold limit value for monochlorobenzene is 350 mg/m^3. The U.S. EPA draft ambient water quality criterion for monochlorobenzene is 20/µg/l based on the threshold concentration for odor and taste (U.S. EPA, 1979).

Trichlorobenzene: The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value for 1,2,4-trichlorobenzene is 40 mg/m^3 (5 ppm).

The U.S. EPA (1979) draft ambient water quality criterion for 1,2,4-trichlorobenzene is 13 µg/l based on the threshold concentration for odor and taste.

Tetrachlorobenzene: The U.S. EPA (1979) draft ambient water quality criterion for tetrachlorobenzene is 17 µg/l.

Pentachlorobenzene: The U.S. EPA (1979) draft ambient water quality criterion for pentachlorobenzene is 0.5 µg/l.

Hexachlorobenzene: The value of 0.6 µg/kg/day hexachlorobenzene was suggested by FAO/WHO as a reasonable upper limit for residues in food for human consumption (FAO/WHO, 1974). The Louisiana State Department of Agriculture has set the tolerated level of hexachlorobenzene in meat fat a 0.3 mg/kg (U.S. EPA, 1976). The FAO/WHO recommendations for residues in foodstuffs were 0.5 mg/kg in fat for milk and eggs, and 1 mg/kg in fat for meat and poultry (FAO/WHO, 1974). Based on cancer bioassy data, and using the "one-hit" model, the EPA (1979) has estimated levels of hexachlorobenzene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumption (per day)	Risk Levels And Corresponding Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.0125 ng/l	0.125 ng.l	1.25 ng/l
Consumption of fish and shellfish only.	0	0.126 ng/l	0.126 ng/l	1.26 ng/l

B. Aquatic

The drafted criteria to protect freshwater aquatic life as is follows: (U.S. EPA, 1979)

Compound	24-hr. Average µg/l	Concentration not to be exceeded at anytime µg/l
Chlorobenzene	1,500	3,500
1,2,4-trichlorobenzene	210	470
1,2,3,5-tetrachlorobenzene	170	390
1,2,4,5-tetrachlorobenzene	97	220
Pentachlorbenzene	16	36

The drafted criteria to protect saltwater aquatic life are as follows: (U.S. EPA, 1979)

Compound	24-hr. Average µg/l	Concentration not to be exceeded at anytime µg/l
Chlorobenzene	120	280
1,2,4-Trichlorobenzene	3.4	7.8
1,2,3,5-Tetrachlorbenzene	2.6	5.9
1,2,45-Tetrachlorobenzene	9.6	26
Pentachlorobenzene	1.3	2.9

CHLORINATED BENZENES

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No. 37

Chlorinated Ethanes

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 chlorinated ethanes and has found sufficient evidence to indicate that this compound is carcinogenic.

CHLORINATED ETHANES

SUMMARY

Four of the chlorinated ethanes have been shown to produce tumors in experimental animal studies conducted by the National Cancer Institute (NCI). These four are 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane, and hexachloroethane. Animal tumors were also produced by administration of 1,1,1-trichloroethane, but this bioassay is being repeated due to premature deaths in one initial study.

Two of the chlorinated ethanes, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, have shown mutagenic activity in the Ames *Salmonella* assay and in *E. coli*. 1,2-Dichloroethane has also shown mutagenic action in pea plants and in *Drosophila*.

No evidence is available indicating that the chloroethanes produce teratogenic effects. Some toxic effects on fetal development have been shown following administration of 1,2-dichloroethane and hexachloroethane.

Symptoms produced by toxic exposure to the chloroethanes include central nervous system disorders, liver and kidney damage, and cardiac effects.

Aquatic toxicity data for the effects of chlorinated ethanes to freshwater and marine life are few. Acute studies have indicated that hexachloroethane is the most toxic of the chlorinated ethanes reviewed. Marine organisms tend to be more sensitive than freshwater organisms with acute toxicity values as low as 540 μg/l being reported.

CHLORINATED ETHANES

I. INTRODUCTION

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

The chloroethanes (see table 1) are hydrocarbons in which one or more of the hydrogen atoms have been replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. Monochloroethane is a gas at room temperature, hexachloroethane is a solid, and the remaining compounds are liquids. All chloroethanes show some solubility in water, and all, except monochloroethane, are more dense than water.

The chloroethanes are used as solvents, cleaning and degreasing agents, in the manufacture of plastics and textiles, and in the chemical synthesis of a number of compounds.

<u>Current production</u>:

monochloroethane	335×10^3 tons/yr in 1976
1,2-dichloroethane	$4{,}000 \times 10^3$ tons/yr in 1976
1,1,1-trichloroethane	215×10^3 tons/yr in 1976

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979).

II. EXPOSURE

The chloroethanes are present in raw and finished waters due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water or treatment of sewage. Water monitoring studies

have shown the following levels of various chloroethanes: 1,2-dichloroethane, 0.2-8 μg/l; 1,1,2-trichloroethane, 0.1-8.5 μg/l; 1,1,1,2-tetrachloroethane, 0.11 μg/l (U.S. EPA, 1979). In general, air levels of chloroethanes are produced by evaporation of volatile chloroethanes widely used as degreasing agents and in dry cleaning operations (U.S. EPA, 1979). Industrial monitoring studies have shown air levels of 1,1,1-trichloroethane ranging from 1.5 to 396 ppm (U.S. EPA, 1979).

TABLE 1

Chloroethanes and Synonyms

Compound Name	Synonyms	
Monochloroethane	Chloroethane	Ethyl chloride
1,1,-Dichloroethane	Ethylidene Dichloride	Ethylidene Chloride
1,2-Dichloroethane	Ethylene Dichloride	Ethylene Chloride
1,1,1-Trichloroethane	Methyl Chloroform	Chlorothene
1,1,2-Trichloroethane	Ethane Trichloride	Vinyl Trichloride
1,1,1,2-Tetrachloroethane	Tetrachloroethane	
1,1,2,2-Tetrachloroethane	Acetylene Tetrachloride	Sym-Tetrachloroethane
Pentachloroethane	Pentalin	Ethane Pentachloride
Hexachloroethane	Perchloroethane	

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. The two most widely used solvents, 1,2-dichloroethane and 1,1,1-trichloroethane, are the compounds most often detected in foods. Analysis of several foods indicated 1,1,1-trichloro-

ethane levels of 1-10 μg/kg (Walter, et al. 1976), while levels of 1,2-dichloroethane found in 11 of 17 species have been reported to be 2-23 μg/g (Page and Kennedy, 1975). Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976).

The U.S. EPA (1979) has derived the following weighted average bioconcentration factors for the edible portions of fish and shellfish consumed by Americans: 1,2-dichloroethane, 4.6; 1,1,1-trichloroethane, 21; 1,1,2,2-tetrachloroethane, 18; pentachloroethane, 150; hexachloroethane, 320. These estimates were based on the measured steady-state bioconcentration studies in bluegill. Bioconcentration factors for 1,1,2-trichloroethane (6.3) and 1,1,1,2-tetrachloroethane (18) were derived by EPA (1979) using octanol-water partition coefficients.

III. PHARMACOKINETICS

A. Absorption

The chloroethanes are absorbed rapidly following ingestion or inhalation (U.S. EPA, 1979). Dermal absorption is thought to be slower in rabbits based on studies by Smyth, et al. (1969). However, rapid dermal absorption has been seen in guinea pigs with the same trichloroethane (Jakobson, et al. 1977).

Human studies on the absorption of inhaled 1,1,2,2-tetrachloroethane indicate that the compound is completely absorbed after exposure to trace levels of radiolabeled vapor (Morgan, et al., 1970, 1972). At higher exposure levels absorption is rapid in man and animals, but obviously not complete.

B. Distribution

Studies on the distribution of 1,1,1-trichloroethane in mice following inhalation exposure have shown levels in the liver to be twice that found in the kidney and brain (Holmberg, et al. 1977). Postmortem examination of human tissues showed 1,1,1-trichloroethane in body fat (highest concentration) kidneys, liver, and brain (Walter, et al. 1976). Due to the lipid solubility of chloroethanes, body distribution may be expected to be widespread. Stahl, et al. (1969) have noted that human tissue samples of liver, brain, kidney, muscle, lung, and blood contained 1,1,1-trichloroethane following acute exposure, with the liver containing the highest concentration.

Passage of 1,1,1,2-tetrachloroethane across the placenta has been reported by Truhaut, et al. (1974) in rabbits and rats.

C. Metabolism

The metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation to corresponding alcohols (Monster, 1979; Truhaut, 1972). Oxidation reactions may produce unsaturated metabolites which are then transformed to the alcohol and ester (Yllner, 1971 a,b,c,d).

Metabolism appears to involve the activity of the mixed function oxidase enzyme system (Van Dyke and Wineman, 1971). Animal experiments by Yllner (1971 a,b,c,d,e) indicated that the percentage of administered compound metabolized decreased with increasing dose, suggesting saturation of metabolic pathways.

D. Excretion

The chloroethanes are excreted primarily in the urine and in expired air (U.S. EPA, 1979). As much as 60 to 80 percent of an inhaled dose of 1,1,1-trichloroethane (70 or 140 ppm for 4 hours) was expired unchanged by human volunteers (Monster, et al. 1979). Animal studies conducted by Yllner (1971 a,b,c,d) indicate that largest amount of chloroethanes, administered by intraperitoneal (i.p.) injection is excreted in the urine; this is followed by expiration (in the changed or unchanged form), with very little excretion in the feces. Excretion appears to be rapid, since 90 percent of i.p. administered doses of 1,2-dichloroethane or 1,1,2-trichloroethane were eliminated in the first 24 hours (U.S. EPA, 1979). However, the detection of chloroethanes in postmortem tissue samples indicates that some portion of these compounds persists in the body (Walter, et al. 1976).

IV. EFFECTS

A. Carcinogenicity

Several chlorinated ethanes have been shown to produce a variety of tumors in rats and mice in experiments utilizing oral administration. Tumor types observed after compound administration include squamous cell carcinoma of the stomach, hemangiosarcoma, adenocarcinoma of the mammary gland, and hepatocellular carcinoma (NCI, 1978a,b,c,d). The four chlorinated ethanes which have been classified as carcinogens based on animal studies are: 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane,

and hexachloroethane. Increased tumor production was also noted in animals treated with 1,1,1-trichloroethane, but high mortality during this study (NCI, 1977) caused retesting of the compound to be initiated. *In vitro* transformation of rat embryo cells and subsequent fibrosarcoma production by these cells when injected *in vivo*, indicate that 1,1,1-trichloroethane does have carcinogenic potential (Price, et al. 1978).

B. Mutagenicity

Two of the chlorinated ethanes, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, have shown mutagenic activity in the Ames *Salmonella* assay and for DNA polymerase deficient strain of *E. coli* (Brem, et al. 1974). In these two systems, 1,1,2,2-tetrachloroethane showed higher mutagenic activity than 1,2-dichloroethane (Rosenkranz, 1977).

Mutagenic effects have been produced by 1,2-dichloroethane in pea plants (Kirichek, 1974) and in *Drosophila* (Nylander, et al. 1978). Several metabolites of dichloroethane (chloroacetaldehyde, chloroethanol, and S-chloroethyl cysteine have also been shown to produce mutations in the Ames assay (U.S. EPA, 1979).

Testing of hexachloroethane in the Ames *Salmonella* assay or in a yeast assay system failed to show any mutagenic activity (Weeks, et al. 1979).

C. Teratogenicity

Inhalation exposure of pregnant rats and mice to 1,1,1-trichloroethane was shown to produce some soft

tissue and skeletal deformities; this incidence was not judged statistically significant by the Fisher Exact probability test (Schwetz, et al. 1975).

Testing of hexachloroethane administered to rats by intubation or inhalation exposure did not show an increase in teratogenic effects (Weeks, et al. 1979). Inhalation exposure of pregnant rats to 1,2-dichloroethane also failed to demonstrate teratogenic effects (Schwetz, et al. 1974; Vozovaya, 1974).

D. Other Reproductive Effects

Decreased litter size, reduced fetal weights and a reduction in live births have been reported in rats exposed to 1,2-dichloroethane (57 mg/m^3m four hours/day, six days/week) by inhalation (Vozovaya, 1974). 1,1-Dichloroethane retarded fetal development at exposures of 6,000 ppm. (Schwetz, et al. 1974). Higher fetal resorption rates and a decreased number of live fetuses per litter were observed in rats following administration of hexachloroethane by intubation (15, 48 or 260 ppm, 6 hours/day) or inhalation (50, 100 or 500 mg/kg/day) (Weeks, et al. 1979).

E. Chronic Toxicity

Neurologic changes and liver and kidney damage have been noted following long term human exposure to 1,2-dichloroethane (NIOSH, 1978). Cardiac effects (overstimulation) have been noted following human exposure to 1,1-dichloroethane (U.S. EPA, 1979).

Central nervous system disorders have been reported in humans exposed to 1,1,1-trichloroethane. Symptoms noted

were altered reaction time, perceptual speed, manual dexterity, and equilibrium (U.S. EPA, 1979).

Animal studies indicate that the general symptoms of toxicity resulting from exposure to the chloroethanes involve effects in the central nervous system, cardiovascular system, pulmonary system, and the liver and kidney (U.S. EPA, 1979). Laboratory animals and humans exposed to chloroethanes show similar symptoms of toxicity (U.S. EPA, 1979).

Based on data derived from animal studies, the U.S. EPA (1979) has concluded that the relative toxicity of the chloroethanes is as follows: 1,2-dichloroethane > 1,1,2,2-tetrachloroethane > 1,1,2-trichloroethane > hexachloroethane 1,1-dichloroethane > 1,1,1-trichloroethane > monochloroethane.

F. Other Relevant Information

The hepatotoxicity of 1,1,2-trichloroethane was increased in mice following acetone or isopropyl alcohol pretreatment (Traiger and Plaa, 1974). Similarly, ethanol pretreatment of mice increased the hepatic effects of 1,1,1-trichloroethane (Klassen and Plaa, 1966).

Hexobarbital sleeping times in rats were reported to be decreased following inhalation exposure to 1,1,1-trichloroethane (3,000 ppm), indicating an effect of the compound on stimulation of hepatic microsomal enzymes (Fuller, et al. 1970).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity studies were conducted on three species of freshwater organisms and two marine species.

For freshwater fish, 96-hour static LC_{50} values for the bluegill sunfish, Lepomis macrochirus, ranged from 980 µg/l hexachloroethane to 431,000 µg/l 1,2-dichloroethane, while the range of 48-hour LC_{50} values for the freshwater invertebrate Daphnia magna was 8,070 µg/l to 218,000 µg/l for hexachloroethane and 1,2-dichloroethane respectively. Among marine organisms, the sheepshead minnow (Cyprinodon vagiegatus) produced LC_{50} values ranging from 2,400 µg/l for hexachloroethane to 116,000 µg/l for pentachloroethane. The marine mysid shrimp (Mysidopsis bahia) produced LC_{50} values ranging from 940 µg/l for hexachloroethane to 113,000 µg/l for 1,2-dichloroethane. The general order of acute toxicities for the chlorinated ethanes reviewed for freshwater fish is: hexachloroethane (highest toxicity), 1,1,2,2-tetrachloroethane, 1,1,2-trichloroethane, pentachloroethane, and 1,2-dichloroethane (U.S. EPA, 1979).

B. Chronic Toxicity

The only chronic study available for the chlorinated ethanes is for pentachloroethane's chronic effects on the marine shrimp (Mysidopsis bahia), which produced a chronic value of 580 µg/l (U.S EPA, 1978).

C. Plant Effects

Effective EC_{50} concentrations, based on chlorophyll a and cell numbers for the freshwater algae Selenastrum capriconutum ranges from 87,000 µg/l for hexachloroethane to 146,000 µg/l for 1,1,2,2-tetrachloroethane, with pentachloroethane being intermediate in its phytotoxicity. For the marine algae Skeletonema costatum, a greater sensi-

tivity was indicated by effective EC_{50}- concentrations based on cell numbers and chlorophyll a ranging from 6,230 µg/l for 1,1,2,2-tetrachloroethane and 7,750 µg/l for hexachloroethane to 58,200 µg/l for pentachloroethane.

D. Residues

The bioconcentration value was greatest for hexachloroethane with a value of 139 µg/l being reported for bluegill. Bioconcentration values of 2, 8, and 9 were obtained for 1,2-dichloro, 1,1,2,2-tetrachloro, and 1,1,1-trichloroethane for bluegills. 1,1,2-Trichloroethane and 1,1,1,2-tetrachloroethane used the octanol/water coefficients to derive BCF's of 22 and 62, respectively.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

Based on the NCI carcinogenesis bioassay data, and using a linear, non-threshold model, the U.S. EPA (1979) has estimated levels of four chloroethanes in ambient water that will result in an additional cancer risk of 10^{-5}: 1,2-dichloroethane, 7.0 µg/l; 1,1,2-trichloroethane, 2.7 µg/l; 1,1,2,2-tetrachloroethane, 1.8 µg/l; hexachloroethane, 5.9 µg/l. A draft ambient water quality criterion to protect human health has been derived by EPA for 1,1,1-trichloroethane based on mammalian toxicity data at the level of 15.7 mg/l.

Insufficient mammalian toxicological data prevented derivation of a water criterion for monochloroethane, 1,1-dichloroethane, 1,1,1,2-tetrachloroethane, or pentachloroethane (U.S. EPA, 1979).

The following compounds have had eight hour, TWA exposure standards established by OSHA: monochloroethane, 1,000 ppm; 1,1-dichloroethane, 100 ppm; 1,2-dichloroethane, 50 ppm; 1,1,1-trichloroethane, 350 ppm; 1,1,2-trichloroethane, 10 ppm; 1,1,2,2-tetrachloroethane, 5 ppm; hexachloroethane, 1 ppm.

B. Aquatic

Criteria for protecting freshwater organisms have been drafted for five of the chlorinated hydrocarbons: 62 µg/l (average concentation) not to exceed 140 µg/l for hexachloroethane; 170 µg/l not to exceed 380 µg/l for 1,1,2,2-tetrachloroethane; 440 µg/l not to exceed 1,000 µg/l for pentachloroethane; 3,900 µg/l not to exceed 8,800 µg/l for 1,2-dichloroethane; and 5,300 µg/l not to exceed 12,000 µg/l for 1,1,1-trichloroethane. For marine organisms, criteria have been drafted as: 7 µg/l (average concentration) not to exceed 16 µg/l for hexachloroethane; 38 µg/l not to exceed 87 µg/l for pentachloroethane; 70 µg/l not to exceed 160 µg/l for 1,1,2,2-tetrachloroethane; 240 µg/l not to exceed 540 µg/l for 1,1,1-trichloroethane; and 880 µg/l not to exceed 2,000 µg/l for 1,2-dichloroethane.

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No. 38

Chlorinated Naphthalenes

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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

CHLORINATED NAPTHALENES

Summary

Chlorinated naphthalenes have been used in a variety of industries, usually as mixtures. Chronic toxicity varies with the degree of chlorination, with the more highly chlorinated species being more toxic. The clinical signs of toxicity in humans are damage to liver, heart, pancreas, gall bladder, lungs, adrenal glands, and kidney. No animal or human studies have been presented on the carcinogenicity, mutagenicity, or teratogenicity of polychlorinated naphthalenes.

Very little data on aquatic toxicity are available for individual chlorinated naphthalenes. 48-Hour and 96-hour LC_{50} values of octachloronaphthalene over 500,000 µg/l have been reported for Daphnia magna and the bluegill, respectively. A freshwater alga also resulted in a 96-hour LC_{50} value for octachloronaphthalene of over 500,000 µg/l.

Toxicity studies with aquatic organisms are confined to tests with 1-chloronaphthalene on one freshwater fish and two algal species (one fresh and one saltwater). All tests have reported 96-hour LC_{50} values of between 320 and 2,270 µg/l. Exposure of sheepshead minnow to 1-chloronaphthalene in an embryo-larval study resulted in a chronic value of 328 µg/l.

CHLORINATED NAPTHALENES

I. INTRODUCTION

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

Chlorinated naphthalenes consist of two fused six carbon-membered aromatic rings where any or all of the eight hydrogen atoms can be replaced with chlorine. The physical properties of the chlorinated naphthalenes are generally dependent on the degree of chlorination. Melting points range from 17°C for 1-chloronaphthalene to 198°C for 1,2,3,4-tetrachloronaphthalene. As the degree of chlorination increases, the specific gravity, boiling point, fire and flash points all increase, while the vapor pressure and water solubility decrease. Chlorinated naphthalenes have been used as the paper impregnant in automobile capacitors (mixtures of tri- and tetrachloronaphthalenes), and as oil additives for engine cleaning, and in fabric dyeing (mixtures of mono- and dichloronaphthalenes). In 1956, the total U.S. production of chlorinated naphthalenes was approximately 3,175 metric tons (Hardie, 1964).

II. EXPOSURE

A. Water

To date, polychlorinated naphthalenes have not been identified in drinking waters (U.S. EPA, 1979). However, these compounds have been found in waters or sediments adjacent to point sources or areas of heavy polychlorinated biphenyl contamination.

B. Food

Polychlorinated naphthalenes appear to be biomagnified in the aquatic ecosystem, with the degree of biomagnification being greater for the more highly chlorinated polychlorinated compounds (Walsh, et al. 1977).

Erickson, et al. (1978) also noted a higher relative biomagnification of the lowest chlorinated naphthalenes by the fruit of apple trees grown on contaminated soil. The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for Halowax 1014 (a mixture of chlorinated naphthalenes) to be 4,800 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured non-steady-state bioconcentration studies in brown shrimp.

C. Inhalation

Erickson, et al. (1978) found ambient air concentrations of polychlorinated naphthalenes ranging from 0.025 to 2.90 $\mu g/m^3$ near a polychlorinated naphthalene plant. Concentrations of trichloronaphthalene were as high as 0.95 $\mu g/m^3$, while hexachloronaphthalene concentrations never exceeded 0.007 $\mu g/m^3$.

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature.

B. Distribution

In the rat fed 1,2-dichloronaphthalene, the chemical and its metabolites were found primarily in the intestine, kidney, and adipose tissue (Chu, et al. 1977).

C. Metabolism

There appears to be appreciable metabolism in mammals of polychlorinated naphthalenes containing four chlorine atoms or less (U.S. EPA, 1979). Cornish and Block (1958) investigated the excretion of polychlorinated naphthalenes in rabbits and found 79 percent of 1-chloronaphthalene, 93 percent of dichloronaphthalene, and 45 percent of tetrachloronaphthalene

were excreted in the urine as metabolites of the parent compounds. Metabolism may involve hydroxylation alone or hydroxylation in combination with dechlorination. In some cases, an arene oxide intermediate may be formed (Ruzo, et al. 1976).

D. Excretion

In rats fed 1,2-dichloronaphthalene, initially more of the chemical and its metabolites were found in the urine; however, by the end of seven days a greater proportion had been excreted in the feces (Chu, et al. 1977). In the first 24 hours, 62 percent of the dose was excreted in the bile, as compared to 18.9 percent lost in the feces. This suggests that there is an appreciable reabsorption and enterohepatic recirculation of this particular chlorinated naphthalene.

IV. EFFECTS

No animal or human studies have been reported on the carcinogenicity, mutagenicity, or teratogenicity of chlorinated naphthalenes. No other reproductive effects were found in the available literature.

A. Chronic Toxicity

Chronic dermal exposure to penta- and hexachlorinated naphthalenes causes a form of chloracne which, if persistent, can progress to form a cyst or sterile abcess (Jones, 1941; Shelley and Kligman, 1957; Kleinfeld, et al. 1972). Workers exposed to these two isomers complained of eye irritation, headaches, fatigue, vertigo, nausea, loss of appetite, and weight loss (Kleinfeld, et al. 1972). More severe exposure to the fumes of polychlorinated naphthalenes has produced severe liver damage, together with damage to the heart, pancreas, gall bladder, lungs, adrenal glands, and kidney tubules (Greenburg, et al. 1939). Chronic toxicity in animals appears to be qualitatively the same (U.S. EPA, 1979). Polychlorinated naphthalenes containing

three or fewer chlorine atoms were found to be nontoxic, while tetrachloronaphthalene resulted in mild liver disease at levels as high as 0.7 mg/kg/-day; the higher chlorinated naphthalenes produce more severe disease at lower doses (Bell, 1953). Because of their insolubility, hepta- and octachloronaphthalene were less toxic when given in suspension than when given in solution.

B. Other Relevant Information

Drinker, et al. (1937) showed enhancement of hepatoxicity of a mixture of ethanol/carbon tetrachloride in rats pretreated with 1.16 mg/m^3 of a penta-/hexachloronaphthalene mixture in air for six weeks. In a similar study trichloronaphthalene was inactive.

V. AQUATIC TOXICITY

A. Acute Toxicity

The 96-hour LC_{50} value reported for the bluegill, Lepomis macrochirus, exposed to 1-chloronaphthalene is 2,270 µg/l (U.S. EPA, 1978). With saltwater species, exposure of the sheepshead minnow, Cyprinodon varigatus, and mysid shrimp, Mysidopsis bahia, to 1-chloronaphthalene provided 96-hour LC_{50} values of 1,290 and 370 µg/l, respectively. Daphnia magna and the bluegill, Lepomis macrochirus, have a slight sensitivity to octachloronaphthalene, with respective 48-hour and 96-hour LC_{50} values greater than 530,000 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

In the only chronic study reported (embryo-larval), exposure of 1-chloronaphthalene to the sheepshead minnow resulted in a chronic value of 329 µg/l (U.S. EPA, 1978).

C. Plant Effects

A freshwater alga, Selenastrum capricornutum, and a saltwater alga, Skeletonema costatum, when exposed to 1-chloronaphthalene, both produced 96-hour EC_{50} values ranging from 1,000 to 1,300 µg/l based on cell numbers.

Octachloronaphthalene exposure to Selenastrum capricornutum resulted in a 96-hour EC_{50} value of over 500,000 µg/l based on cell numbers (U.S. EPA, 1978).

D. Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The only standards for polychlorinated naphthalenes are the ACGIH Threshold Limit Values (TLV) adopted by the Occupational Safety and Health Administration and are as follow:

	ACGIH (1977) Threshold Limit Values	
Trichloronaphthalene	5	mg/m^3
Tetrachloronaphthalene	2	mg/m^3
Pentachloronaphthalene	0.5	mg/m^3
Hexachloronaphthalene	0.2	mg/m^3
Octachloronaphthalene	0.1	mg/m^3

There are no state or federal water quality or ambient air quality standards for chlorinated naphthalenes.

The U.S. EPA is presently evaluating the available data and has recommended that a single acceptable daily intake (ADI) of 70 µg/man/day be used for the tri-, tetra-, penta-, hexa-, and octa-chlorinated naphthalenes. This ADI will be used to derive the human health criteria for the chlorinated naphthalenes.

B. Aquatic

For 1-chloronaphthalene, the draft criterion to protect freshwater aquatic life is 29 μg/l as a 24-hour average, not to exceed 67 μg/l at any time. For saltwater aquatic species, the draft criteron is 2.8 μg/l as a 24-hour average, not to exceed 6.4 μg/l at any time (U.S. EPA, 1979).

CHLORINATED NAPHTHALENE

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No. 39

Chlorinated Phenols

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

The National Cancer Institute (1979) has recently published the results of a bioassay indicating that 2,4,6-trichlorophenol induced cancer in rats and mice. This study was not included in the Ambient Water Quality Criteria Document (U.S. EPA, 1979) and has not been reviewed for this hazard profile.

CHLORINATED PHENOLS

SUMMARY

Mammalian data supporting chronic effects for most of these compounds is limited. Insufficient data exist to indicate that any of the chlorinated phenols are carcinogens. In skin painting studies, 3-chlorophenol and 2,4,5-trichlorophenol promoted papillomas. A lifetime feeding study with 2,4,6-trichlorophenol was inconclusive and only provided weak suspicion of carcinogenicity. 2,4,6-Trichlorophenol gave some evidence of mutagenicity in two assays. Tetrachlorophenol was not found to be fetotoxic in animals. Chronic exposure to 4-chlorophenol produced myoneural disorders in humans and animals. Adverse health effects in workers exposed to 2,4,5-trichlorophenol may have been due to 2,3,7,8-tetrachlorodibenzo-p-dioxin contamination of the chlorophenol.

Workers chronically exposed to tetrachlorophenol, pentachlorophenol, and small amounts of chlorodibenzodioxins developed severe skin irritations, respiratory difficulties, and headaches. Chlorophenols are uncouplers of oxidative phosphorylation. 2,6-Dichlorophenol and trichlorocresol are convulsants. Chlorocresol has caused several cases of local and generalized reactions.

In acute toxicity tests, 4-chloro-3-methylphenol has been proven toxic at concentrations as low as 30 μg/l in freshwater fish, whereas other freshwater and marine organisms appear to be more resistant. The tainting of rainbow trout flesh has been demonstrated at exposures of 15 to 84 μg/l for several of the chlorinated phenols.

I. INTRODUCTION

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

The chlorinated phenols represent a group of commercially produced substituted phenols and cresols also referred to as chlorophenols or chlorocresols. The compounds 2-chlorophenol, 2,4-dichlorophenol, 2,4,6-trichlorophenol, and pentachlorophenol are discussed in separate hazard profiles.

Purified chlorinated phenols are colorless, crystalline solids (with the exception of 2-chlorophenol which is a liquid), while the technical grades may be light tan or slightly pink due to impurities. Chlorophenols have pungent odors. In general, the volatility of chlorinated phenols decreases and the melting and boiling points increase as the number of substituted chlorine atoms increases. Although the solubility of chlorinated phenols in aqueous solutions is relatively low, it increases markedly when the pH of the solution exceeds the specific pKa. The solubilities of chlorinated phenols and chlorocresols (with the exception of 2,4,6-trichloro-m-cresol) range from soluble to very soluble in relatively non-polar solvents such as benzene and petroleum ether (U.S. EPA, 1979).

The chlorinated phenols that are most important commercially are 4-chlorophenol, 2,4-dichlorophenol, 2,4,5-trichlorophenol, 2,3,4,6-tetrachlorophenol, pentachlorophenol, and 4-chloro-o-cresol. Many of the chlorophenols have no commercial application but are produced to some extent as byproducts of the commercially important compounds. The highly toxic polychlorinated dibenzo-p-dioxins may be formed during the chemical synthesis of some chlorophenols. During the chlorination of drinking waters and wastewater effluents, chlorophenols may be inadvertently produced (U.S. EPA, 1979).

Chlorinated phenols are used as intermediates in the synthesis of dyes, pigments, phenolic resins, pesticides, and herbicides. Certain chlorophenols are used directly as flea repellants, fungicides, wood preservatives, mold inhibitors, antiseptics, disinfectants, and antigumming agents for gasoline.

It is generally accepted that chlorinated phenols will undergo photolysis in aqueous solutions as a result of ultraviolet irradiation and that photodegradation leads to the substitution of hydroxyl groups in place of the chlorine atoms with subsequent polymerization (U.S. EPA, 1979). Microbial degradation of chlorophenols has been reported by numerous investigators (U.S. EPA, 1979).

3-CHLOROPHENOL and 4-CHLOROPHENOL

II. EXPOSURE

Monochlorophenols have been found in surface waters in the Netherlands at concentrations of 2 to 20 μg/l (Piet and DeGrunt, 1975). Ingestion of chlorobenzene can give rise to internal exposure to 2-, 3-, and 4-chlorophenols, as chlorobenzene is metabolized to monochlorophenols (Lindsay-Smith, et al. 1972). No data were found demonstrating the presence of monochlorophenol in food.

For 4-chlorophenol the U.S. EPA has estimated the weighted average bioconcentration factor for the edible portions of all aquatic organisms consumed by Americans to be 12. This estimate is based on the octanol/water partition coefficient.

Data were not found in the available literature regarding inhalation exposure.

III. PHARMACOKINETICS

Systematic studies of the pharmacokinetics of 3- or 4-chlorophenol are not available. Dogs excreted 87 percent of administered 4-chlorophenol in the urine as sulfuric and glucuronic conjugates (Karpow, 1893).

IV. EFFECTS

A. Carcinogenicity

Information is not adequate to determine whether 3- or 4-chlorophenol possess carcinogenic properties. A 20 percent solution of 3-chlorophenol promoted papillomas when repeatedly applied to the backs of mice after initiation with dimethylbenzanthrene (Boutwell and Bosch, 1959).

B. Mutagenicity, Teratogenicity and Other Reproductive Effects

Pertinent data cannot be located in the available literature regarding mutagenicity, teratogenicity and other reproductive effects.

C. Chronic Toxicity

Rats exposed 6 hrs/day for four months to 2 mg 4-chlorophenol/m^3 showed a temporary weight loss and increased myoneural excitability. Body temperature and hematological parameters were not altered (Gurova, 1964). In a survey comparing the health of workers, 4-chlorophenol exposed workers had a significantly higher incidence of neurological disorders compared to unexposed workers in the same plant. Peripheral nerve stimulation studies showed increased myoneural excitability in exposed workers. The minimum detection distance in a two-point touch discrimination test was increased (Gurova, 1964).

D. Other Relevant Information

3- and 4-Chlorophenol are weak uncouplers of oxidative phosphorylation (Mitsuda, et al. 1963; Weinback and Garbus, 1965).

2,5-DICHLOROPHENOL, 2,6-DICHLOROPHENOL, 3,4-DICHLOROPHENOL, and 3,5-DICHLOROPHENOL

II. EXPOSURE

Unspecified dichlorophenol isomers have been detected in concentrations of 0.01 to 1.5 μg/l in Dutch surface waters (Piet and DeGrunt, 1975). Dichlorophenols have been found in flue gas condensates from municipal incinerators (Olie, et al. 1977). No data on exposure from foods or the dermal route were found. Exposure to other chemicals can result in exposure to dichlorophenols (i.e., dichlorobenzenes, lindane, and the alpha and delta isomers of 1,2,3,4,5,6-hexachlorocyclohexane are metabolized by mammals to dichlorophenols) (Kohli, et al. 1976; Foster and Saha, 1978).

III. PHARMACOKINETICS

Pharmacokinetic data specific to these dichlorophenol isomers could not be located in the available literature.

IV. EFFECTS

A. Carcinogenicity

Pertinent data cannot be located in the available literature.

B. Mutagenicity

2,3-, 2,4-, 2,5-, 2,6-, 3,4-, and 3,5-Dichlorophenols were found to be non-mutagenic in the Ames test with or without microsomal activation (Rasaner and Hattula, 1977).

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data cannot be located in the available literature regarding teratogenicity, other reproductive effects and chronic toxicity.

D. Other Relevant Information

2,6-Dichlorophenol is a convulsant (Farquharson, et al. 1958).

II. EXPOSURE

Trichlorophenols have been detected in surface waters in Holland at concentrations ranging from 0.003 to 0.1 μg/l (Piet and DeGrunt, 1975). 2,4,5-Trichlorophenol can be formed from the chlorination of phenol in water (Burttschell, et al. 1959).

One possible source of trichlorophenol exposure for humans is through the food chain, as a result of the ingestion by grazing animals of the chlorophenoxy acid herbicides 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and silvex (2-(2,4,5-trichlorophenoxy)-propionic acid). Residues of the herbicides on sprayed forage are estimated to be 100-300 ppm. Studies in which cattle and sheep were fed these herbicides at 300, 1000 and 2000 ppm (Clark, et al. 1976) showed the presence of 2,4,5-trichlorophenol in various tissues. In lactating cows fed 2,4,5-T at 100 ppm, an occasional residue of 0.06 ppm or less of trichlorophenol was detected in milk (Bjerke, et al. 1972).

Exposure to other chemicals such as trichlorobenzenes, lindane, the alpha and delta isomers of 1,2,3,4,5,6-hexachlorocyclohexane, isomers of benzene hexachloride, and the insecticide Ronnel can result in exposure to trichlorophenols via metabolic degradation of the parent compound (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factors for the edible portions of all aquatic organisms consumed by Americans to be 130 for 2,4,5-trichlorophenol and 110 for 2,4,6-trichlorophenol. These estimates are based on the octanol/water partition coefficients for these chemicals.

Trichlorophenols are found in flue gas condensates from municipal incinerators (Olie, et al. 1977). 2,4,5-Trichlorophenol was detected in 1.7 percent of urine samples collected from the general population (Kutz, et al. 1978).

III. PHARMACOKINETICS

A. Absorption and Distribution

Information dealing with tissue distribution after administration of trichlorophenols could not be located in the available literature. Feeding of 2,4,5-T and silvex to sheep and cattle produced high levels of 2,4,5-trichlorophenol in liver and kidney and low levels in muscle and fat (Clark, et al. 1976).

B. Metabolism

Pertinent data could not be located in the available literature.

C. Excretion

In rats, 82 percent of an administered dose (1 ppm in the diet for 3 days) of 2,4,6-trichlorophenol was eliminated in the urine and 22 percent in the feces. Radiolabelled trichlorophenol was not detected in liver, lung or fat obtained 5 days after the last dose (Korte, et al. 1978). The approximate blood half-life for 2,4,5-trichlorophenol is 20 hours, after dosing of sheep with Erbon (an herbicide which is metabolized to 2,4,5-trichlorophenol) (Wright, et al. 1970).

IV. EFFECTS

A. Carcinogenicity

A 21 percent solution of 2,4,5-trichlorophenol in acetone promoted papillomas but not carcinomas in mice after initiation with dimethylbenzan-

threne (Boutwell and Bosch, 1959). 2,4,6-Trichlorophenol showed no promoting activity.

Results from a study of mice receiving 2,4,6-trichlorophenol in the diet throughout their lifespans (18 months) were inconclusive. The incidence of tumors, while higher than that for compounds classified as noncarcinogens, was not significantly increased (Innes, et al. 1969).

B. Mutagenicity

2,4,6-Trichlorophenol (400 mg) increased the mutation rate but not the rate of intragenic recombination in a strain of Saccharomyces cerevisiae (Fahrig, et al. 1978). Two of the 340 offspring from mice injected with 50 mg/kg of 2,4,6-trichlorophenol during gestation were reported to have changes in hair coat color (spots) of genetic significance. At 100 mg/kg, 1 out of 175 offspring had a spot (U.S. EPA, 1979). 2,3,5-, 2,3,6-, 2,4,5-, and 2,4,6-Trichlorophenol were found to be nonmutagenic in the Ames test with and without microsomal activation (Rasanen and Hattula, 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

When rats were fed 2,4,5-trichlorophenol (99 percent pure) for 98 days (McCollister, et al. 1961), levels of 1000 mg trichlorophenol/kg feed (assumed to be equivalent to 100 mg/kg body weight) or less produced no adverse effects as judged by behavior, mortality, food consumption, growth, terminal hematology, body and organ weights, and gross or microscopic pathology. At 10,000 mg/kg diet (1000 mg/kg body weight), growth was slowed in females. Histopathologic changes were noted in liver and kidney. There

were no hematologic changes. At 3000 mg/kg feed (300 mg/kg body weight), milder histopathologic changes in liver and kidney were observed. The histopathologic changes were considered to be reversible.

Adverse health effects including chloracne, hyperpigmentation, hirsutism and elevated uroporphyrins were described in 29 workers involved in the manufacture of 2,4-D and 2,4,5-T (Bleiberg, et al. 1964). It is likely that some of these symptoms represent 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicosis (U.S. EPA, 1979).

E. Other Relevant Information

Trichlorophenols are uncouplers of oxidative phosphorylation (Weinback and Garbus, 1965; Mitsuda, et al. 1963).

TETRACHLOROPHENOL

II. EXPOSURE

There are three isomers of tetrachlorophenol: 2,3,4,5-, 2,3,5,6-, and, most importantly, 2,3,4,6-tetrachlorophenol. Commercial pentachlorophenol contains three to 10 percent tetrachlorophenol (Goldstein, et al. 1977; Schwetz, et al. 1978). Commercial tetrachlorophenol contains pentachlorophenol (27 percent) and toxic nonphenolic impurities such as chlorodibenzofurans and chlorodioxin isomers (Schwetz, et al. 1974). There are reports suggesting the presence of lower chlorophenols in drinking water, but the presence of tetrachlorophenol has not been documented (U.S. EPA, 1979). Exposure to other chemicals such as tetrachlorobenzenes can result in exposure to tetrachlorophenols via degradation of the parent compound (Kohli, et al. 1976).

Data could not be located in the available literature on ingestion from foods. The U.S. EPA (1979) has estimated a weighted average bioconcentra-

tion factor for 2,3,4,6-tetrachlorophenol of 320 for the edible portion of aquatic organisms consumed by Americans. This estimate is based on the octanol/water partition coefficient of 2,3,4,5-tetrachlorophenol.

Tetrachlorophenols have been found in flue gas condensates from municipal incinerators (Olie, et al. 1977).

II. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data could not be located in the available literature regarding absorption and distribution.

B. Metabolism and Excretion

In rats, over 98 percent of an intraperitoneally administered dose of 2,3,5,6-tetrachlorophenol was recovered in the urine in 24 hours. About 66 percent was excreted as the unchanged compound and 35 percent as tetrachloro-p-hydroquinone. About 94 percent of the intraperitoneal dose of 2,3,4,6-tetrachlorophenol was recovered in the urine in 24 hours, primarily as the unchanged compound with trace amounts of trichloro-p-hydroquinone. Fifty-one percent of the intraperitoneal dose of 2,3,4,5-tetrachlorophenol was recovered in the urine in 24 hours, followed by an additional seven percent in the second 24 hours, primarily as the unchanged compound with trace amounts of trichloro-p-hydroquinone. In these experiments, the urine was boiled to split any conjugates (Alhborg and Larsson, 1978).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

2,3,4,6-Tetrachlorophenol was reported to be nonmutagenic in the Ames test, both with and without microsomal activation (Rasanen, et al. 1977).

C. Teratogenicity

Tetrachlorophenol did not induce teratogenic effects in rats at doses of 10 or 30 mg/kg administered on days six through 15 of gestation (Schwetz, et al. 1974).

D. Other Reproductive Effects

Tetrachlorophenol produced fetotoxic effects (subcutaneous edema and delayed ossification of skull bones) in rats at doses of 10 and 30 mg/kg administered on days six through 15 of gestation (Schwetz, et al. 1974).

E. Chronic Toxicity

Workers exposed to wood dust containing 100-800 ppm 2,3,4,6-tetrachlorophenol, 30-40 ppm pentachlorophenol, 10-50 ppm chlorophenoxyphenols, 1-10 ppm chlorodibenzofurans and less than 0.5 ppm chlorodibenzo-p-dioxins developed severe skin irritations, respiratory difficulties and headaches (Levin, et al. 1976).

No toxicity studies of 90 days or longer were found in the available literature.

F. Other Relevant Information

2,3,4,6-Tetrachlorophenol is a strong uncoupler of oxidative phosphorylation (Mitsuda, et al. 1963; Weinback and Garbus, 1965).

CHLOROCRESOLS

II. EXPOSURE

There are no published data available for the determination of current human exposure to chlorocresols (U.S. EPA, 1979). p-Chloro-m-cresol (4-chloro-3-methylphenol) has been detected in chlorinated sewage treatment effluent (Jolley, et al. 1975). Another potential source of chlorocresols is the herbicide MCPA (4-chloro-2-methylphenoxyacetate), which (in its tech-

nical grade) is contaminated with four percent 4-chloro-o-cresol (Rasanen, et al. 1977) and which can be degraded to 5-chloro-o-cresol (Gaunt and Evans, 1971).

III. PHARMACOKINETICS

A. Absorption

Chlorocresol (unspecified isomer) permeated human autopsy skin more readily than either 2- or 4-chlorophenol, but less readily than 2,4,6-trichlorophenol (Roberts, et al. 1977).

B. Distribution and Metabolism

Pertinent data could not be located in the available literature.

C. Excretion

Fifteen to 20 percent of a subcutaneous dose of p-chloro-m-cresol given to a rabbit was recovered in the urine. The same compound given intramuscularly was not recovered in the urine to any appreciable extent (Zondek and Shapiro, 1943).

IV. EFFECTS

A. Carcinogenicity

Pertinent information could not be located in the available literature.

B. Mutagenicity

3-Chloro-o-cresol, 4-chloro-o-cresol and 5-chloro-o-cresol were reported to be nonmutagenic in the Ames test, with and without microsomal activation (Rasanen, et al. 1977).

C. Teratogenicity and Other Reproductive Effects

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

D. Chronic Toxicity

No information on chronic toxicity in humans or toxicity studies of 90 days or longer in experimental animals were presented in the Ambient Water Quality Criteria Document (U.S. EPA, 1979). p-Chloro-m-cresol given subcutaneously to young rats for 14 days (80 mg/kg/day) produced mild inflammation at the injection site but did not affect growth or produce lesions in kidney, liver, or spleen (Wien, 1939). Rabbits (weighing 1.5-2.3 kg) injected subcutaneously with 12.5 mg p-chloro-m-cresol/day suffered no obvious ill effects (Wien, 1939). Liver and kidney were normal histologically.

E. Other Relevant Information

Chlorocresol, a preservative in heparin solutions, caused several cases of generalized and local reactions (Hancock and Naysmith, 1975; Ainley, et al. 1977). Systemic reactions included collapse, pallor, sweating, hypotension, tachycardia and rashes. Trichlorocresol is also a convulsant (Eichholz and Wigand, 1931).

CHLORINATED PHENOLS

I. AQUATIC TOXICITY

A. Acute Toxicity

The acute toxicity of eight chlorophenols was determined in nine bioassays. Acute 96-hour LC_{50} values for freshwater fish ranged from 30 µg/l for the fathead minnow, Pimephales promelas, for 4-chloro-3-methylphenol (U.S. EPA, 1972) to 9,040 µg/l for the fathead minnow for 2,4,6-trichlorophenol (Phipps, et al. manuscript). Among the freshwater invertebrates, Daphnia magna was assayed with seven chlorophenols in eight 48-hour static bioassays. Acute LC_{50} values ranged from 290 µg/l for 2,3,4,6-tetrachlorophenol and 4-chloro-2-methylphenol to 6,040 µg/l for 2,4,6-tri-

chlorophenol (U.S. EPA, 1978). Acute 96-hour static LC_{50} values in the sheepshead minnow ranged from 1,660 µg/l for 2,4,5-trichlorophenol to 5,350 µg/l for 4-chlorophenol. The only marine invertebrate species acutely tested has been the mysid shrimp, Mysidopsis bahia , with acute 96-hour static LC_{50} values reported by the U.S. EPA (1978) as: 3,830 µg/l for 2,4,5-trichlorophenol; 21,900 µg/l for 2,3,5,6-tetrachlorophenol, and 29,700 µg/l for 4-chlorophenol.

B. Chronic Toxicity

No data other than that presented in the specific hazard profile for 2-chlorophenol, 2,4-dichlorophenol, and pentachlorophenol were available for freshwater organisms. An embryo-larval study provided a chronic value of 180 µg/l for sheepshead minnows, Cyprinodon variegatus, exposed to 2,4-dichloro-6-methylphenol (U.S. EPA, 1978).

C. Effects on Plants

Effective concentrations for 15 tests on four species of freshwater plants ranged from chlorosis LC_{50} of 603 µg/l for 2,3,4,6-tetrachlorophenol to 598,584 µg/l for 2-chloro-6-methylphenol in the duckweed, Lemna minor (Blackman, et al. 1955). The marine algae, Skeletonema costatum, has been used to assess the relative toxicities of three chlorinated phenols. Effective concentrations, based on chlorophyll a content and cell growth, of 440 and 500 µg/l were obtained for 2,3,5,6-tetrachlorophenol. 2,4,5-Trichlorophenol and 4-chlorophenol were roughly two and seven times as potent, respectively, as 2,3,5,6-tetrachlorophenol.

D. Residues

Steady-state bioconcentration factors have not been calculated for the chlorinated phenols. However, based upon octanol/water partition coefficients, the following bioconcentration factors have been estimated for

aquatic organisms with a lipid content of eight percent: 41 for 4-chlorophenol; 440 for 2,4,5-trichlorophenol; 380 for 2,4,6-trichlorophenol; 1,100 for 2,3,4,6-tetrachlorophenol; and 470 for 4-chloro-3-methylphenol.

E. Miscellaneous

The tainting of fish flesh by exposure of rainbow trout, Salmo gairdneri, to various chlorinated phenols has derived a range of estimated concentrations not impairing the flavor of cooked fish from 15 µg/l for 2-chlorophenol to 84 µg/l for 2,3-dichlorophenol (Schulze, 1961; Shumway and Palensky, 1973).

II. 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. Draft criteria recommended for chlorinated phenols by the U.S. EPA (1979) are given in the following table:

Draft Ambient Water Quality Criteria

Compound	Criterion from Organoleptic Effects	Criterion from Toxicological Data
Monochlorophenols		
3-chlorophenol	50 µg/l	none
4-chlorophenol	30 µg/l	none
Dichlorophenols		
2,5-dichlorophenol	3.0 µg/l	none
2,6-dichlorophenol	3.0 µg/l	none
Trichlorophenols		
2,4,5-trichlorophenol	10 µg/l	1600 µg/l
2,4,6-trichlorophenol	100 µg/l	
Tetrachlorophenol*		
2,3,4,6-tetrachlorophenol	915 µg/l	263 µg/l

Chlorocresol

Insufficient data on which to base a criterion

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*The criterion will be based on toxicological effects (U.S. EPA, 1979).

8. Aquatic

The proposed draft criterion for 2,4,6-trichlorophenol is 52 µg/l, not to exceed 150 µg/l in freshwater environments. No additional criterion for other chlorinated phenols can presently be derived for either freshwater or marine organisms because of insufficient data (U.S. EPA, 1979).

CHLORINATED PHENOLS

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No. 40

Chloroacetaldehyde

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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

CHLOROACETALDEHYDE

Summary

No carcinogenic effects were observed in female ICR Ha Swiss mice following administration of chloroacetaldehyde via dermal application or subcutaneous injection. Mutagenic effects, varying from weak to strong, have been reported in the yeasts *Schizosaccharomyces pombe* and *Saccharomyces cerivisiae* and in certain *Salmonella* bacterial tester strains. There is no evidence in the available literature to indicate that chloroacetaldehyde produces teratogenic effects. Occupational exposure studies have shown chloroacetaldehyde to be a severe irritant of the eyes, mucous membranes and skin.

Data concerning the effects of chloroacetaldehyde on aquatic organisms were not found in the available literature.

CHLOROACETALDEHYDE

INTRODUCTION

Chloroacetaldehyde (C_2H_3ClO) is a clear, colorless liquid with a pungent odor. Its physical properties include: boiling point, 90.0-100.1°C (40 percent sol.); freezing point, -16.3°C (40 percent sol.); and vapor pressure, 100 mm at 45°C (40 percent sol.). Synonyms for chloroacetaldehyde are: monochloroacetaldehyde, 2-chloroacetaldehyde and chloroaldehyde. It is soluable in water, acetone and methanol. Primary uses of chloroacetaldehyde include: use as a fungicide, use in the manufacture of 2-aminothiazole, and use in the removal of bark from tree trunks.

II. EXPOSURE

No monitoring data are available to indicate ambient air or water levels of chloroacetaldehyde, nor is any information available on possible exposure from food.

Occupational routes of human exposure to chloroacetaldehyde are primarily through inhalation and skin absorption.

Bioaccumulation data on chloroacetaldehyde were not found in the available literature. However, 2-chloroacetaldehyde is known to be a chemically reactive compound and its half-life in aqueous solution has been reported as slightly greater than 24 hours (Van Duuren et al., 1972).

III. PHARMACOKINETICS

A. Absorption

Exposure to chloroacetaldehyde is primarily through inhalation and skin absorption.

Chloroacetaldehyde proved to be very lethal by inhalation. In an inhalation study conducted by Lawrence et al. (1972), mice were placed in a chloroacetaldehyde-free chamber and air containing chloroacetaldehyde vapor was then passed

through the chamber. The time of exposure required to kill 50% of the animals, LT_{50}, was 2.57 min. (the chamber atmosphere was calculated to have reached 45% equilibrium within that time.)

In comparison studies conducted on chloroacetaldehyde and 2-chloroethanol, chloroacetaldehyde was reported as exhibiting greater irritant activity, but having lesser penetrant capacity (Lawrence et al., 1972).

B. Distribution

Information on the distribution of chloroacetaldehyde was not found in the available literature.

C. Metabolism

Chloroacetaldehyde appears to be a metabolite of a number of compounds including 1,2-dichloroethane, chloroethanol and vinyl chloride (McCann et al., 1975).

Johnson (1967) conducted in vitro studies on rat livers, the results of which indicated that S-carboxymethylglutathione was probably formed via chloroacetaldehyde metabolic action. Based upon these studies, Johnson suggested that the same metabolic mechanism was operative in the in vivo conversion of chloroethanol to S-carboxymethylglutathione.

In recent studies, Watanabe et al. (1976a,b) reported that chloroacetaldehyde would conjugate with glutathione and cysteine leading ultimately to the types of urinary metabolites found in animals exposed to vinyl chloride. The authors reported that as nonprotein free sulfhydral concentrations are depleted, the alkylating metabolites, one of which is chloroacetaldehyde, are likely to react with protein, DNA and RNA, eliciting proportionally greater toxicity. This is in agreement with other studies conducted on vinyl chloride metabolism (Hefner et al., 1975; Bolt et al., 1977).

Chloroacetaldehyde was shown to cause the destruction of lung hemoprotein, cytochrome P450, as well as liver microsomal cytochrome P450, with no requirement for NADPH (Harper and Patel, 1978). The results suggested that the aldehydes tested, one of which was chloroacetaldehyde, were the toxic intermediates which inactivated pulmonary enzymes following exposure to some environmental agents.

D. Excretion

Information specifically on the rates and routes of chloroacetaldehyde elimination was not found in the available literature. Studies on vinyl chloride and ethylene dichloride, however, indicate that chloroacetaldehyde, as an intermediate metabolite, may ultimately convert to a number of urinary metabolites--including chloroacetic acid, S-carboxymethylcysteine and thiodiacetic acid--depending on the particular metabolic pathway involved in the biotransformation of the parent compound (Johnson, 1967; Yllner, 1971; Watanabe, 1976a,b).

IV. EFFECTS

A. Carcinogenicity

In a study on the carcinogenic activity of alkylating agents, Van Duuren et al. (1974) exposed female ICR Ha Swiss mice to 2-chloroacetaldehyde (assayed as diethylacetal). The routes of administration were via skin and subcutaneous injection. The authors reported no significant tumor induction. Later studies confirmed these findings (Goldschmidt, personal communication, 1977). However, in a report by McCann et al. (1975), the authors stated that previous reports of changes of respiratory epithelium in lungs of rats exposed to chloroacetaldehyde were suggestive of premalignant conditions.

B. Mutagenicity

Many studies have been reported which show that chloroacetaldehyde exhibits varying degrees of mutagenic activity (Huberman et al., 1975; Border

and Webster, 1976; Elmore et al., 1976; Rosenkranz, 1977). Loprieno et al. (1977) reported that 2-chloroacetaldehyde showed only feeble genetic activity when tested in the yeasts Schizosaccharomyces pombe and Saccharomyces cerevisiae. However, McCann et al. (1975) reported that chloroacetaldehyde was quite effective in reverting Salmonella bacterial tester strain TA 100, but did not revert TA 1535. In a later study, Rosenkranz (1977) found that 2-chloroacetaldehyde did display some mutagenic activity towards TA 1535.

In a study conducted by Elmore et al. (1976) the authors reported that the chloroacetaldehyde monomer and monomer hydrate were more mutagenically active that the dimer hydrate and the trimer.

Rannug et al. (1976) reported that the mutagenic effectiveness of chloroacetaldehyde is about 10^4 times higher than expected from kinetic data.

C. Teratogenicity and Other Reproductive Effects

Pertinent information could not be found in the available literature.

D. Chronic Toxicity

No chronic information could be found in the available literature. However, extensive toxicity studies conducted by Lawrence et al. (1972) revealed some subacute effects of chloroacetaldehyde on Sprague-Dawley and Black Bethesda rats. Groups of rats received .001879 and .003758 ml/kg of chloroacetaldehyde (representing 0.3 and 0.6 of the acute LD_{50} dose, respectively) daily for 30 consecutive days. Hematologic tests at the end of 30 days showed that there was a significant decrease in hemoglobin, hematocrit, and erthrocytes in the high dose group; the low dose group showed an increase in monocytes accompanied by a decrease in lymphocytes. The animals were sacrificed and organ-to-body weight ratios were calculated. Ratios for both brain and lungs were significantly greater in the low dose group, while the high dose group showed a significant increase in the brain, gonads, heart, kidneys, liver, lungs and spleen.

Histological examination did not reveal any abnormalities attributable to chloroacetaldehyde except for the lungs which showed more severe bronchitis, bronchiolitis and bronchopneumonia than were seen in controls.

In another subacute (subchronic) study, chloroacetaldehyde was administered to rats in doses of .00032, .00080, .00160 and .00320 ml/kg, three times a week for 12 weeks. Hematologic determinations showed no significant differences between controls and the two lower dose groups, while animals administered .0016 ml/kg showed a decrease in red cell count and lymphocytes and an increase in segmented neutrophiles; the highest dose group showed a significant decrease in red blood cells and hemoglobin with an increase in clotting time and segmented neutrophiles. Organ-to-body weight ratios were determined for several organs and, although there were some significant differences from controls, there were no apparent dose-related responses.

D. Acute Toxicity

Lawrence et al. (1972) conducted a series of acute toxicity tests on ICR mice, Sprague-Dawley and Black Bethesda rats, New Zealand albino rabbits and Hartlez strain guinea pigs. The results were reported as follows: the LD_{50}s (ml/kg) for chloroacetaldehyde administered intraperitoneally ranged from .00598 in mice to .00464 in rabbits; the LD_{50}s (ml/kg) for chloroacetaldehyde administered intragastrically were reported as .06918 in male mice, .07507 in female rats and .08665 in male rats; the dermal LD_{50} (ml/kg) in rabbits was reported as .2243; and the inhalation LT_{50} in mice was reported as 2.57 min.

E. Other Relevent Information

Case studies show that contact with a strong solution of chloroacetaldehyde in the human eye will likely result in permanent impairment of vision and skin contact with a potent solution will result in burns (Proctor and Hughes, 1978).

V. AQUATIC TOXICITY

Data concerning the effects of chloroacetaldehyde on aquatic organisms were not found in the available literature.

VI. EXISTING GUIDELINES

The 8-hour, TWA occupational exposure limit established for chloroacetaldehyde is 1 ppm. This TLV of 1 ppm was set to prevent irritation (ACGIH, 1976).

CHLOROACETALDEHYDE

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No. 41

Chloroalkyl Ethers

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

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

SPECIAL NOTATION

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

CHLOROALKYL ETHERS

SUMMARY

Bis(chloromethyl)ether (BCME), chloromethyl methyl ether (CMME), and bis(2-chloroethyl)ether (BCEE) have shown carcinogenic effects in animal studies following administration by various routes. Epidemiological studies in the United States, Germany, and Japan have indicated that workers exposed to BCME and CMME developed an increased incidence of respiratory tract tumors.

Testing of BCME, CMME, BCEE, and bis(2-chloroisopropyl)-ether (BCIE) in the Ames *Salmonella* assay and in *E. coli* have indicated that these compounds have mutagenic activity. Cytogenetic studies of lymphocytes from workers exposed to BCME and CMME have reported an increased frequency of aberrations, which appear to be reversible.

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

The information base for freshwater organisms and chloroalkyl ethers is limited to a few toxicity tests of 2-chloroethyl vinyl ether and bis(2-chloroethyl)ether. The reported 96-hour LC_{50} value for bis(2-chloroethyl)ether in the bluegill is greater than 600,000 µg/l. A "no effect" value of 19,000 µg/l was observed using the fathead minnow in an embryo-larval test. Bis(2-chloroethyl)ether has a reported bioconcentration factor of 11 in a 14-day exposure to bluegills. The half-life is from four to seven days. The reported 96-hour LC_{50} value for the bluegill and 2-chloroethyl vinyl ether is 194,000 µg/l.

CHLOROALKYL ETHERS

I. INTRODUCTION

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

The chloroalkyl ethers are compounds with a hydrogen atom in one or both of the aliphatic ether chains substituted by a chlorine atom. The chemical reactivity of these compounds varies greatly, depending on the nature of the aliphatic groups and the placement of the chlorine atoms. The most reactive compounds are those with short aliphatic groups and those in which chlorine substitution is closest to the ether oxygen (alpha-chloro) (U.S. EPA, 1979).

As an indication of their high reactivity, chloromethyl methyl ether (CMME), bis(chloromethyl)ether (BCME), 1-chloroethyl ethyl ester, and 1-chloroethyl methyl ether decompose rapidly in water. The beta-chloroethers, bis(2-chloroethyl)-ether (BCEE) and bis(2-chloroisopropyl)ether (BCIE) are more stable in aqueous systems; they are practically insoluble in water but miscible with most organic solvents (U.S. EPA, 1979).

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

While the short chain alpha-chloroalkyl ethers (BCME,, CMME) are very unstable in aqueous systems, they appear to be relatively stable in the atmosphere (Tou and Kallos, 1974). Bis(chloromethyl)ether will form spontaneously in the pres-

ence of both hydrogen chloride and formaldehyde (Frankel, et al. 1974).

II. EXPOSURE

The beta-chloroalkyl ethers have been monitored in water. Industrial effluents from chemical plants involved in the manufacture of glycol products, rubber, and insecticides may contain high levels of these ethers (U.S. EPA, 1979). The highest concentrations in drinking water of bis(2-chloroethyl)ether, bis(2-chloroisopropyl)ether, and bis-1,2-(2-chloroethoxy)ethane (BCEXE) reported by the U.S. EPA (1975) are 0.5, 1.58, and 0.03 µg/l, respectively. The average concentration of these compounds in drinking water is in the nanogram range (U.S. EPA, 1979). Chloroalkyl ethers have been detected in the atmosphere, and human inhalation exposure appears to be limited to occupational settings.

The chloroalkyl ethers have not been monitored in food (U.S. EPA, 1979). The betachloroalkyl ethers, because of their relative stability and low water solubility, may have a tendency to be bioaccumulated. The U.S. EPA (1979) has estimated the weighted bioconcentration factor to be 25 for the edible portions of fish and shellfish consumed by Americans. This is based on the measured steady-state bioconcentration studies in bluegills. Bioconcentration factors for BCME (31) and BCIE (106) have been derived using a proportionality constant related to octanol/water partition coefficients (U.S. EPA, 1979). Dermal exposure for the chloroalkyl ethers has not been determined (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Experiments with radio-labelled BCIE and BCEE in female rats and monkeys have indicated that both compounds are readily absorbed in the blood following oral administration (Smith, et al., 1977; Lingg, et al., 1978). Pertinent data could not be located in the available literature retrieved on dermal or inhalation absorption of the alkyl ethers.

B. Distribution

Species differences in the distribution of radio-labelled BCIE have been reported by Smith, et al. (1977). Monkeys, as compared to rats, retain higher amounts of radioactivity in the liver, muscle, and brain. Urine and expired air from the rat contained higher levels of radioactivity than those found in the monkey. Blood levels of BCIE in monkeys reached a peak within two hours following oral administration and then declined in a biphasic manner ($t_{1/2}$'s = 5 hours and 2 days for the first and second phases, respectively).

C. Metabolism

The biotransformation of BCEE in rats following oral administration appears to involve cleavage of the ether linkage and subsequent conjugation (Lingg, et al., 1978). Thiodiglycolic acid and chloroethanol-D-glucuronide were identified as urinary metabolites of BCEE. Metabolites of BCIE identified in the rat included 1-chloro-2-propanol, propylene oxide, 2-(1-methyl-2-chloroethoxy)-propionic acid, and carbon dioxide (Smith, et al., 1977).

D. Excretion

BCEE administered orally to rats was excreted rapidly, with more than 60 percent of the compound excreted within 24 hours. Virtually all of this elimination was via the urine (Lingg, et al., 1978).

IV. EFFECTS

A. Carcinogenicity

There are several studies with bis(chloromethyl)-ether (BCME), chloromethyl methyl ether (CMME), and bis(2-chloroethyl)ether (BCEE) that show carcinogenic effects. BCME induced malignant tumors of the male rat respiratory tract following inhalation exposure (Kuschner, et al., 1975). Application of BCME and BCEXE to the skin of mice produced skin tumors (Van Duuren, et al., 1968), while subcutaneous injection of BCME to newborn mice induced pulmonary tumors (Gargus, et al., 1969).

Oral administration of bis(2-chloroethyl)ether (BCEE) to mice has been shown to increase the incidence of hepatocellular carcinomas in males (Innes, et al., 1969).

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

Both BCME and CMME have been shown to accelerate the rate of lung tumor formation in Strain A mice following inhalation exposure (Leong, et al., 1971). BCME and BCEE have shown tumor initiating activity for mouse skin, while CMME showed only weak initiating activity (U.S. EPA, 1979).

Preliminary results of a National Cancer Institute study indicate that oral administration of BCIE does not produce an increase in tumor incidence (U.S. EPA, 1979).

B. Mutagenicity

Testing of the chloroalkyl ethers in the Ames *Salmonella* assay on *E. coli* have indicated that BCME, CMME, BCIE, and BCEE all produced mutagenic effects (U.S. EPA, 1979). BCEE has also been reported to induce mutations in *Saccharomyces cerevisiae* (U.S. EPA, 1979). Neither BCEE nor BCIE showed mutagenic effects in the heritable translocation test in mice (Jorganson, et al. 1977). An increase in cytogenetic aberrations in the lymphocytes of workers exposed to BCME and CMME was reported by Zudova and Landa (1977); the frequency of aberrations decreased following the removal of workers from exposure.

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

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

Animal studies have indicated that chronic exposure to BCIE produces liver necrosis in mice. Exposure in rats causes major effects on the lungs, including congestion and pneumonia (U.S. EPA, 1979).

E. Other Relevant Information

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

V. AQUATIC TOXICITY

A. Acute Toxicity

The reported static 96-hour LC_{50} value for the bluegill (Lepomis macrochirus) with 2-chloroethyl vinyl ether (concentration unmeasured) is 194,000 µg/l (U.S. EPA, 1978). The 96-hour LC_{50} values for the bluegill could not be determined in a static test for bis(2-chloroethyl)ether with exposure concentrations as high as 600,000 µg/l. The concentration of the ether was not monitored during the bioassay. Pertinent data could not be located in the available literature on saltwater species.

B. Chronic Toxicity

An embryo-larval test was conducted with bis(2-chloroethyl)ether and the fathead minnow, (Pimephales promelas). Adverse effects were not observed at test concentrations as high as 19,000 µg/l.

C. Plant Effects

Pertinent data could not be located in the available literature.

D. Residues

Using bis(2-chloroethyl)ether, a bioconcentration factor of 11 was determined during a 14-day exposure of bluegills (U.S. EPA, 1979). The half-life was observed to be between four and seven days.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

Based on animal carcinogenesis bioassays, and using a linear, nonthreshold model, the U.S. EPA (1979) has estimated the following ambient water levels of chloroalkyl ethers which will produce an increased cancer risk of 10^{-5}: BCIE, 11.5μg/l; BCEE, 0.42 μg/l; and BCME 0.02 ng/l.

Eight-hour TWA exposure values (TLV) for the following chloroalkyl ethers have been recommended by the American Conference of Governmental and Industrial Hygienists (ACGIH, 1978): BCME, 1 ppb; BCEE, 5 ppm.

B. Aquatic

Freshwater and saltwater drafted criteria have not been derived for any chloroalkyl ethers because of insufficient data (U.S. EPA, 1979).

CHLOROALKYL ETHERS

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No. 42

Chlorobenzene

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.

CHLOROBENZENE

Summary

There is little data on the quantities of chlorobenzene in air, water and food, although this compound has been identified in these media. Chronic exposure to chlorobenzene appears to cause a variety of pathologies under different experimental regimens; however, the liver and kidney appear to be affected in a number of species. There have been no studies conducted to evaluate the mutagenic, teratogenic, or carcinogenic potential of chlorobenzene.

Four species of freshwater fish have 96-hour LC_{50} values ranging from 24,000 to 51,620 µg/l. Hardness does not significantly affect the values. In saltwater, a fish and shrimp had reported 96-hour LC_{50} values of 10,500 µg/l and 6,400 µg/l, respectively. No chronic data involving chlorobenzene are available. Algae, both fresh and saltwater, are considerably less sensitive to chlorobenzene toxicity than fish and invertebrates.

I. INTRODUCTION

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

Chlorobenzene, most often referred to as monochlorobenzene (MCB; C_6H_5Cl; molecular weight 112.56), is a colorless liquid with a pleasant aroma. Monochlorobenzene has a melting point of -45.6°C, a boiling point of 131-132°C, a water solubility of 488 mg/l at 25°C, and a density of 1.107 g/ml. Monochlorobenzene has been used as a synthetic intermediate in the production of phenol, DDT, and aniline. It is also used as a solvent in the manufacture of adhesives, paints, polishes, waxes, diisocyanates, pharmaceuticals and natural rubber (U.S. EPA, 1979).

Data on current production derived from U.S. International Trade Commission reports show that between 1969 and 1975, the U.S. annual production of monochlorobenzene decreased by 50 percent, from approximately 600 million pounds to approximately 300 million pounds (U.S. EPA, 1977).

II. EXPOSURE

A. Water

Based on the vapor pressure, water solubility, and molecular weight of chlorobenzene, Mackay and Leinonen (1975) estimated the half-life of evaporation from water to be 5.8 hours. Monochlorobenzene has been detected in ground water, "uncontaminated" upland water, and in waters contaminated either by industrial, municipal or agricultural waste. The concentrations ranged from 0.1 to 27 μg/l, with raw waters having the lowest concentration and municipal waste the highest (U.S. EPA, 1975, 1977). These estimates should be considered as gross estimates of exposure, due to the volatile nature of monochlorobenzene.

B. Food

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of monochlorobenzene to be 13 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on octanol/-water partition coefficients.

C. Inhalation

Data have not been found in the available literature which deal with exposure to chlorobenzene outside of the industrial working environment.

III. PHARMACOKINETICS

A. Absorption

There is little question, based on human effects and mammalian toxicity studies, that chlorobenzene is absorbed through the lungs and from the gastrointestinal tract (U.S. EPA, 1977).

B. Distribution

Because chlorobenzene is highly lipophilic and hydrophobic, it would be expected that it would be distributed throughout total body water space, with body lipid providing a deposition site (U.S. EPA, 1979).

C. Metabolism

Chlorobenzene is metabolised via an NADPH-cytochrome P-448 dependent microsomal enzyme system. The first product, and rate limiting step, is a epoxidation; this is followed by formation of diphenolic and monophenolic compounds (U.S. EPA, 1979). Various conjugates of these phenolic derivatives are the primary excretory products (Lu, et al. 1974). Evidence indicates that the metabolism of monochlorobenzene results in the formation of toxic intermediates (Kohli, et al. 1976). Brodie, et al. (1971) induced microsomal enzymes with phenobarbital and showed a potentiationin in the toxicity of monochlorobenzene. However, the use of 3-methylcho-

lanthrene to induce microsomal enzymes provided protection for rats (Oesch, et al. 1973). The metabolism of chlorobenzene may also lead to the formation of carcinogenic active intermediates (Kohli, et al. 1976).

D. Excretion

The predominant route of elimination is through the formation of conjugates of the metabolites of monochlorobenzene and elimination of these conjugates by the urine (U.S. EPA, 1979). The types of conjugates formed vary with species (Williams, et al. 1975). In the rabbit, 27 percent of an administered dose appeared unchanged in the expired air (Williams, 1959).

IV. EFFECTS

Pertinent data could not be located in the available literature on the carcinogenicity, mutagenicity, teratogenicity, or other reproductive effects of chlorobenzene.

A. Chronic Toxicity

Data on the chronic toxicity of chlorobenzene is sparse and somewhat contradictory. "Histopathological changes" have been noted in lungs, liver and kidneys following inhalation of monochlorobenzene (200, 475, and 1,000 ppm) in rats, rabbits and guinea pigs (Irish, 1963). Oral administration of doses of 12.5, 50 and 250 mg/kg/day to rats produced little pathological change, except for growth retardation in males (Knapp, et al. 1971).

B. Other Relevant Information

Chlorobenzene appears to increase the activity of microsomal NADPH-cytochrome P-450 dependent enzyme systems. Induction of microsomal enzyme activity has been shown to enhance the metabolism of a wide variety of drugs, pesticides and other xenobiotics (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

Pickering and Henderson (1966) reported observed 96-hour LC_{50} values for goldfish, Carassius auratus, guppy, Poecilia reticulatus, and bluegill, Lepomis macrochirus, to be 51,620, 45,530, and 24,000 µg/l, respectively, for chlorobenzene. Two 96-hour LC_{50} values for chlorobenzene and fathead minnows, Pimephales promelas, are 33,930 µg/l in soft water (20 mg/l) and 29,120 µg/l in hard water (360 mg/l), indicating that hardness does not significantly affect the acute toxicity of chlorobenzene (U.S. EPA, 1978). With Daphnia magna, an observed 48-hour EC_{50} value of 86,000 µg/l was reported. In saltwater studies, sheepshead minnow had a reported unadjusted LC_{50} (96-hour) value of 10,500 µg/l, with a 96-hour EC_{50} of 16,400 µg/l for mysid shrimp (U.S. EPA, 1978).

B. Chronic Toxicity

No chronic toxicity studies have been reported on the chronic toxicity of chlorobenzene and any salt or freshwater species.

C. Plant Effects

The freshwater alga Selenastrum capricornutum is considerably less sensitive than fish and Daphnia magna. Based on cell numbers, the species has a reported 96-hour EC_{50} value of 224,000 µg/l. The saltwater alga, Skeletonema costatum, had a 96-hour EC_{50}, based on cell numbers of 341,000 µg/l.

D. Residues

A bioconcentration factor of 44 was obtained assuming an 8 percent lipid content of fish.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) threshold limit value for chlorobenzene is 350 mg/m^3. The acceptable daily intake (ADI) was calculated to be 1.008 mg/day. The U.S. EPA (1979) draft water criterion for chlorobenzene is 20 µg/l, based on threshold concentration for odor and taste.

B. Aquatic

For chlorobenzene, the drafted criterion to protect freshwater aquatic life is 1,500 µg/l as a 24-hour average; the concentration should not exceed 3,500 µg/l at any time. To protect saltwater aquatic life, a draft criterion of 120 µg/l as a 24-hour average with a concentration not exceeding 280 µg/l at any time has been recommended (U.S. EPA, 1979).

CHLOROBENZENE

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No. 43

p-Chloro-m-cresol

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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p-CHLORO-m-CRESOL

SUMMARY

p-Chloro-m-cresol has been found to be susceptible to biodegradation under aerobic conditions in a synthetic sewage sludge. It has been found to be formed by the chlorination of waters receiving effluents from electric power-generating plants and by the chlorination of the effluent from a domestic sewage treatment facility.

Very little information on the health effects of p-chloro-m-cresol was located. p-Chloro-m-cresol has been characterized as very toxic in humans, although support for this statement is limited. In rats, a subcutaneous LD_{50} of 400 mg/kg and an oral LD_{Lo} of 500 mg/kg have been reported.

I. INTRODUCTION

p-Chloro-m-cresol (4-chlor[illegible]methylphenol; C_7H_7ClO; molecular weight 142.58) is a solid (dimorphous crystals) at room temperature. The pure compound is odorless, but it has a phenolic odor in its most common, impure form. Its melting point is 55.5°C and its boiling point is 235°C. It is soluble in water and many organic solvents (Windholz 1976).

A review of the production range (includes importation) statistics for p-chloro-m-cresol (CAS No. [illegible]-50-7) as listed in the initial TSCA Inventory (U.S. EPA 1979) shows that between 10,000 and 90,000 pounds of this chemical were produced/imported in 1977.*

p-Chloro-m-cresol is used as an external germicide and as a preservative for glues, gums, paints, inks, textiles and leather goods (Hawley 1971). It is also used as a preservative in cosmetics (Wilson 1975, Liem 1977). EPA (1973) indicates that p-chloro-m-cresol is "cleared for use in adhesives used in food packaging."

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

II. EXPOSURE

A. Environmental Fate

Voets et al. (1976) reported that p-chloro-m-cresol was quite susceptible to microbial breakdown under aerobic conditions in an organic medium (synthetic sewage sludge), while degradation under aerobic conditions in a mineral solution (simulating oligotrophic aquatic systems) was relatively difficult. No degradation was observed in either system under anaerobic conditions.

B. Bioconcentration

No studies on the bioconcentration potential of this compound were found. Based on its solubility, p-chloro-m-cresol would not be expected to have a high bioconcentration potential.

C. Exposure

Human exposure to p-chloro-m-cresol occurs through its presence in certain cosmetics and in a variety of other consumer products in which it is used as a preservative (Wilson 1975, Liem 1977).

p-Chloro-m-cresol has been found to be formed by the chlorination of water from a lake and a river receiving cooling waters from electric power-generating plants, at concentrations of 0.2 ug/l and 0.7 ug/l, respectively. It has also been found to be formed by the chlorination of the effluent from a domestic sewage treatment facility at a concentration of 1.5 ug/l (Jolley et al. 1975).

III. PHARMACOKINETICS

No information was found.

IV. HEALTH EFFECTS

Very little toxicological data for p-chloro-m-cresol was available. The subcutaneous LD_{50} for p-chloro-m-cresol in rats is 400 mg/kg (NIOSH 1975). The oral LD_{Lo} for p-chloro-m-cresol in rats is 500 mg/kg. In mice the intraperitoneal LD_{Lo} is 30 mg/kg and the subcutaneous LD_{Lo} is 200 mg/kg

(U.S. DHEW 1978). One author has rated p-chloro-m-cresol as very toxic, with a probable lethal dose to humans of 50-500 mg/kg. (Von Oettingen as quoted in Gosselin et al. 1976). p-Chloro-m-cresol was also reported as non-irritating to skin in concentrations of 0.5 to 1.0% in alcohol.

V. AQUATIC TOXICITY

A. Acute

The only information available is that for *Daphnia pulex*. The 96-hour LC_{50} for p-chloro-m-cresol exposure is 3.1 mg/L (Jolley et al. 1977).

VI. GUIDELINES

No guidelines for exposure to p-chloro-m-cresol were located.

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No. 44

Chloroethane

Health and Environmental Effects

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

APRIL 30, 1980

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CHLOROETHANE

SUMMARY

There is no available evidence which indicates that monochloroethane produces carcinogenic, mutagenic, or teratogenic effects. Symptoms produced by human poisoning with monochloroethane include central nervous system depression, respiratory failure, and cardiac arrhythmias. The results of animal studies indicate that liver, kidney, and cardiac toxicity may be produced by monochloroethane.

Data examining the toxic effects of chloroethane on aquatic organisms were not available.

CHLOROETHANE

I. INTRODUCTION

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

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms have been replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. Monochloroethane (chloroethane, M.W. 64.52) is a gas at room temperature. The compound has a boiling point of 13.1°C, a melting point of -138.7°C, a specific gravity of 0.9214, and a solubility of 5.74 g/l in water (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds.

The 1976 production of monochloroethane was 335×10^3 tons/year (U.S. EPA, 1979a).

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes present in raw and finished waters are due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water

or treatment of sewage. Air levels of chloroethanes are produced by evaporation of these volatile compounds widely used as degreasing agents and in dry cleaning operations (U.S. EPA, 1979a).

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976). Data on the levels of monochloroethanes in foods is not available.

An average bioconcentration factor for monochloroethane in fish and shellfish has not been derived by the EPA.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature on monochloroethane for absorption, distribution, metabolism, and excretion. However, the reader is referred to a more general treatment of chloroethanes (U.S. EPA, 1979b), which indicates rapid absorption of chloroethanes following oral or inhalation exposure; widespread distribution of the chloroethanes throughout the body; enzymatic dechlorination and oxidation to the alcohol and ester forms; and excretion of the chloromethanes primarily in the urine and expired air. Specifically for monochloroethane, absorption following dermal application is minor; and excretion appears to be rapid, with the major portion of the injected compound excreted in the first 24 hours (U.S. EPA, 1979a).

IV. EFFECTS

Pertinent data could not be located in the available literature on monochloroethane for carcinogenicity, mutagenicity, teratogenicity and other reproductive effects.

A. Chronic Toxicity

Human symptons of monochloroethane poisoning indicate central nervous system depression, respiratory failure, and cardivascular symptoms, including cardiac arrhythmias (U.S. EPA, 1979a). Animal toxicity has indicated kidney damage and fatty infiltration of the liver, kidney, and heart (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDLINES AND STANDARDS

A. Human

The eight-hour TWA standard prepared by OSHA for monochloroethane is 1,000 ppm.

Sufficient data are not available to derive a criterion to protect human health from exposure to monochloroethane in ambient water.

B. Aquatic

There are not sufficient toxicological data to calculate exposure criteria.

CHLOROETHANE

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No. 45

Chloroethene

Health and Environmental Effects

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

APRIL 30, 1980

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CHLOROETHENE

(VINYL CHLORIDE)

Summary

Vinyl chloride has been used for over 40 years in the production of polyvinyl chloride. Animal studies indicate that vinyl chloride is not teratogenic, but it has been found to be mutagenic in several biologic test systems. Vinyl chloride has been found to be carcinogenic in laboratory animals and has been positively associated with angiosarcoma of the liver in humans. Recently "vinyl chloride disease", a multisystem disorder, has been described in workers exposed to vinyl chloride.

Data are lacking concerning the effects of vinyl chloride in freshwater and saltwater aquatic life.

CHLOROETHENE

(VINYL CHLORIDE)

I. INTRODUCTION

Vinyl chloride (CH_2CHCl; molecular weight 62.5) is a highly flammable chloro-olefinic hydrocarbon which emits a sweet or pleasant odor, and has a vapor density slightly more than twice that of air. Its physical properties include: melting point, -153.8°C; and solubility in water, 0.11g/100 g at 28°C. It is soluble in alcohol and very soluble in ether and carbon tetrachloride (Weast, 1972). Many salts of metals (including silver, copper, iron, platinum, iridium) have the ability to complex with vinyl chloride resulting in its increased solubility in water. Conversely, alkali metal salts, such as sodium or potassium chloride, may decrease the solubility of vinyl chloride in aqueous solutions (Fox, 1978).

Vinyl chloride has been used for over 40 years in the production of polyvinyl chloride (PVC), which in turn is the most widely used material in the manufacture of plastics. Production of vinyl chloride in the U.S. reached slightly over 5 billion pounds in 1977 (U.S. Int. Trade Comm, 1978).

Vinyl chloride and polyvinyl chloride are used in the manufacture of numerous products in building and construction, the automotive industry, for electrical wire insulation and cables, piping, industrial and household equipment, packaging for food products, medical supplies, and are depended upon heavily by the rubber, paper and glass industries (Maltoni, 1976a).

In the U.S. about 1500 workers were employed in monomer synthesis and an additional 5000 in polymerization operations (Falk,

et al. 1974). As many as 350,000 workers were estimated to be associated with fabricating plants (U.S. EPA, 1974). By 1976, it was estimated that worldwide nearly one million persons were associated with manufacturing goods derived from PVC (Maltoni, 1976a). Potential sources of population exposure to vinyl chloride are emissions from PVC fabricating plants, release of monomers from various plastic products, and emissions from the incineration of PVC products (U.S. EPA, 1975).

II. EXPOSURE

A. Water

Small amounts of vinyl chloride may be present in public water supplies as a result of industrial waste water discharges. The levels of vinyl chloride in effluents vary considerably depending on the extent of in-plant treatment of waste water. Vinyl chloride in samples of waste water from seven areas ranged from 0.05 ppm to 20 ppm, typical levels being 2-3 ppm (U.S. EPA, 1974). The low solubility and high volatility of vinyl chloride tend to limit the amounts found in water; however, the presence of certain salts may increase the solubility and therefore could create situations of concern (U.S. EPA, 1975).

Polyvinyl chloride pipe used in water distribution systems provides another source of low levels of vinyl chloride in drinking water. In a study by the U.S. EPA of five water distribution systems which used PVC pipes, water from the newest, longest pipe system had the highest vinyl chloride concentration (1.4 μg/l) while the two oldest systems only had traces of vinyl chloride (0.3 μg/l and 0.6 μg/l) (Dressman and McFarren, 1978). The National

Science Foundation (NSF) has adopted a voluntary standard of 10 ppm or less of residual monomer in finished pipe and fittings. Three times a year NSF samples water supplies in several cities. In 1977, more than 95 percent of the samples conformed to the standard; however, levels of 5.6 μg/l and 0.27 μg/l vinyl chloride have been detected in at least two cities.

B. Food

Small quantities of vinyl chloride are ingested by humans when the entrained monomer migrates into foods packaged in PVC wrappings and containers. The solubility of vinyl chloride in foods packaged in water is low (0.11 percent); however, the monomer is soluble in alcohols and mineral oil. In 1973, the U.S. Treasury Department banned the use of vinyl chloride polymers for packaging alcoholic beverages (Int. Agency Res. Cancer, 1974). The FDA analyzed a number of PVC packaged products in 1974. The concentrations ranged from "not detectable" to 9,000 ppb.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of vinyl chloride to be 1.9 for the edible portions of fresh and shellfish consumed by Americans. This estimate was based on the octanol/water coefficient of vinyl chloride.

C. Inhalation

Inhalation of vinyl chloride is the principal route of exposure to people working in or living near vinyl chloride industries. After 1960, Dow Chemical Co. was successful in reducing exposures to workers to about 25 ppm level, though levels up to 500 ppm still occurred. Inhalation exposures drastically dropped after appropriate controls were instituted following case reports of vinyl chloride induced angiosarcoma of the liver in workers and experimental animals (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Vinyl chloride is rapidly absorbed through the lungs and enters the blood stream (Duprat, et al. 1977).

B. Distribution

The liver of rats accumulates the greatest percentage of vinyl chloride and/or metabolites of vinyl chloride 72 hours after a single oral dose (Watanabe, et al. 1976). Ten minutes after a 5-minute inhalation exposure to vinyl chloride at 10,000 ppm, the compound was found in the liver, bile duct, stomach, and kidney of rats (Duprat, et al. 1977). Immediately after exposure by inhalation to ^{14}C-vinyl chloride at 50 ppm for 5 hours, the percent incorporated as ^{14}C/radioactivity per gram of tissue was highest for kidney (2.13), liver (1.86), and spleen (0.73). Forty-eight hours after the beginning of exposure, labeled material could still be detected in these tissues.

C. Metabolism

Detoxification of vinyl chloride takes place primarily in the liver by oxidation to polar compounds which can be conjugated to glutathione and/or cysteine (Hefner, et al. 1975). These covalently bond metabolites are then excreted in the urine.

Vinyl chloride is metabolized extensively by rats *in vivo* and the metabolic pathways appear to be saturable. The postulated primary metabolic pathway involves alcohol dehydrogenase and, for rats, appears to be saturated by exposures to concentrations exceeding 220 to 250 ppm. In rats exposed to higher concentrations, metabolism of vinyl chloride is postulated to occur via a secondary

pathway involving epoxidation and/or peroxidation. Present data indicates that vinyl chloride is metabolized to an activated carcinogen electrophile and is capable of covalent reaction with nucleophilic groups or cellular macromolecules (U.S. EPA, 1979).

There is ample evidence that the mixed function oxidase (MFO) system may be involved in the metabolism of vinyl chloride. Rat liver microsomes catalyze the covalent binding of vinyl chloride metabolites to protein and nucleic acids; chloroethylene oxide is thought to be the primary microsomal metabolite capable of alkylating these cellular macromolecules (Kappus, et al. 1975; 1976; Laib and Bolt, 1977). Hathway (1977) reports *in vitro* depurination of calf thymus DNA by chloroacetaldehyde identical to that observed in hepatocyte DNA following the administration of vinyl chloride to rats *in vitro*.

D. Excretion

Watanabe, et al. (1976) monitored the elimination of vinyl chloride for 72 hours following a single oral dose administered to rats. The total ^{14}C-activity recovered at each dose level ranged from 82-92 percent. At a dose level of 1 mg/kg, 2 percent was exhaled as vinyl chloride, 13 percent was exhaled as carbon dioxide, 59 percent was eliminated in the urine and 2 percent in the feces. Excretion of vinyl chloride at a dose level of 100 mg/kg was 66 percent exhaled as vinyl chloride, 2.5 percent as carbon dioxide, 11 percent in the urine and 0.5 percent in the feces. Administration by inhalation produced almost the same results.

Green and Hathway (1975) found that more than 96 percent of 250 μg ^{14}C-vinyl chloride administered via intragastric, intra-

venous or intraperitoneal routes was excreted within 24 hours. The rats given vinyl chloride by the intragastric route exhaled 3.7 percent as vinyl chloride, 12.6 percent as CO_2; 71.5 percent of the labeled material was in the urine and 2.8 percent in the feces. Intravenous injections resulted in 9.9 percent exhaled as vinyl chloride, 10.3 percent as CO_2; 41.5 percent in the urine and 1.6 percent in the feces.

IV. EFFECTS

A. Carcinogenicity

The carcinogenicity of vinyl chloride has been investigated in several animal studies. Viola, et al. (1971) induced skin epidermoid carcinomas, lung carcinomas or bone steochrondromas in 24/25 male rats exposed to 30,000 ppm vinyl chloride intermittently for 12 months. Tumors appeared between 10 and 11 months. Caputo, et al. (1974) observed carcinomas and sarcomas in all groups of male and female rats inhaling various concentrations of vinyl chloride except those exposed to 50 ppm.

Maltoni and Lefemine (1974a,b; 1975) reported on a series of experiments concerning the effects on rats, mice, and hamsters of inhalation exposure to vinyl chloride at concentrations ranging from 50 to 10,000 ppm for varying periods of time. The animals were observed for their entire lifetime. Angiosarcomas of the liver occurred in all three species, as well as tumors at several other sites. A differential response between the sexes was not reported.

Maltoni (1976b) observed four subcutaneous angiosarcomas, four zymbal gland carcinomas, and one nephroblastoma in

66 offspring of rats exposed by inhalation 4 hours/day to 10,000 or 6,000 ppm vinyl chloride from the 12th to 18th day of gestation. Liver angiosarcomas were also observed in rats administered vinyl chloride via stomach tube for 52 weeks.

Recent experiments by Lee, et al. (1977) with rats and mice confirm the carcinogenicity of vinyl chloride. Each species was exposed to 50,250 or 1000 ppm vinyl chloride or 55 ppm vinylene chloride 6 hr/day, 5 days/week for 1-12 months. After 12 months, bronchioalveolar adenomas, mammary gland tumors, and angiosarcomas in the liver and other sites developed in mice exposed to all three dose levels of vinyl chloride. Rats exposed to 250 ppm or 100 ppm vinyl chloride developed angiosarcoma in the liver, lung and other sites (Lee, et al. 1978).

The primary effect associated with vinyl chloride exposure in man is an increased risk of cancer in several organs including angiosarcoma of the liver. Liver angiosarcoma is an extremely rare liver cancer in humans, with 26 cases reported annually in the U.S. (Natl. Cancer Inst., 1975). Human data on the carcinogenic effects of vinyl chloride have been obtained primarily from cases of occupational exposures of workers. The latent period has been estimated to be 15-20 years; however, recent case reports indicate a longer average latent period (Spirtas and Kaminski, 1978).

A number of epidemiological studies of vinyl chloride have been reported (U.S. EPA, 1979). Tabershaw/Cooper Associates (1974) found no increase in the overall mortality rate for vinyl chloride workers nor significant increases in standard mortality

rates (SMR's) for malignant neoplasms. Reexamination of this data by Ott, et al. (1975) including more clearly defined exposure levels confirmed the previous findings: no increase over that expected for malignant neoplasms in the low exposure group (TWA 10-100 ppm vinyl chloride) and a non-significant increase in deaths due to malignant neoplasms in the high exposure group (TWA, greater than 200 ppm).

However, liver cancer death were twelve-fold, and brain cancer deaths were five-fold greater than that expected in a study by Wagoner (1974). Likewise, Monson, et al. (1974) found death due to cancer to be 50 percent higher than expected in vinyl chloride workers who died from 1947-1973, including a 900 percent increase in cancers of the liver and biliary tract.

In the most recent update of the NIOSH register, a total of 64 cases of hepatic angiosarcoma have been identified worldwide among vinyl chloride exposed industrial workers (Spirtas and Kaminski, 1978). Twenty-three of these cases were reported in the United States. Six cases were documented since 1975.

B. Mutagenicity

Vinyl chloride has been found to be mutagenic in a number of biological systems including: metabolically activated systems using Salmonella typhimurium; back mutation systems using Escherichia coli; forward mutation and gene coversion in yeast; and germ cells of Drosophila and Chinese hamster V79 cells (U.S. EPA, 1979).

The dominant lethal assay was used to test the mutagenicity of inhaled vinyl chloride in mice. Levels as high as 30,000

ppm (6 hours/day for 5 days) yielded negative results (Anderson, et al. 1976).

Several investigators have observed a significantly higher incidence of chromosomal aberrations in the lymphocytes of workers chronically exposed to high levels of vinyl chloride (Ducatman, et al. 1975; Purchase, et al. 1975; Funes-Cravioto, et al. 1975).

C. Teratogenicity

Animal studies using mice, rats and rabbits, indicate that inhalation of vinyl chloride does not induce gross teratogenic abnormalities in offspring of mothers exposed 7 hours daily to concentrations ranging from 50 to 2,500 ppm (John, et al. 1977); however, excess occurrences of minor skeletal abnormalities were noted. Increased fetal death was noted at the higher exposure levels. These findings were confirmed by Radike, et al. (1977a) who exposed rats to 600-6,000 ppm vinyl chloride, 4 hours daily on the 9th to the 21st day of gestation.

Further examination is needed of reported high rates of congenital defects in three small communities in which vinyl chloride polymerization plants are located (U.S. EPA, 1979).

D. Other Reproductive Effects

No effect on fertility in mice was noted in a dominant lethal assay conducted by Anderson, et al. (1976).

E. Chronic Toxicity

There are numerous clinical indications that chronic exposure to vinyl chloride is toxic to humans (U.S. EPA, 1979). Hepatitis-like changes, angioneurosis, Raynaud's syndrome, derma-

titis, acroosteolysis, thyroid insufficiency, and hepatomegaly have been reported around the world. Other long term effects include functional disturbances of the central nervous system with adrenergic sensory polyneuritis (Smirnova and Granik, 1970); thrombocytopenia, splenomegaly, liver malfunction with fibrosis, pulmonary changes (Lange, et al. 1974); and alterations in serum enzyme levels (Makk, et al. 1976).

F. Other Relevant Information

Pretreatment of rats with pyrazole (an alcohol dehydrogenose inhibitor) and ethanol inhibits the metabolism of vinyl chloride (Hefner, et al. 1975). This indicates the involvement of alcohol dehydrogenose in the metabolism of vinyl chloride.

The chronic ingestion of alcohol was found to increase the incidence of liver tumors and tumors in other sites in individuals exposed to vinyl chloride (Radike, 1977b).

Jaeger (1975) conducted experiments to determine the interaction between vinylidene chloride (1,1-DCE) and vinyl chloride. In this experiment, the effects of 4-hour exposures to 200 ppm of 1,1-DCE and 1,000 ppm vinyl chloride were less than if 1,1-DCE was given alone.

V. AQUATIC TOXICITY

A. Pertinent information relevant to acute and chronic toxicity, plant effects and residues for vinyl chloride were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The current federal OSHA standard for vinyl chloride is 1 ppm (TWA) with a maximum of 5 ppm for a period of no longer than 15 minutes in 1 day. (39 FR 35890 (Oct. 4, 1979)).

In 1974, a notice to cancel registrations of pesticide spray products containing vinyl chloride as a propellant was issued (39 FR 14753 (April 26, 1974)). Other aerosol products, such as hair spray, utilizing vinyl chloride as a propellant were banned from the market in the U.S. and other countries (Int. Agency Res. Cancer, 1974). The U.S. EPA proposed in 1975 and 1976 an emission standard of 10 ppm vinyl chloride at the stack for industry.

The draft ambient water quality criterion for vinyl chloride has been set to reduce the human lifetime cancer risk level to 10^{-5}, 10^{-6} and 10^{-7} (U.S. EPA, 1979). The corresponding criteria are 517 µg/l, 51.7 µg/l and 5.17 µg/l, respectively. The data base from which this criterion has been derived is currently being reviewed, therefore, this criteria to protect human health may change.

B. Aquatic

Fresh or salt water criteria could not be derived because of insufficient data (U.S. EPA, 1979).

CHLOROETHENE
(VINYL CHLORIDE)

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No. 46

2-Chloroethyl Vinyl Ether

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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

2-CHLOROETHYL VINYL ETHER

SUMMARY

Very little information is available for 2-chloroethyl vinyl ether. It appears to be relatively stable except under acidic conditions. There is some potential for bioconcentration of the compound in exposed organisms. No exposure data were available, although 2-chloroethyl vinyl ether has been identified in industrial effluent discharges.

The acute toxicity of 2-chloroethyl vinyl ether is relatively low: oral LD_{50}: 250 mg/kg; dermal LD_{50} 3.2 mL/kg; LC_{LO}: 250 ppm (4 hrs). Eye irritation has been reported following exposure to 2-chloroethyl vinyl ether. No other data on health effects were available.

I. INTRODUCTION

2-Chloroethyl vinyl ether ($ClCH_2CH_2OCH{=}CH_2$; molecular weight 106.55) is a liquid having the following physical/chemical properties (Windholz, 1976; Weast, 1972; U.S. EPA, 1979c):

Boiling point (760 mm Hg):	109°C
Melting point:	-70°C
Density:	1.0475^{20}
Solubility:	Soluble in water to the extent of 6g/L; very soluble in alcohol and ether

The compound finds use in the manufacture of anesthetics, sedatives, and cellulose ethers (Windholz, 1976).

A review of the production range (includes importation) statistics for 2-chloroethyl vinyl ether (CAS No. 110-75-8) which is listed in the initial TSCA inventory (1979a) has shown that none of this chemical was produced or imported in 1977*.

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*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise confidential business information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40CFR710).

II. EXPOSURE

A. Environmental Rate

The β-chloroalkyl ethers have been shown to be quite stable to hydrolysis and to persist for extended periods without biodegradation (U.S. EPA, 1979b). 2-Chloroethyl ethyl ether (a β-chloroalkyl other) is stable to sodium hydroxide solutions but will undergo hydrolysis in the presence of dilute acids to acetaldehyde and 2-chloroethanol (Windholz 1976). Conventional treatment systems may be inadequate to sufficiently remove the β-chloroalkyl ethers once present in water supplies (U.S. EPA 1979b; U.S. EPA 1975).

B. Bioconcentration

A calculated bioconcentration factor of 34.2 (U.S. EPA, 1979b) points to some potential for 2-chloroethyl vinyl ether accumulation in exposed organisms.

C. Environmental Occurrence

There is no specific information available on general population exposure to 2-chloroethyl vinyl ether. The compound has been identified three times in the water of Louisville, Kentucky (3/74): twice in effluent facturing plants and once in the effluent from a latex plant (U.S. EPA 1976). No concentration levels were given.

NIOSH, utilizing data from the National Occupational Hazards Survey (NOHS 1977) has compiled a listing summarizing occupational exposure to 2-chloroethyl vinyl ether (Table 1). As shown, NIOSH estimates 23,473 people are exposed annually to the compound. The number of potentially exposed individuals is greatest for the following areas: fabricated metal products; wholesale trade; leather, rubber and plastic, and chemical products.

III. PHARMACOKINETICS

Vinyl ethers readily undergo acid catalysed hydrolysis to give alcohols and aldehydes, e.g., 2-chloroethyl vinyl ether is hydrolyzed to 2-chloroethanol and acetaldehyde (Salomaa et al. 1966).

TABLE 1

PROJECTED NUMBERS BY INDUSTRY

HAZARD DESCRIPTION

84673 Chloroethyl Vinyl Ether, 2-

SIC CODE	DESCRIPTION	ESTIMATED PLANTS	ESTIMATED PEOPLE	ESTIMATED EXPOSURES
25	Furniture and fixtures	193	920	920
28	Chemicals and allied products	103	1,683	1,683
30	Rubber and plastic products	89	1,669	1,669
31	Leather and leather products	45	2,279	2,279
34	Fabricated metal products	61	9,149	9,149
35	Machinery, except electrical	35	35	35
36	Electrical equipment and supplies	54	432	432
37	Transportation equipment	92	553	553
38	Instruments and related products	24	299	299
39	Miscellaneous manufacturing industries	119	240	240
50	Wholesale trade	1,239	6,194	6,194
73	Miscellaneous business services	5	20	20
TOTAL		2,059	23,473	23,473

IV. HEALTH EFFECTS

A. Mutagenicity

Although no information on the mutagenicity of 2-chloroethyl vinyl ether was available, its hydrolysis product, 2-chloroethanol, has been shown to be mutagenic in *Salmonella typhimurium* TA 1535 (Rannug et al. 1976), TA100 and TA98 (McCann et al. 1976), as well as *Klebsiella pneumonia* (Voogd et al. 1972).

B. Other Toxicity

Very little toxicological data for 2-chloroethyl vinyl ether is available. The oral LD_{50} for 2-chloroethyl vinyl ether in rats is 250 mg/kg (U.S. EPA, 1975, Patty 1963). Dermal exposure to the shaven skin of rabbits for 24 hours resulted in an LD_{50} of 3.2 mL/kg (U.S. EPA, 1976). The acute inhalation toxicity of 2-chloroethyl vinyl ether in rats was determined following single four-hour exposures. The lowest lethal concentration was 250 ppm (U.S. EPA, 1975). In a similar inhalation study, 1/6 rats exposed by inhalation to 500 ppm died during the 14-day observation period (U.S. EPA, 1975).

Primary skin irritation and eye irritation studies have also been conducted for 2-chloroethyl vinyl ether. Dermal exposure to undiluted 2-chloroethyl vinyl ether did not cause even slight erythema. Application of 0.5 mL undiluted 2-chloroethyl vinyl ether to the eyes of rabbits resulted in severe eye injury (U.S. EPA, 1975).

V. AQUATIC TOXICITY

A. Acute

The adjusted 96-hour LC_{50} for blue gill exposure to 2-chloroethyl vinyl ether is 194,000 ug/L (U.S. EPA, 1979b). Dividing by the species sensitivity factor (3.9), a Final Fish Acute Value of 50,000 ug/L is obtained (Table 1). There is no data on invertebrate or plant exposure.

VI. EXISTING GUIDELINES

No guidelines were located.

Table 2. Freshwater fish acute values (U.S. EPA, 1979b)

Organism	Bioassay Method	Test Conc.**	Chemical Description	Time (hrs)	LC_{50} (ug/L)	Adjusted LC_{50} (ug/L)
Bluegill, *Lepomis macrochirus*	S	U	2-chloroethyl vinyl ether	96	354,000	194,000

* S = static

** U = unmeasured

Geometric mean of adjusted values: 2-chloroethyl vinyl ether = 194,000 ug/L

$$\frac{194,000}{3.9} = 50,000 \text{ ug/L}$$

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No. 47

Chloroform (Carbon Trichloromethane)

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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 chloroform and has found sufficient evidence to indicate that this compound is carcinogenic.

CHLOROFORM

SUMMARY

Chloroform has been found to induce hepatocellular carcinomas in mice and kidney epithelial tumors in rats. Hepatomas have also been induced in mice, but necrosis may be a prerequisite to tumor formation. Bacterial assays involving chloroform have yielded no mutagenic effects. Chloroform has produced teratogenic effects when administered to pregnant rats.

Reported 96-hour LC_{50} values for two common freshwater fish range from 43,800 to 115,000 µg/l in static tests. A 48-hour static test with *Daphnia magna* yielded an LC_{50} of 28,900 µg/l. The observed 96-hour LC_{50} for the saltwater pink shrimp is 81,500 µg/l. In a life cycle chronic test, the chronic value was 2,546 µg/l for *Daphnia magna*. Pertinent information on chloroform toxicity to plants could not be located in the available literature. In the only residue study reported, the bluegill concentrated chloroform six times after a 14-day exposure. The tissue half-life was less than one day suggesting that residues of chloroform would not be an environmental hazard to aquatic life.

CHLOROFORM

I. INTRODUCTION

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

Chloroform ($CHCl_3$; molecular weight 119.39) is a clear, colorless liquid with a pleasant, etheric, non-irritating odor and taste (Hardie, 1964; Windholz, 1976). It has the following physical/chemical properties (Hardie, 1964; Irish, 1972; Windholz, 1976):

Boiling Point:	61-62°C
Melting Point:	-63.5°C
Flash Point:	none (none-flammable)
Solubility:	Water - 7.42×10^6 µg/l at 25°C Miscible with alcohol, benzene, ether, petroleum ether, carbon tetrachloride, carbon disulfide, and oils.
Vapor Pressure:	200 mm Hg at 25°C

Current Production: 1.2×10^5 metric tons/year (U.S. EPA, 1978a).

Chloroform is currently used either as a solvent or as an intermediate in the production of refrigerants (principleus), plastics, and pharmaceuticals (U.S. EPA, 1975).

Chloroform is relatively stable under normal environmental conditions. When exposed to sunlight, it decomposes slowly in air but is relatively stable in water. The measured half-life for hydrolyis was found to be 15 months (Natl. Acad. Sci., 1978a). Degradation in water can occur in the presence of metals and is accelerated by aeration (Hardie, 1964).

For additional information regarding halomethanes as a class the reader is referred to the Hazard Profile on halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

Chloroform appears to be ubiquitous in the environment. A major source of chloroform contamination is from the chlorination of water and wastewater (U.S. EPA, 1975; Bellar, et al., 1974). Industrial spills may occasionally be a pulse source of transient high level contamination (Nat. Acad. Sci., 1978a; Neely, et al., 1976; Brass and Thomas, 1978).

Based on available monitoring data including information from the National Organics Monitoring Survey (NOMS), the U.S. EPA (1978b) has estimated the uptake of chloroform by adult humans from air, water, and food:

Source	Adult mg/yr	Percent uptake
	Maximum Conditions	
Atmosphere	204	36
Water	343	61
Food Supply	16	3
Total	563	100.00
	Minimum Conditions	
Atmosphere	0.41	13
Water	0.73	23
Food Supply	2.00	64
Total	3.14	100.00
	Mean Conditions	
Atmosphere	20.0	22
Water	64.0	69
Food Supply	9.00	10
Total	93	100.00

A similar estimate, not using NOMS data, has been made by the National Academy of Sciences (Nat. Acad. Sci., 1978a).

The U.S. EPA (1979a) has estimated the bioconcentration factor for chloroform to be 14 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

III. PHARMACOKINETICS

A. Absorption

The efficiency of chloroform absorption by the gastrointestinal tract is virtually 100 percent in humans (Fry, et al., 1972). The corresponding value by inhalation is 49 to 77 percent (Lehmann and Hassegawa, 1910). Quantitative estimates of dermal absorption efficiency were not encountered. Since chloroform was used as an anesthetic via dermal administration, some dermal absorption by humans can be assumed (U.S. EPA, 1979a).

B. Distribution

Chloroform is transported to all mammalian body organs and is also transported across the placenta. Strain differences for chloroform distribution in mice have been documented by Vessell, et al., (1976).

C. Metabolism

Most absorbed chloroform is not metabolized by mammals. Toxication, rather than detoxication, appears to be the major consequence of metabolism and probably involves mixed-function oxidase (MFO) enzyme systems. This observa-

tion is based on enhancement of chloroform toxicity by MFO inducers and the diminution of toxicity by MFO inhibitors (Ilett, et al., 1973, McLean, 1970). At least in the liver, covalent binding of a metabolite to tissue is associated with tissue damage (Lavigne and Marchand, 1974). Limited human data (two people) suggest that about 50 percent of absorbed chloroform is metabolized to CO_2 (Fry, et al., 1972; Chiou, 1975).

D. Excretion

In humans, the half-life of chloroform in the blood and expired air is 1.5 hours (Chiou, 1975). Most unchanged chloroform and CO_2 generated from chloroform are eliminated via the lungs. Chlorine generated from chloroform metabolism is eliminated via the urine (Taylor, et al., 1974; Fry, et al., 1972).

IV. EFFECTS

A. Carcinogenicity

Eschenbrenner and Miller (1945) demonstrated that oral doses of chloroform administered over a 16-month period induced hepatomas in strain A mice. Based on variations in dosing schedules, these researchers concluded that necrosis was prerequisite to tumor induction.

In the National Cancer Institute bioassay of chloroform (NCI, 1976), hepatocellular carcinomas were induced in mice (Table 1) and kidney epithelial tumors were induced in male rats (Table 2), following oral doses over extended periods of time.

Ten epidemiologic studies have been conducted on the association of human exposure to chloroform and/or other trihalomethanes with cancer. A review of these studies by the National Academy of Sciences (NAS, 1978b) indicated that these studies suggest that higher concentrations of trihalomethanes in drinking water may be associated with an increased frequency of cancer of the bladder. One of these studies (McCabe, 1975) claimed to demonstrate a statistically significant correlation between age, sex, race, adjusted death rate for total cancer, and chloroform levels.

B. Mutagenicity

Chloroform yielded negative results in the Ames assay (Simmon, et al. 1977).

C. Teratogenicity

At oral dose levels causing signs of maternal toxicity, chloroform had fetotoxic effects on rabbits (100 mg/kg/day) and rats (316 mg/kg/day) (Thompson, et al., 1974). Fetal abnormalities (acaudia, imperforate anus, subcutaneous edema, missing ribs, and delayed ossification) were induced when pregnant rats were exposed to airborne chloroform at 489 and 1,466 mg/m^3, 7 hrs/day, on days 6 to 15 of gestation. At 147 mg/m^3, the only effects were significant increases in delayed skull ossification and wavy ribs (Schwetz, et al., 1974).

Table 1. Hepatocellular Carcinoma Incidence in Mice[a]

	Controls		Low Dose	High Dose
	Colony	Matched		
Male	5/77	1/18	138 mg/kg 18/50	277 mg/kg 44/45
	(6%)	(6%)	(30%)	(98%)
Female	1/80	0/20	238 mg/kg 36/45	477 mg/kg 39/41
	(1%)	(0%)	(80%)	(95%)

Table 2. Statistically Significant Tumor Incidence in Rats[a]

	Males			
	Controls		Low Dose	High Dose
	Colony	Matched		
Kidney epithelial tumors/animals	0/99	0/19	90 mg/kg 4/50 (8%)	180/mg/kg 12/50 (24%)
P value	0.0000	0.0016		

[a]Source: National Cancer Institute, 1976.

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

The NIOSH Criteria Document (1974) tabulates data on the effect of chronic chloroform exposure in humans. The primary target organs appear to be the liver and kidneys, with some signs of neurological disorders. These effects have been documented only with occupational exposures.

With the exception of the possible relationship to cancer (Section IV.A), chronic toxic effects in humans, attributable to ambient levels of chloroform, have not been documented.

The chronic effects of chloroform in experimental mammals is similar to the effects seen in humans: liver necrosis and kidney degeneration (Torkelson, et al., 1976; U.S. EPA, 1979a).

F. Other Relevant Information

Ethanol pretreatment of mice reportedly enhances the toxic effects of chloroform on the liver (Kutob and Plaa, 1961); as does high fat and low protein diets (Van Oettingen, 1964; McLean, 1970). These data were generated using experimental mammals.

V. AQUATIC TOXICITY

A. Acute Toxicity

Bentley, et al. (1975) observed the 96-hour LC_{50} values for rainbow trout, (*Salmo gairdneri*), of 43,800 and 66,800 μg/l and for bluegills (*Lepomis macrochirus*), 100,000 to 115,000 μg/l, all in static tests. A 48-hour static test with *Daphnia magna* resulted in an LC_{50} of 28,900 μg/l (U.S. EPA 1979a). The observed 96-hour LC_{50} for the pink shrimp (*Panaeus duorarum*) is 81,500 μg/l. (Bentley, et al., 1975).

B. Chronic Toxicity

The chronic effects of chloroform on *Daphnia magna* were determined using flow-through methods with measured concentrations. The chronic effect level was 2,546 μg/l (U.S. EPA, 1979a). No other chronic data were available.

C. Plant Effects

Pertinent information could not be located in the available literature concerning acute chronic toxicity of chloroform to plants.

D. Residues

In the only residue study reported, the bluegill (*Lepomis macrochirus*) bioconcentrated chloroform six times after a 14-day exposure (U.S. EPA, 1979a). The tissue half-life was less than one day.

VI. EXISTING GUIDELINES AND STANDARDS

Both the human health and aquatic criteria derived by U.S. EPA (1979a), which are summarized below, are being reviewed; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on the NCI mice data, and using the "one-hit" model, the EPA (1979a) has estimated levels of chloroform in ambient water which will result in specified risk levels of human cancer:

Exposure Assumption (per day)	Risk Levels and Corresponding Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.021 µg/l	0.21 µg/l	2.1 µg/l
Consumption of fish shellfish only.	0	0.175 µg/l	1.75 µg/l	17.5 µg/l

The above risks assume that drinking water treatment and distribution will have no impact on the chloroform concentration.

The NIOSH time-weighted average exposure criterion for chloroform is 2 ppm or 9.8 mg/m^3.

The FDA prohibits the use of chloroform in drugs, cosmetics, or food contact material (14 FR 15026, 15029 April 9, 1976).

Refer to the Halomethane Hazard Profile for discussion of criterion derivation (U.S. EPA, 1979b).

B. Aquatic

For chloroform, the draft criterion to protect freshwater aquatic life, based on chronic invertebrate toxicity, is 500 µg/l as a 24-hour average and the concentration should not (based on acute effects) exceed 1,200 µg/l at any time (U.S. EPA, 1979a). To protect saltwater aquatic life, the concentration of chloroform should not exceed 620 µg/l as a 24-hour average and the concentration should not exceed 1,400 µg/l at anytime (U.S. EPA, 1979a). These were calculated from an experiment on a marine invertebrate.

CHLOROFORM

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No. 48

Chloromethane

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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

CHLOROMETHANE

SUMMARY

Chloromethane is toxic to humans by its action on the central nervous system. In acute toxicity, symptoms consist of blurring vision, headache, vertigo, loss of coordination, slurring of speech, staggering, mental confusion, nausea, and vomiting. Information is not available on chronic toxicity, teratogenicity, or carcinogenicity. Chloromethane is highly mutagenic to the bacteria, *Salmonella typhimurium*.

Only three toxicity tests have been conducted on three species of fish yielding acute values ranging from 147,000 to 300,000 µg/l. Tests on aquatic invertebrates or plants have not been conducted.

CHLOROMETHANE

I. INTRODUCTION

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

Chloromethane (CH_3Cl; methyl chloride; molecular weight 50.49) is a colorless, flammable, almost odorless gas at room temperature and pressure (Windholz, 1976). Chloromethane has a melting point of -97.7°C, a boiling point of -24.2°C, a specific gravity of 0.973 g/ml at -10°C, and a water solubility of 5.38×10^6 µg/l. It is used as a refrigerant, a methylating agent, a dewaxing agent, and catalytic solvent in synthetic rubber production (MacDonald, 1964). However, its primary use is as a chemical intermediate (Natl. Acad. Sci., 1978). Chloromethane is released to the environment by manufacturing and use emissions, by synthesis during chlorination of drinking water and municipal sewage, and by natural synthesis, with the oceans as the primary site (Lovelock, 1975). For additional information regarding the halomethanes as a class, the reader is referred to the Hazard Profile on Halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

The U.S. EPA (1975) has identified chloromethane qualitatively in finished drinking waters in the U.S. However, there are no data on its concentration in drinking water, raw water, or waste-water (U.S. EPA, 1979a), probably because it is more reactive than other chlorinated methanes (Natl. Acad. Sci., 1978).

B. Food

There is no information on the presence of chloromethane in food. There is no bioconcentration factor for chloromethane (U.S. EPA, 1979a).

C. Inhalation

Saltwater atmospheric background concentrations of chloromethane averaging about 0.0025 mg/m^3 have been reported (Grimsrud and Rasmussen, 1975; Singh, et al. 1977). This is higher than reported average continental background and urban levels and suggests that the oceans are a major source of global chloromethane (National Acad. Sci., 1978). Localized sources, such as burning of tobacco or other combustion processes, may produce high indoor-air concentrations of chloromethane (up to 0.04 mg/m^3) (Natl. Acad. Sci., 1978). Chloromethane is the predominant halomethane in indoor air, and is generally in concentrations two to ten times ambient background levels.

III. PHARMACOKINETICS

A. Absorption

Chloromethane is absorbed readily via the lungs, and to a less significant extent via the skin. Poisonings involving gastrointestinal absorption have not been reported (Natl. Acad. Sci., 1977; Davis, et al., 1977).

B. Distribution

Uptake of chloromethane by the blood is rapid but results in only moderate blood levels with continued exposure. Signs and pathology of intoxications suggest

wide tissue (blood, nervous tissue, liver, and kidney) distribution of absorbed chloromethane (Natl. Acad. Sci., 1978).

C. Metabolism

Decomposition and sequestration of chloromethane result primarily by reaction with sulfhydryl groups in intracellular enzymes and proteins (Natl. Acad. Sci., 1977).

IV. EFFECTS

A. Carcinogenicity

Pertinent information could not be located in the available literature.

B. Mutagenicity

Simmon and coworkers (1977) reported that chloromethane was mutagenic to Salmonella tryphimurium strain TA 100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required, and the number of revertants per plate was directly dose-related. Also, Andrews, et al. (1976) have demonstrated that chloromethane was mutagenic to S. typhimurium strain TA1535 in the presence and absence of added liver homogenate preparations.

C. Teratogenicity and Other Reproductive Effects

Information on positive evidence of teratogenisis or other reproductive effects was not available in the literature.

D. Chronic Toxicity

Under prolonged exposures to chloromethane (duration not specified) increased mucous flow and reduced mucosta-

tic effect of other agents (e.g., nitrogen oxides) were noted in cats (Weissbecker, et al., 1971).

E. Other Relevant Information

In acute human intoxication, chloromethane produces central nervous system depression, and systemic poisoning cases have also involved hepatic and renal injury (Hansen, er al., 1953; Spevac, et al., 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

A single 96-hour static renewal test serves as the only acute study for freshwater providing an adjusted LC_{50} value of 550,000 µg/l for the bluegill sunfish (Lepomis macrochirus). (Dawson, et al., 1977). Studies on freshwater invertebrates were not found. For the marine fish, the tidewater silversides (Menidia beryllina), a 96-hour static renewal assayed provided an LC_{50} value of 270,000 µg/l (Dawson, et al., 1977). Acute studies on marine invertebrates were not found.

B. Chronic Toxicity

In a review of the available literature, chronic testing with chloromethane has not been reported.

C. Plant Effects

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human nor the aquatic criteria derived by U.S. EPA, 1979a, which are summarized below, have gone

through the process of public review; therefore, there is a possibly that these criteria may be changed.

A. Human

OSHA (1976) has established the maximum acceptable time-weighted average air concentrations for daily eight-hour occupational exposure at 210 mg/m^3. The U.S. EPA (1979a) Draft Water Quality Criteria for Chloromethane is 2 μg/l. Refer to the Halomethanes Hazard Profile for discussion of criteria derivation (U.S. EPA, 1979b).

B. Aquatic

Criterion recommended to protect freshwater organisms have been drafted as 7,000 μg/l, not to exceed 16,000 μg/l for a 24-hour average concentration. For marine life, the criterion has been drafted as 3,700 μg/l, not to exceed 8,400 μg/l as a 24-hour average concentration.

CHLOROMETHANE

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No. 49

2-Chloronaphthalene

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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2-CHLORONAPHTHALENE

SUMMARY

Monochlorinated naphthalenes are relatively insoluble in water. They can be slowly degraded by bacteria and are subject to photochemical decomposition. Monochlorinated naphthalenes appear to bioconcentrate in plants and animals exposed to the substances. 2-Chloronaphthalene has been identified as a pollutant in a variety of industries.

No information was located on the carcinogenicity, mutagenicity, or teratogenicity of 2-chloronaphthalene or other monochlorinated naphthalenes. The metabolism of some chlorinated naphthalenes, however, proceeds through an epoxide mechanism. If an epoxide is formed as an intermediate in the metabolism of 2-chloronaphthalene, it could react with cellular macromolecules possibly resulting in cytotoxicity, mutagenicity, oncogenicity, or other effects.

I. INTRODUCTION

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

2-Chloronaphthalene ($C_{10}H_7Cl$; molecular weight 162) is a crystalline solid with a melting point of 61°C and a boiling point of 256°C. Its density at 16°C is 1.27. It is insoluble in water and soluble in many organic solvents (Weast; 1972 and Hardie, 1964).

A review of the production range (includes importation) statistics for 2-chloronaphthalene (CAS. No. 91-58-7) which is listed in the inital TSCA Inventory (1979a) has shown that between 1,000 and 9,000 pounds of this chemical were produced/imported in 1977.*/

Monochloronaphthalenes and mixtures of mono- and dichloronaphthalenes have been used for chemical-resistant gauge fluids and instrument seals, as heat exchange fluids, high-boiling specialty solvents (e.g., for solution polymerization), color dispersions, engine crankcase additives to dissolve sludges and gums, and as ingredients in motor tuneup compounds. Monochloronaphthalene was formerly used as a wood preservative (Dressler, 1979).

II. EXPOSURE

A. Environmental Fate

Polychlorinated naphthalenes do not occur naturally in the environment. Potential environmental accumulation can occur around points of manufacture of the compounds or products containing them, near sites of disposal of polychorinated naphthalene-containing wastes, and, because polychlorinated

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

biphenyls (PCBs) are to some extent contaminated by polychlorinated naphthalenes (Vos *et al*. 1970; Bowes *et al*. 1975) near sites of heavy PCB contamination.

Because polychlorinated naphthalenes are relatively insoluble in water, they are not expected to migrate far from their point of disposition. The use of mono- and dichlorinated naphthalenes as an engine oil additive and as a polymerization solvent in the fabric industry suggests possible contamination of soil or water.

Walker and Wiltshire (1955) found that soil bacteria when first grown on naphthalene could also grow on 1-chloronaphthalene, producing a diol and chlorosalicylic acid. Canonica *et al*. (1957) found similar results for 2-chloronaphthalene. Okey and Bogan (1965) studied the utilization of chlorinated substrates by activated sludge and found that naphthalene was degraded at a fairly rapid rate, while 1-and 2-chloronaphthalenes were handled more slowly.

Ruzo *et al*. (1975) studied the photodegradation of 2-chloronaphthalene in methanol. The major reaction pathways seen were dechlorination and dimerization. Jaffe and Orchin (1966) indicated that any 2-chloronaphthalene present at the surface of water could be degraded by sunlight to naphthalene. In the aquatic environment, 2-chloronaphthalene can exist as a surface film, be adsorbed by sediments, or accumulated by biota.

B. Bioconcentration

Monochlorinated naphthalenes appear to bioconcentrate in the aquatic environment. Adult grass shrimp (Palaemonetes pugio) were exposed to a mixture of mono- and dichloro naphthalenes for 15 days. The concentration of chloronaphthalenes detected in the shrimp was 63 times that of the experimental environment. When removed from the contaminated environment, however, the concentration in the shrimp returned to virtually zero within 5 days (Green and Neff, 1977).

Erickson et al. (1978a) reported a higher relative bioconcentration of the lower chlorinated naphthalenes in the fruit of apple trees grown on contaminated soil. The soil was found to have a polychlorinated naphthalene level of 190 ug/kg of which 1.6 ug/kg consisted of monochloronaphthalenes. While the apples grown on this soil had only 90 ug/kg of polychlorinated naphthalenes, the level of monochloronaphthalene was 62 ug/kg.

C. Environmental Occurrence

2-Chloronaphthalene has been identified as a pollutant in a variety of industries, e.g. organic chemical, rubber, power generation, and foundries (U.S. EPA, 1979c).

Chlorinated naphthalenes have been found more consistently in air and soil samples than in associated rivers and streams (Erickson et al., 1978b). The air samples contained mainly the mono-, di- and trichlorinated naphthalenes, while soil contained mostly the tri-, tetra- and pentachlorinated derivatives.

To date polychlorinated naphthalenes have not been identified in either drinking water or market basket food. The Food and Drug Administration has had polychlorinated naphthalene

monitoring capability for foods since 1970, but has not reported their occurrence in food (U.S. EPA, 1975).

III. PHARMACOKINETICS

Ruzo *et al*. (1976b) reported the presence of 2-chloronaphthalene in the brain, kidney, and liver of pigs six hours after injection. Small concentrations of 3-chloro-2-naphthol, a metabolite , were seen in the kidney and liver with large amounts occurring in the urine and bile. The metabolism of some chlorinated napthalenes proceeds through an epoxide mechanism (Ruzo *et al*. 1975, 1976ab; Chu *et al*., 1977ab).

IV. HEALTH EFFECTS

A. Teratogenicity, Mutagenicity, and Carcinogenicity

No information was located on the carcinogenicity, mutagenicity, or teratogenicity of polychlorinated naphthalenes.

If an epoxide is formed as an intermediate in the metabolism of 2-chloronaphthalene, it could react with cellular macromolecules. Binding might occur with protein, RNA, and DNA resulting in possible cytotoxicity, mutagenicity, oncogenicity, or other effects (Garner, 1976; Heidelberger, 1973; Wyndham and Safe, 1978).

B. Other Toxity

In man, the first disease recognized as being associated with occupational exposure to higher polychlorinated naphthalenes was chloracne. Occurrence of this disease was associated with the manufacture or use of polychloronaphthalene-treated electrical cables. Kleinfeld *et al*. (1972) noted that workers at

an electric coil manufacturing plant had no cases of chloracne while using a mono- and dichloronaphthalene mixture. When a tetra-/pentachlorinated naphthalene mixture was substituted for the original mixture, 56 of the 59 potentially exposed workers developed chloracne within a "short" time.

The lower chlorinated naphthalenes appear to have low acute toxicity. Mixtures of mono-/dichloronaphthalenes and tri-/tetrachloronaphthalenes at 500 mg/g in a mineral oil suspension applied to the skin of the human ear caused no response over a 30-day period. A mixture of penta-/hexachloronaphthalenes given under the same conditions caused chloroacne (Shelley and Kligman, 1957).

The oral LD50 for rats and mice is 2078 mg/kg and 886 mg/kg respectively (NIOSH, 1978). No mortality or illness was reported in rabbits given 500 mg/kg orally (Cornish and Block, 1958).

V. AQUATIC EFFECTS

The LC50 (ppb) of a mixture of 60% mono- and 40% dichloronaphthalenes in grass shrimp (*Palaemonetes pugio*)is as follows:

	72-hr	96-hr
post larval stage	-	449
adult	370	325

(Green and Neff, 1977)

VI. EXISTING GUIDELINES

There are no existing guidelines for 2-chloronaphthalene.

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No. 50

2-Chlorophenol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

DISCLAIMER

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2-CHLOROPHENOL

SUMMARY

Insufficient data exist to indicate that 2-chlorophenol is a carcinogenic agent. 2-Chlorophenol appears to act as a nonspecific irritant in promoting tumors in skin painting studies. No information is available on mutagenicity, teratogenicity, or subacute and chronic toxicity. 2-Chlorophenol is a weak uncoupler of oxidative phosphorylation and a convulsant.

2-Chlorophenol is acutely toxic to freshwater fish at concentrations ranging from 6,590 to 20,170 µg/l. No marine studies are available. Concentrations greater than 60 µg/l have been reported to taint cooked rainbow trout flesh in flavor impairment studies.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for 2-Chlorophenol (U.S. EPA, 1979).

2-Chlorophenol (ortho-chlorophenol) is a liquid having the empirical formula C_6H_5Cl (molecular weight: 128.56). It has the following physical/chemical properties (Rodd, 1954; Judson and Kilpatrick, 1949; Sax, 1975; Stecher, 1968; Henshaw, 1971):

Melting Point:	8.7°C
Boiling Point Range:	175-176°C
Vapor Pressure:	1 mm Hg at 12.1°C
Solubility:	Slightly soluble (1g/l) in water at 25°C and neutral pH

2-Chlorophenol is a commercially produced chemical used as an intermediate in the production of higher chlorophenols and phenolic resins and has been utilized in a process for extracting sulfur and nitrogen compounds from coal (U.S. EPA, 1979).

2-Chlorophenol undergoes photolysis in aqueous solutions as a result of UV irradiaton (Omura and Matsuura, 1971; Joschek and Miller, 1966). Laboratory studies suggest that microbial oxidation could be a degradation route for 2-chlorophenol (Loos, et al., 1966; Sidwell, 1971; Nachtigall and Butler, 1974). However, studies performed by Ettinger and Ruchhoft (1950) on the persistency of 2-chlorophenol in sewage and polluted river water indicated that the removal of monochlorophenols requires the presence of an adapted microflora.

II. EXPOSURE

A. Water

The generation of waste from the commercial production and use of 2-chlorophenol (U.S. EPA, 1979) and the inadvertent synthesis of 2-chlorophenol due to chlorination of water contaminated with phenol (Aly, 1968: Barnhart and Campbell, 1972; Jolley, 1973; Jolley, et al., 1975) are potential sources of contamination of water with 2-chlorophenol. However, no data regarding 2-chlorophenol concentrations in finished drinking water are available (U.S. EPA, 1979).

B. Food

Information on levels of 2-chlorophenol in foods is not available. Any contamination of foods is probably indirect as a result of use and subsequent metabolism of phenoxyalkanoic herbicides (U.S. EPA, 1979). Although residues of 2,4-dichlorophenol were found in tissues of animals fed 2,4-D and nemacide containing food (Clark, et al. 1975); Sherman, et al. 1972), no evidences were cited to indicate the presence of 2-chlorophenol; moreover, there was no contamination of 2-chlorophenol in milk and cream obtained from cows fed 2,4-D treated food (Bjerke, et al. 1972).

The potential for airborne exposure to 2-chlorophenol in the general environment, excluding occupational exposure, has not been reported (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for 2-chlorophenol and the edible portion of fish and shellfish consumed by Americans at

490. This estimate is based on measured steady state bioconcentration studies in bluegills.

C. Inhalation

Pertinent data regarding concentrations of 2-chlorophenol in ambient air could not be found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Data dealing directly with the absorption of 2-chlorophenol by humans and experimental animals has not been found. Chlorophenol compounds are generally considered to be readily absorbed, as would be expected from their high lipid solubility and low degree of ionization at physiological pH (Doedens, 1963; Farquharson, et al., 1958). Toxicity studies indicate that 2-chlorophenol is absorbed through the skin.

B. Distribution

Pertinent data regarding tissue distribution of 2-chlorophenol was not located in the available literature.

C. Metabolism

Data regarding the metabolism of 2-chlorophenol in humans was not available (U.S. EPA, 1979). Based on experimental work in two species, it appears that the metabolism of 2-chlorophenol in mammals is similar to that of phenol in regard to the formation and excretion of sulfate and glucuronide conjugates (Von Oettingen, 1949; Lindsay-Smith, et al. 1972) Conversion of chlorobenzene to monochlorophenols, including 2-chlorophenol, has been shown <u>in vitro</u> with rat