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

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

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

and Goldschmidt, 1976). The combination of fluoranthene and benzo(a)pyrene produced an increased number of papillomas and carcinomas, with shortened latency period (Van Duuren and Goldschmidt, 1976).

B. Mutagenicity

Fluoranthene failed to show mutagenic activity in the Ames Salmonella assay in the presence of enzyme activation mix (Tokiwa, et al. 1977; La Voie, et al. 1979).

C. Teratogenicity

Pertinent information could not be located in the available literature. Certain PAH compounds (7,12-dimethylbenz(a)anthracene and derivatives) have been shown to produce teratogenic effects in the rat (Currie, et al. 1970; Bird, et al. 1970).

D. Other Reproductive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

Pertinent information could not be located in the available literature.

V. AQUATIC TOXICITY

A. Acute Toxicity

The 96-hour LC_{50} value for the bluegill, Lepomis macrochirus, is reported to be 3,980 µg/l (U.S. EPA, 1978). The sheepshead minnow, Cyprinodon variegatus, was exposed to concentrations of fluoranthene as high as 560,000 µg/l with no observed LC_{50} value (U.S. EPA, 1978). The fresh-

water invertebrate Daphnia magna appears to have a low sensitivity to fluoranthene with a reported 48-hour EC_{50} value of 325,000 µg/l. The 96-hour LC_{50} value for the salt-water mysid shrimp, Mysidopsis bahia, is 16 µg/l.

B. Chronic Toxicity

There are no chronic toxicity data presented on exposure of fluoranthene to freshwater species. A chronic value for the mysid shrimp is 16 µg/l.

C. Plant Effects

The freshwater alga, Selenastrum capricornutum, when exposed to fluoranthene resulted in a 96-hour EC_{50} value for cell number of 54,400 µg/l. On the same criterion, the 96-hour EC_{50} value for the marine alga, Skeletonema costatum, is 45,600 µg/l (U.S. EPA, 1979).

D. Residues

No measured steady-state bioconcentration factor (BCF) is available for fluoranthene. A BCF of 3,100 can be estimated using the octanol/water partition coefficient of 79,000.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The World Health Organization (1970) has established a recommended standard of 0.2 µg/l for all PAH compounds in drinking water.

Based on the no-effect level determined in a single animal study (Hoffman, et al. 1972), the U.S. EPA (1979) has estimated a draft ambient water criterion of 200 µg/l for fluoranthene. However, the lower level derived for

total PAH compounds is expected to have precedence for fluoranthene.

B. Aquatic

For fluoranthene, the draft criterion to protect freshwater aquatic life is 250 µg/l as a 24-hour average, not to exceed 560 µg/l at any time. For saltwater life, the criterion is 0.30 µg/l as a 24-hour average, not to exceed 0.69 µg/l at any time.

FLUOROANTHENE

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No. 104

Formaldehyde

Health and Environmental Effects

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APRIL 30, 1980

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DISCLAIMER

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

FORMALDEHYDE

SUMMARY

The major source of formaldehyde contamination in the environment is combustion processes, especially automobile emissions. Formaldehyde is a recognized component of photochemical smog. A recent source of concern is the release of formaldehyde from resins used in home construction and insulation.

Bioaccumulation of formaldehyde is considered unlikely due to its high chemical reactivity. Formaldehyde rapidly degrades in the atmosphere by photochemical processes; however, it can also be formed by the photochemical oxidation of atmospheric hydrocarbons.

Formaldehyde is rapidly absorbed via the lungs or gut; following absorption into the blood, however, formaldehyde disappears rapidly due to reactions with tissue components and because of its metabolism.

The U.S. EPA's Carcinogen Assessment Group recently concluded that "there is substantial evidence that formaldehyde is likely to be a human carcinogen." This finding was based on preliminary results from a chronic inhalation study of formaldehyde which reported carcinomas of the nasal cavity in 3 rats after 16 months of exposure. This type of tumor is extremely rare is unexposed rats of the strain used in the study.

There is an extensive data base showing that formaldehyde is mutagenic in microorganisms, plants, insects, cultured mammalian cells, and mice. It was negative in a teratogenicity assay. Formaldehyde is known to be a mucous membrane irritant in humans;

it is also known to be an allergen in sensitive individuals.

I. INTRODUCTION

This profile is based on a U.S. EPA report entitled "Investigation of Selected Potential Environmental Contaminants: Formaldehyde" (1976) and other selected references.

Formaldehyde (HCHO; molecular weight 30.03) is a colorless gas having a pungent odor and an irritating effect on mucous membranes. It has the following physical/chemical properties (U.S. EPA, 1976; Windholz, 1976):

Boiling Point:	-19.2°C
Melting Point:	-92°C
Density in Air:	1.067
Solubility:	soluble in water and many organic solvents.

A review of the production range (includes importation) statistics for formaldehyde (CAS No. 50-00-0) which is listed in the initial TSCA Inventory (1979a) has shown that between 2 billion and 7 billion pounds of this chemical were produced/imported in 1977.*/

Formaldehyde is usually sold as an aqueous solution containing 37% formaldehyde by weight; it is also available as a linear

*/ 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).

polymer known as paraformaldehyde and a cyclic trimer known as trioxane. Formaldehyde is used in the production of urea-formaldehyde resins, phenol-formaldehyde resins, polyacetal resins, various other resins, and as an intermediate in the production of a variety of chemicals. Manufacture of resins consumes over 50% of annual domestic formaldehyde production. Urea-formaldehyde and phenol-formaldehyde resins are used as adhesives for particle board and plywood, and in making foam insulation. Polyacetal resins are used to mold a large variety of plastic parts for automobiles, appliances, hardware, and so on (U.S. EPA, 1976).

II. EXPOSURE

NIOSH (1976) estimates that 1,750,000 workers are potentially exposed to formaldehyde in the workplace.

A. Environmental Fate

Formaldehyde and nascent forms of formaldehyde can undergo several types of reactions in the environment including depolymerization, oxidation-reduction, and reactions with other atmospheric and aquatic pollutants. Formaldehyde can react photochemically in the atmosphere to form H and HCO radicals; once formed, these radicals can undergo a wide variety of atmospheric reactions (U.S. EPA, 1976). Hydrogen peroxide can also be formed during photodecomposition of formaldehyde (Purcell and Cohen, 1967; Bufalini *et al.*, 1972). The atmospheric half-life of formaldehyde is less than one hour in sunlight (Bufalini *et al.*, 1972).

Even though formaldehyde is often used as a bacteriocide, there are some microorganisms which can degrade the chemical (U.S. EPA, 1976). Kamata (1966) studied biological degradation of formaldehyde in lake water. Under aerobic conditions in the laboratory, known quantities of formaldehyde were decomposed in about 30 hours at 20°C; anaerobic decomposition took about 48 hours. No decomposition was noted in sterilized lake water.

Paraformaldehyde slowly hydrolyzes and depolymerizes as it dissolves in water to yield aqueous formaldehyde. Trioxane has more chemical and thermal stability; it is inert under aqueous neutral or alkaline conditions. In dilute acid solutions, it slowly depolymerizes (U.S. EPA, 1976).

B. Bioconcentration

Formaldehyde is a natural metabolic product and does not bioconcentrate (U.S. EPA, 1976).

C. Environmental Occurrence

Environmental contamination from formaldehyde manufacture and industrial use is small and localized compared with other sources. Combustion and incineration processes comprise the major sources of formaldehyde emissions. Stationary sources of formaldehyde emissions include power plants, manufacturing facilities, home consumption of fuels, incinerators, and petroleum refineries. Mobile sources of formaldehyde emissions include automobiles, diesels, and aircraft. The automobile, however, is the largest source of formaldehyde pollution. It is estimated that over 800 million pounds of formaldehyde were released to the air in the United States in 1975; of this amount, over 600

million pounds are estimated to result from the use of automobiles. In addition to formaldehyde, automobile exhaust also contains large quantities of hydrocarbons. Through photochemical processes in the atmosphere, these hydrocarbons are oxidized to formaldehyde, among other things, further adding to the environmental load of formaldehyde (U.S. EPA, 1976).

Urea-formaldehyde foam insulation has been implicated as a source of formaldehyde fumes in homes insulated with this material. Wood laminates (plywood, chip board, and particle board) commonly used in the construction of mobile homes are also known to release formaldehyde vapors into the home atmosphere (U.S. EPA, 1979b).

III. PHARMACOKINETICS

A. Absorption

Under normal conditions formaldehyde can enter the body through dermal and occular contact, inhalation and ingestion. On dermal contact, formaldehyde reacts with proteins of the skin resulting in crosslinking and precipitation of the proteins. Inhalation of formaldehyde vapors produces irritation and inflammation of the bronchi and lungs; once in the lungs, formaldehyde can be absorbed into the blood. Ingestion of formaldehyde is followed immediately by inflammation of the mucosa of the mouth, throat, and gastrointestinal tract (U.S. EPA, 1976). Absorption appears to occur in the intestines (Malorny *et al.*, 1965).

B. Distribution

Following absorption into the blood stream, formaldehyde disappears rapidly due to condensation reactions with tissue components and oxidation to formic acid (U.S. EPA, 1976).

C. Metabolism

The main metabolic pathway for formaldehyde appears to involve initial oxidation to formic acid, followed by further oxidation to CO_2 and H_2O. In rats fed radiolabeled formaldehyde, 40% of the radiolabel was recovered as respiratory CO_2 (Buss et al., 1964). Liver and red blood cells appear to be the major sites for the oxidation of formaldehyde to formic acid (U.S. EPA, 1976; Malorny et al., 1965).

D. Excretion

Some of the formic acid metabolite is excreted in the urine as the sodium salt; most, however, is oxidized to CO_2 and eliminated via the lungs (U.S. EPA, 1976).

IV. HEALTH EFFECTS

A. Carcinogenicity

Watanabe et al. (1954) observed sarcomas at the site of injection in 4 of 10 rats given weekly subcutaneous injections of formaldehyde over 15 months (total dose 260 mg per rat). Tumors of the liver and omentum were reported in two other rats. The authors do not mention any controls.

Groups of mice were exposed to formaldehyde by inhalation at 41 ppm and 81 ppm for one hour a day thrice weekly for 35 weeks. After the initial 35-week exposure to 41 ppm, the mice were

exposed for an additional 29 weeks at 122 ppm. No tumors or metaplasias were found, although numerous changes were observed in respiratory tissues (Horton et al., 1963). The study is considered flawed for several reasons: mice were not observed for a lifetime; survival was poor; many tissues were not examined histologically (U.S. EPA, 1976; U.S. EPA, 1979b).

In a lifetime inhalation study of the combination of hydrochloric acid (10.6 ppm) and formaldehyde (14.6 ppm) vapors in rats, 25/100 animals developed squamous cell carcinomas of the nasal cavity (Nelson, 1979). Nelson also reported that bis-chloromethyl ether, a known carcinogen, was detected in the exposure atmosphere; however, concentrations were not reported.

In a report of interim results (after 16 months of a 2-year study) from a chronic inhalation study of formaldehyde in rats and mice, the Chemical Industry Institute of Toxicology (1979) reported that squamous cell carcinomas of the nasal cavity were observed in three male rats exposed to 15 ppm of formaldehyde (highest dose tested). This type of tumor is extremely rare in unexposed rat of the strain used in this study.

Following receipt of the CIIT (1979) study, the U.S. EPA's Carcinogen Assessment Group (1979c) concluded that "there is substantial evidence that formaldehyde is likely to be a human carcinogen." The unit risk calculation (the lifetime cancer risk associated with continuous exposure to 1 ug/m^3 of formaldehyde) based on the preliminary results from CIIT is estimated to be 3.4 $x10^{-5}$. This estimate may change when the final results of the CIIT study become available.

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B. Mutagenicity

There is an extensive data base showing that formaldehyde is mutagenic in several species including mice, Drosophila, plants, Saccharomyces cerevisiae, Neurospora Crassa, and several species of bacteria. Formaldehyde also produced unscheduled DNA synthesis in a human cell line. These and other early reports of mutagenic activity have been reviewed by Auerbach et al. (1977) and U.S. EPA (1976).

Reports in the recent literature have supported the finding that formaldehyde is a mutagen: Magana-Schwencke et al. (1978) in a study with S. cerevisiae; Wilkens and MacLeod (1976) in E. coli; Martin et al. (1978) in an unscheduled DNA synthesis test in human HeLa cells; Obe and Beek (1979) in sister chromatid exchange assays in a Chinese hamster ovary (CHO) cell line and in cultured human lymphocytes.

C. Teratogenicity

Formaldehyde has been found negative in teratogenicity assays in beagle dogs (Hurni and Ohden, 1973) and rats (Gofmekler and Bonashevskaya, 1969).

D. Other Reproductive Effects

No changes were observed in the testes of male rats exposed to air concentrations of 1 mg/m^3 of formaldehyde for 10 days (Gofmekler and Bonashevskaya, 1969).

E. Other Chronic Toxicity

Groups of rats, guinea pigs, rabbits, monkeys, and dogs were continuously exposed to approximately 4.6 mg/m^3 of formaldehyde for 90 days. Hematologic values were normal, however, some

interstitial inflammation occurred in the lungs of all species (Coon *et al.*, 1970).

F. Other Relevant Information

Formaldehyde vapor is quite irritating and is a major cause of the mucous membrane irritation experienced by people exposed to smog. Dermatitis from exposure to formaldehyde is a common problem in workers and consumers who contact the chemical regularly. Formaldehyde is also known to be an allergen in sensitive individuals (U.S. EPA, 1976).

V. AQUATIC EFFECTS

The use of formalin (aqueous formaldehyde) as a chemotherapeutant for control of fungus on fish eggs and ectoparasites on fish is a widely accepted and successful technique. However, unless certain criteria are met formalin may cause acute toxic effects in fish (U.S. EPA, 1976). The acute toxicity of formalin to fish has been reviewed by the U.S. Department of Interior (1973). Analysis of toxicity levels indicates that a wide range of tolerances exist for different species; striped bass appear to be the most sensitive with an LC_{50} of 15 to 35 ppm.

The LC_{50} of formaldehyde for *Daphnia magna* is reported to range between 100 to 1000 ppm (Dowden and Bennett, 1965). The 48-hour median threshold limit (TLm) for *Daphnia* was about 2 ppm (McKee and Wolf, 1971).

No effects were observed in crayfish (*Procambarus blandingi*) exposed to 100 ul/l of formalin (concentration unspecified) for 12 to 72 hours (Helm, 1964).

VI. EXISTING GUIDELINES

The OSHA standard for formaldehyde in workplace air is a time weighted average (TWA) of 3 ppm with a ceiling concentration of 5 ppm (39 CFR 23540). The NIOSH recommended standard is a ceiling concentration of 1.2 mg/m^3 (about 0.8 ppm) (NIOSH, 1976). The ACGIH (1977) recommends a ceiling value of 2 ppm (3 mg/m^3).

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No. 105

Formic Acid

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

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FORMIC ACID

Summary

There is no information available on the possible carcinogenic, mutagenic, teratogenic, or adverse reproductive effects of formic acid.

Formic acid has been reported to produce albuminuria and hematuria in humans following chronic exposure. Exposure to high levels of the compound may produce circulatory collapse, renal failure, and secondary ischemic lesions in the liver and heart.

Formic acid is toxic to freshwater organisms at concentrations ranging from 120,000 to 2,500,000 ug/l. *Daphnia magna* was the most sensitive freshwater species tested. Marine crustaceans were adversely affected by exposure to formic acid at concentrations from 80,000 to 90,000 ug/l.

FORMIC ACID

I. INTRODUCTION

Formic acid (CAS registry number 64-18-6) is a colorless, clear, fuming liquid with a pungent odor (Hawley, 1971; Windholz, 1976; Walker, 1966). It is a naturally formed product, produced by bees, wasps, and ants (Casarett and Doull, 1975). Formic acid has widespread occurrence in a large variety of plants, including pine needles, stinging nettles, and foods (Furia and Bellanca, 1971; Walker, 1966). Industrially, it is made by heating carbon monoxide with sodium hydroxide under heat and pressure, or it may be formed as a coproduct from butane oxidation (Walker, 1966). It has the following physical and chemical constants (Windholz, 1976; Walker, 1966):

Property	Pure	90%	85%
Formula:	CH_2O_2	---	---
Molecular Weight:	46.02	---	---
Melting Point:	8.4°C	-4°C	-12°C
Boiling Point:	100.5°C	---	---
Density:	1.220^{20}_{4}	1.202^{25}_{25}	1.194^{25}_{25}
Vapor Pressure:	33.1 torr @ 20°C		
Solubility:	Miscible in water, alcohol, and ether; soluble in acetone, benzene, and toluene		
Demand (1979):	67.5 million lbs. (CMR, 1979)		

Formic acid is marketed industrially in 85, 90, and 98 percent aqueous solutions. It is also available at 99+ percent purity on a semicommercial scale. Formic acid is used primarily as a volatile acidulating agent; in textile dyeing and finishing, including carpet printing; in chemical synthesis and pharmaceuticals; and in tanning and leather treatment (CMR, 1979; Walker, 1966).

II. EXPOSURE

A. Water

Formic acid has been detected in raw sewage, in effluents from sewage treatment plants, and in river water (Mueller, et al. 1958). It has also been identified in effluents from chemical plants and paper mills (U.S. EPA, 1976).

B. Food

A large variety of plants contain free formic acid; it has been detected in pine needles, stinging nettle, and fruits (Walker, 1966). It has been identified in a number of essential oils, including petitgrain lemon and bitter orange (Furia and Bellanca, 1971). Formic acid is also reported to be a constitutent of strawberry aroma (Furia and Bellanca, 1971). In the U.S. this chemical may be used as a food additive; allowable limits in food range from 1 ppm in non-alcoholic beverages to 18 ppm in candy (Furia and Bellanca, 1971). It may also occur in food as a result of migration from packaging materials (Sax, 1975).

C. Inhalation

Ambient air concentrations of formic acid range from 4 to 72 ppb (Graedel, 1978). Emission sources include forest fires, plants, tobacco smoke, lacquer manufacture, and combustion of plastics (Graedel, 1978). It

has also been identified in the liquid condensate from the pyrolysis of solid municipal waste (Orphey and Jerman, 1970).

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Acute toxicity studies in animals and poisoning incidents in man indicate that formic acid is absorbed from the respiratory tract and from the gastrointestinal tract (Patty, 1963; NIOSH, 1977).

B. Distribution

Pertinent data were not found in the available literature.

C. Metabolism

Formate may be oxidized to produce carbon dioxide by the activity of a catalase-peroxide complex, or it may enter the folate-dependent one carbon pool following activation and proceed to carbon dioxide via these reactions (Palese and Tephly, 1975). Species differences in the relative balance of these two pathways for the metabolism of formate have been postulated in order to explain the greater accumulation of formate in the blood of monkeys administered methanol, compared to rats similarly treated (Palese and Tephly, 1975).

D. Excretion

Following intraperitoneal administration of ^{14}C formate to rats, significant amounts of $^{14}CO_2$ were detected in these samples (Palese and Tephly, 1975).

IV. EFFECTS

A. Pertinent data could not be located in the available literature.

B. Chronic Toxicity

Chronic human exposure to formic acid has been reported to produce albuminuria and hematuria (Windholz, 1976).

C. Other Pertinent Information

Formic acid is severely irritating to th skin, eyes, and respiratory tract (NIOSH, 1977). Gleason (1969) has indicated that exposure to high levels of compound may produce circulatory collapse, renal failure, and secondary ischemic lesions in the liver and heart.

V. AQUATIC TOXICITY

A. Acute Toxicity

Dowden and Bennett (1965) demonstrated a 24-hour LC_{50} value of 175,000 µg/l for bluegill sunfish (Lepomis macrochirus) exposed to formic acid. Bringmann and Kuhn (1959) observed a 48-hour LC_{50} value of 120,000 µg/l for waterfleas (Daphnia magna) exposed to formic acid.

Verschueren (1979) reported that a formic acid concentration of 2,500,000 µg/l was lethal to freshwater scuds (Gammarus pulex) and 1,000,000 µg/l was a perturbation threshold value for the fish Trutta iridea.

Portmann and Wilson (1971) determined 48-hour LC_{50} values ranging from 80,000 to 90,000 µg/l for the marine shore crab (Carcinus maenas) exposed to formic acid in static renewal bioassays.

B. Chronic Toxicity

Pertinent data were not found in the available literature.

C. Plant Effects

McKee and Wolf (1963) reported that formic acid at a concentration of 100,000 µg/l was toxic to the freshwater algae, Scenedesmus sp.

D. Residue

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The eight-hour, TWA exposure limit for occupational exposure to formic acid is 5 ppm (ACGIH, 1977).

B. Aquatic

Hahn and Jensen (1977) have suggested an aquatic toxicity rating range of 100,000 to 1,000,000 µg/l based on 96-hour LC_{50} values for aquatic organisms exposed to formic acid.

FORMIC ACID

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No. 106

Fumaronitrile

Health and Environmental Effects

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

APRIL 30, 1980

-1231-

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.

FUMARONITRILE

Summary

Information on the carinogenic, mutagenic, or teratogenic effects of fumaronitrile was not found in the available literature. LD_{50} values for injected mice and orally dosed rats were 38 and 50 mg/kg, respectively. Reports of chronic toxicity studies were not found in the available literature.

FUMARONITRILE

I. INTRODUCTION

This profile is based upon relevant literature identified through mechanized bibliographic searches such as TOXLINE, BIOSIS, Chemical Abstracts, AGRICOLA and MEDLARS, as well as manual searches. Despite approximately 70 citations for fumaronitrile, approximately 95 percent of these concerned the chemistry of fumaronitrile or its reactions with other chemicals. Apparently, the chief use of fumaronitrile is as a chemical intermediate in the manufacture of other chemicals, rather than end uses as fumaronitrile per se. Undoubtedly, this accounts for its low profile in the toxicological literature.

Fumaronitrile or trans-1,2-dicyanoethylene (molecular weight 78.07) is a solid that melts at 96.8°C (Weast, 1975), has a boiling point of 186°C, and a specific gravity of 0.9416 at 25°C. It is soluble in water, alcohol, ether, acetone, chloroform, and benzene. Fumaronitrile is used as a bactericide (Law, 1968), and as an antiseptic for metal cutting fluids (Wantanabe, et al., 1975). It is used to make polymers with styrene numerous other compounds. This compound is easily isomerized to the cis-form, maleonitrile, which is a bactericide and fungicide (Ono, 1979). It is conveniently synthesized from primary amides under mild conditions (Campagna, et al., 1977).

II. EXPOSURE

Human exposure to fumaronitrile from foods cannot be assessed, due to a lack of monitoring data.

Bioaccumulation data on fumaronitrile were not found in the available literature.

III. PHARMACOKINETICS

Specific information on the metabolism, distribution, absorption, or elimination of fumaronitrile was not found in the available literature.

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity, Reproductive Effects, and Chronic Toxicity

Pertinent data could not be located in the available literature.

B. Acute Toxicity

LD_{50} values for injected mice and orally dosed rats were 38 and 50 mg/kg, respectively (Zeller, et al., 1969).

V. AQUATIC TOXICITY

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

VI. EXISTING GUIDELINES AND STANDARDS

Data concerning existing guidelines and standards for fumaronitrile were not found in the available literature.

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No. 107

Halomethanes

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

-1237-

DISCLAIMER

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HALOMETHANES

Summary

The halomethanes are a subcategory of halogenated hydrocarbons. There is little known concerning the chronic toxicity of these compounds. Acute toxicity results in central nervous system depression and liver damage. The fluorohalomethanes are the least toxic. None of the halomethanes have been demonstrated to be carcinogenic; however, chloro-, bromo-, dichloro-, bromodichloro-, and tribromomethane have been shown to be mutagenic in the Ames assay. There are no available data on the teratogenicity of the halomethanes, although both dichloromethane and bromodichloromethane have been shown to affect the fetus.

Brominated methanes appear to be more toxic to aquatic life th[illegible] chlorinated methanes. Acute toxicity data is rather limited in scope, but reveals toxic concentrations in the range of 11,000 to 550,000 μg/l.

I. INTRODUCTION

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

The halomethanes are a sub-category of halogenated hydrocarbons. This document summarizes the following halomethanes: chloromethane (methyl chloride); bromomethane (methyl bromide, monobromomethane, embafume); dichloromethane (methylene chloride, methylene dichloride, methylene bichloride); tribromomethane (bromoform); trichlorofluoromethane (trichloromonofluoromethane, fluorotrichloromethane, Frigen 11, Freon 11, Arcton 9); and dichlorodifluoromethane (difluorodichloromethane, Freon 12, Frigen 12, Arcton 6, Genetron 12, Halon, Isotron 2) and bromodichloromethane. These halomethanes are either colorless gases or liquids at environmental temperatures and are soluble in water at concentrations from 13×10^6 to 2.5×10^6 µg/l, except for tribromomethane which is only slightly soluble and bromodichloromethane which is insoluble. Halomethanes are used as fumigants, solvents, refrigerants, and in fire extinguishers. Additional information on the physical/chemical properties of chloromethane, dichloromethane, bromomethane, and bromodichloromethane, can be found in the ECAO/EPA (Dec. 1979) hazard profile on these chemicals.

II. EXPOSURE

A. Water

The U.S. EPA (1975) has identified chloromethane, bromomethane, dichloromethane, tribromomethane, and bromodichloromethane in finished drinking waters in the United States. Halogenated hydrocarbons have been found in finished waters at greater concentrations than in raw waters (Symons, et al. 1975), with the concentrations related to the organic content of the raw water. The concentrations of halomethanes detected in one survey of U.S. drinking waters are:

Halomethanes in the U.S. EPA Region V
Organics Survey (83 Sites)

Compound	Percent of Locations with Positive Results	Concentrations (mg/l) Median	Maximum
Bromodichloromethane	78	0.006	0.031
Tribromomethane	14	0.001	0.007
Dichloromethane	8	0.001	0.007

Source: U.S. EPA, 1975

Symons, et al. (1975) concluded that trihalomethanes resulting from chlorination are widespread in chlorinated drinking waters. An unexplained increase in the halomethane concentration of water samples occurred in the distribution system water as compared to the treatment plant water.

B. Food

Bromomethane residues from fumigation decrease rapidly from both atmospheric transfer and reaction with proteins to form inorganic bromide residues. With proper aeration and product processing, most residual bromomethane will disappear rapidly due to methylation reactions and volatilization (Natl. Acad. Sci., 1978; Davis, et al. 1977). The U.S. EPA (1979) has estimated the weighted average bioconcentration factors for dichloromethane and tribromomethane to be 1.5 and 14, respectively, for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of these two compounds. Bioconcentration factors for the other halomethanes have not been determined.

C. Inhalation

Saltwater atmospheric background concentrations of chloromethane and bromomethane, averaging about 0.0025 mg/m^3 and 0.00036 mg/m^3 respectively, have been reported (Grimsrud and Rasmussen, 1975; Singh, et al. 1977). These values are higher than reported average continental background

and urban levels suggesting that the oceans may be a major source of global chloromethane and bromomethane. Outdoor bromomethane concentrations as high as 0.00085 mg/m^3 may occur near light traffic. This results from the combustion of ethylene dibromide, a component of leaded gasoline (Natl. Acad. Sci., 1978). Reported background concentrations of dichloromethane in both continental and saltwater atmospheres are about 0.00012 mg/m^3, while urban air concentrations ranged from less than 0.00007 to 0.0005 mg/m^3. Local high indoor concentrations can be caused by the use of aerosol sprays or solvents (Natl. Acad. Sci., 1978). Concentrations of dichlorodifluoromethane and trichlorofluoromethane in the atmosphere over urban areas are several times those over rural or oceanic areas. This probably indicates that the primary modes of entry into the environment, i.e., use of refrigerants and aerosols, are greater in industrialized and populated areas (Howard, et al. 1974). Average concentrations of trichlorofluoromethane reported for urban atmospheres have ranged from nil to 3×10^{-3} mg/m^3, and concentrations for dichlorofluoromethane ranged from 3.5×10^{-3} to 2.9×10^{-2} mg/m^3.

III. PHARMACOKINETICS

A. Absorption

Absorption via inhalation is of primary importance and is fairly efficient for the halomethanes. Absorption can also occur via the skin and gastrointestinal tract, although this is generally more significant for the nonfluorinated halomethanes than for the fluorocarbons (Natl. Acad. Sci., 1978; Davis, et al. 1977; U.S. EPA, 1976; Howard, et al. 1974).

B. Distribution

Halomethanes are distributed rapidly to various tissues after absorption into the blood. Preferential distribution usually occurs to tissues with high lipid content (U.S. EPA, 1979).

C. Metabolism

Chloromethane and bromomethane undergo reactions with sulfhydryl groups in intracellular enzymes and proteins, while bromochloromethane in the body is hydrolyzed in significant amounts to yield inorganic bromide. Dichloromethane is metabolized to carbon monoxide which increases carboxyhemoglobin in the blood and interferes with oxygen transport (Natl. Acad. Sci., 1978). Tribromomethane is apparently metabolized to carbon monoxide by the cytochrome P-450-dependent mixed function oxidase system (Ahmed, et al. 1977). The fluorinated halomethanes form metabolites which bind to cell constituents, particularly when exposures are long-term (Blake and Mergner, 1974). Metabolic data for bromodichloromethane could not be located in the available literature.

D. Excretion

Elimination of the halomethanes and their metabolites occurs mainly through expired breath and urine (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

None of the halomethanes summarized in this document are considered to be carcinogenic. Theiss and coworkers (1977) examined the tumorigenic activity of tribromomethane, bromodichloromethane, and dichloromethane in strain A mice. Although increased tumor responses were noted with each, in no case were all the requirements met for a positive carcinogenic response, as defined by Shimkin and Stoner (1975). Several epidemiologic studies have

established an association between trihalomethane levels in municipal drinking water supplies in the United States and certain cancer death rates (various sites) (Natl. Acad. Sci., 1978; Cantor and McCabe, 1977). Cantor, et al. (1978) cautioned that these studies have not been controlled for all confounding variables, and the limited monitoring data that were available may not have been an accurate reflection of past exposures.

B. Mutagenicity

Simmon, et al. (1977) reported that chloromethane, bromomethane, and dichloromethane were all mutagenic to Salmonella typhimurium strain TA100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required. Only marginal positive results were obtained with bromoform and bromodichloromethane. Andrews, et al. (1976) and Jongen, et al. (1978) have confirmed the positive Ames results for chloromethane and dichloromethane, respectively. Dichloromethane was negative in mitotic recombination in S. cerevisiae D3 (Simmon, et al. 1977) and in mutagenicity tests in Drosophila (Filippova, et al. 1967). Trichlorofluoromethane and dichlorofluoromethane were negative in the Ames assay (Uehleke, et al. 1977), and dichlorodifluoromethane in a rat feeding study (Sherman, 1974) caused no increase in mutation rates over controls.

C. Teratogenicity

Pertinent information could not be located in the available literature.

D. Other Reproductive Effects

Gynecologic problems have been reported in female workers exposed to dichloromethane and gasoline vapors (Vozovaya, 1974). Evidence of feto-embryotoxicity has been noted in rats and mice exposed to dichloromethane

vapor on gestation days 6 to 15 (Schwetz, et al. 1975). Some fetal anomalies were reported in experiments in which mice were exposed to vapor of bromodichloromethane at 8375 mg/m^3, 7 hours/day during gestation days 6 to 15 (Schwetz, et al. 1975).

E. Chronic Toxicity

Schuller, et al. (1978) have observed a suppression of cellular and humoral immune response indices in female ICR mice exposed by gavage for 90 days to bromodichloromethane at 125 mg/kg daily. Tribromomethane suppressed reticuloendothelial system function (liver and spleen phagocytic uptake of Listeria monocytogenes) in mice exposed 90 days at daily doses of 125 mg/kg or less (Munson, et al. 1977,1978). Information pertinent to the chronic toxicity of the other halomethanes could not be located in the available literature.

F. Other Relevant Information

In general, acute intoxication by halomethanes appears to involve the central nervous system and liver function (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity studies for halomethanes have obtained acute LC_{50} values for the bluegill sunfish (Lepomis machrochirus) of 11,000 µg/l for methylbromide, 29,300 µg/l for bromoform, 224,000 µg/l for methylene chloride and 550,000 for methyl chloride. A static bioassay produced a 96-hour LC_{50} value of 310,000 µg/l methylene chloride for the fathead minnow (Pimephales promelas) while a flow-through assay produced an LC_{50} value of 193,000 µg/l. In freshwater invertebrates two acute studies with Daphnia

magna resulted in LC_{50} values of 46,500 µg/l for bromoform, and 224,000 µg/l for methylene chloride. In marine fish, LC_{50} values for the sheepshead minnow (Cyprinodon variegatus) were 17,900 µg/l for bromoform and 180,958 µg/l for methylene chloride. For the tidewater silversides (Menidia beryllina) LC_{50} values of 12,000 µg/l for methylbromide and 147,610 µg/l for methylene chloride were obtained. Adjusted LC_{50} values for the marine mysid shrimp (Mysidopsis bahia) were 24,400 µg/l for bromoform and 256,000 µg/l for methylene chloride (U.S. EPA, 1979).

B. Chronic Toxicity

The only chronic value for an aquatic species was 9,165 µg/l for the sheepshead minnow.

C. Plant Effects

Effective concentrations for chlorophyll a and cell numbers in freshwater algae Selenastrum capricornutum ranged from 112,000 to 116,000 µg/l for bromoform and 662,000 µg/l for methylene chloride, while effective concentrations for the marine algae (Sketonema costatum) were reported as 11,500 to 12,300 µg/l for bromoform and 662,000 µg/l for methylene chloride (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

Positive associations between human cancer mortality rates and trihalomethanes (chloroform, bromodichloromethane, tribromomethane) in drinking

water have been reported. There have also been positive results for tribromomethane using strain A/St. male mice in the pulmonary adenoma bioassay. Bromomethane, chloromethane, dichloromethane, bromodichloromethane and tribromomethane have been reported as mutagenic in the Ames test without metabolic activation. Dichlorodifluoromethane caused a significant increase in mutant frequency in Neurospora crassa (mold), but was negative in the Ames test. No data implicating trichlorofluoromethane as a possible carcinogen have been published.

Because positive results for the mutagenic endpoint correlate with positive results in in vivo bioassays for oncogenicity, mutagenicity data for the halomethanes suggests that several of the compounds might also be carcinogenic. Since carcinogenicity data currently available for the halomethanes were not adequate for the development of water quality criteria levels, the draft criteria recommended for chloromethane, bromomethane, dichloromethane, tribromomethane and bromodichloromethane are the same as that for chloroform, 2 μg/l.

Chloromethane: OSHA (1976) has established the maximum acceptable time-weighted average air concentration for daily 8-hour occupational exposure at 219 mg/m^3.

Bromomethane: OSHA (1976) has a threshold limit value of 80 mg/m^3 for bromomethane, and the American Conference of Governmental Industrial Hygienists (ACGIH, 1971) has a threshold limit value of 78 mg/m^3.

Dichloromethane: OSHA (1976a,b) has established an 8-hour time-weighted average for dichloromethane of 1,737 mg/m^3, however, NIOSH (1976) has recommended a 10-hour time-weighted average exposure limit of 261 mg/m^3 of dichloromethane in the presence of no more carbon monoxide than 9.9 mg/m^3.

Tribromomethane: OSHA (1976a,b) has established an 8-hour time-weighted average for tribromomethane of 5 mg/m^3.

Bromodichloromethane: There is no currently established occupational exposure standard for bromodichloromethane.

Trichlorofluoromethane and dichlorodifluoromethane: The current OSHA (1976) 8-hour time-weighted average occupational standards for trichlorofluoromethane and dichlorodifluoromethane are 5,600 and 4,950 mg/m^3, respectively. The U.S. EPA (1979) draft water quality criteria for trichlorofluoromethane and dichlorodifluoromethane are 32,000 and 3,000 μg/l, respectively.

B. Aquatic

Draft criteria for the protection of freshwater life have been derived as 24-hour average concentrations for the following halomethanes: methylbromide - 140 μg/l not to exceed 320 μg/l; bromoform - 840 μg/l not to exceed 1,900 μg/l; methylene chloride - 4,000 μg/l not to exceed 9,000 μg/l; and methyl chloride - 7,000 μg/l not to exceed 16,000 μg/l.

Draft criteria for the protection of marine life have been derived as 24- hour average concentrations for the following halomethanes: methylbromide 170 μg/l not to exceed 380 μg/l; bromoform - 180 μg/l not to exceed 420 μg/l; methylene chloride - 1,900 μg/l not to exceed 4,400 μg/l; and methyl chloride - 3,700 μg/l not to exceed 8,400 μg/l.

HALOMETHANES

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No. 108

Heptachlor

Health and Environmental Effects

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APRIL 30, 1980

-1252-

DISCLAIMER

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SPECIAL NOTATION

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

HEPTACHLOR

Summary

Heptachlor is an organochlorinated cyclodiene insecticide, and has been used mostly in its technical, and hence, impure form, in most bioassays up to the present. Nevertheless, it has been found that heptachlor and its metabolite, heptachlor epoxide, induce liver cancer in mice and rats. Heptachlor was mutagenic in two mammalian assays but not in the Ames test. In long-term reproductive studies in rats, heptachlor caused reduction in litter size, decreased lifespan in suckling rats, and cataracts in both parents and offspring. Little is known about other chronic effects of heptachlor except that it induces alterations in glucose homeostasis. It causes convulsions in humans. Heptachlor epoxide, its major metabolite, accumulates in adipose tissue and is more acutely toxic than the parent compound.

Numerous studies indicate that heptachlor is highly toxic, both acutely and chronically, to aquatic life. Ninety-six hour LC_{50} values for freshwater fish range from 7.0 µg/l to 320 µg/l and 24 to 96-hour LC_{50} values for invertebrates from 0.9 µg/l to 80 µg/l. The 96-hour values for saltwater fish range from 0.8 to 194 µg/l. In a 40-week life cycle test with fathead minnows, the determined no-adverse-effect concentration was 0.86 µg/l. All fish exposed at 1.84 µg/l to heptachlor were dead after 60 days. The fathead minnow bioconcentrated heptachlor and its biodegradation product, heptachlor epoxide, 20,000-fold over ambient water concentrations after 276 days exposure. The saltwater sheepshead minnow accumulated these two compounds 37,000-fold after 126 days exposure. Heptachlor epoxide has approximately the same toxicity values as heptachlor.

I. INTRODUCTION

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

Heptachlor is a broad spectrum insecticide of the group of polycyclic chlorinated hydrocarbons called cyclodiene insecticides. From 1971 to 1975 the most important use of heptachlor was to control agricultural soil insects (U.S. EPA, 1979).

Pure heptachlor (chemical name 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene; $C_{10}H_5Cl_7$; molecular weight 373.35) is a white crystalline solid with a camphor-like odor. It has a vapor pressure of 3×10^{-4} mm Hg at 25°C, a solubility in water of 0.056 mg/l at 25 to 29°C, and is readily soluble in relatively nonpolar solvents (U.S. EPA, 1979).

Technical grade heptachlor (approximately 73 percent heptachlor; 21 percent trans chlordane, 5 percent heptachlor epoxide and 2 percent chlordene isomers) is a tan, soft, waxy solid with a melting range of 46 to 74°C and a vapor pressure of 4×10^{-4} mm Hg at 25°C (U.S. EPA, 1979).

Since 1975, insecticidal uses and production volume have declined extensively because of the sole producer's voluntary restriction and the subsequent issuance of a registration suspension notice by the U.S. EPA, August 2, 1976, for all food crop and home use of heptachlor. However, significant commercial use of heptachlor for termite control and non-food crop pests continues.

Heptachlor persists for prolonged periods in the environment. It is converted to the more toxic metabolite, heptachlor epoxide, in the soil (Lichtenstein, 1960; Lichtenstein, et al. 1970, 1971; Nash and Harris, 1972), in plants (Gannon and Decker, 1958), and in mammals (Davidow and

Radomski, 1953a). Heptachlor, in solution or thin films, undergoes photodecomposition to photoheptachlor (Benson, et al. 1971) which is more toxic than the parent compound to insects (Khan, et al. 1969), aquatic invertebrates (Georgacakis and Khan, 1971; Khan, et al. 1973) and rats, bluegill (Lepomis machrochirus) and goldfish (Carassius auratus) (Podowski, et al. 1979). Photoheptachlor epoxide is also formed in sunlight and is more toxic than the parent compound (Ivie, et al. 1972).

Heptachlor and its epoxide will bioconcentrate in numerous species and will accumulate in the food chain (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Various investigators have detected heptachlor and/or heptachlor epoxide in the major river basins of the U.S. at a mean concentration for both of 0.0063 µg/l (U.S. EPA, 1976). Levels of heptachlor ranged from .001 µg/l to 0.035 µg/l and heptachlor/heptachlor epoxide were found in 25 percent of all river samples (Breidenbach, et al. 1967). Average levels in cotton sediments are around 0.8 µg/kg (U.S. EPA, 1979).

B. Food

In their market basket study (1974-1975) for 20 different cities, the FDA showed that 3 of 12 food classes contained residues of heptachlor epoxide ranging from 0.0006 to 0.003 ppm (Johnson and Manske, 1977). Heptachlor epoxide residues greater than 0.03 mg/kg have been found in 14 to 19 percent of red meat, poultry, and dairy products sampled from 1964-1974 (Nisbet, 1977). Heptachlor and/or heptachlor epoxide were found in 32 percent of 590 fish samples obtained nationally, with whole fish residues from 0.01 to 8.33 mg/kg (Henderson, et al. 1969).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for heptachlor in the edible portions of fish and shellfish consumed by Americans to be 5,200. This estimate is based on measured steady-state bioconcentration factors for sheepshead minnows, fathead minnows, and spot (Leiostomus xanthuru).

Human milk can be contaminated with heptachlor epoxide. A nationwide survey indicated that 63.1 percent of 1,936 mothers' milk samples contained heptachlor epoxide residues ranging from 1 to 2,050 µg/l (fat adjusted) (Savage, 1976). Levels of 5 µg/l of the epoxide have been reported in evaporated milk (Ritcey, et al. 1972).

C. Inhalation

Heptachlor volatilizes from treated surfaces, plants, and soil (Nisbet, 1977). Heptachlor, and to a lesser extent heptachlor epoxide, are widespread in ambient air with typical mean concentratons of approximately 0.5 ng/m^3. On the basis of this data, typical human exposure was calculated to be 0.01 ug/person/day (Nisbet, 1977). Thus, it appears that inhalation is not a major route for human exposure to heptachlor. Air downward from treated fields may contain concentrations as high as 600 ng/m^3. Even after three weeks, the air from these fields may contain up to 15.4 ng/m^3. Thus, sprayers, farmers and nearby residents of sprayed fields may receive significant exposures (Nisbet, 1977).

D. Dermal

Gaines (1960) found rat dermal LD_{50} values of 195 and 250 mg/kg for males and females, respectively, compared with oral LD_{50}'s of 100 and 162 mg/kg, respectively, for technical heptachlor. Thus, dermal exposures may be important in humans under the right exposure conditions.

III. PHARMACOKINETICS

A. Absorption

Heptachlor is readily absorbed from the gastrointestinal tract (Radomski and Davidow, 1953; Mizyukova and Kurchatov, 1970; Matsumura and Nelson, 1971). The degree to which heptachlor is absorbed by inhalation has not been reported (Nisbet, 1977). Percutaneous absorption is less efficient than through the gastrointestinal tract, as indicated by comparison of the acute toxicity resulting from dermal vs. oral exposures (Gaines, 1960).

B. Distribution and Metabolism

Heptachlor reaches all tissues of the rat within one hour of a single oral dose and is metabolized to heptachlor epoxide. Heptachlor has been found to bind to hepatic cytochrome P-450, an enzyme of the liver hydroxylation system (Donovan, et al. 1978). By the end of one month traces of heptachlor epoxide were detectable only in fat and liver. Levels of the epoxide in fatty tissues stabilized 3 to 6 months after a single dose of heptachlor (Mizyukova and Kurchatov, 1970). Human fat samples may also contain nonachlor residues derived from technical heptachlor or chlordane exposure (Sovocool and Lewis, 1975). When experimental animals were fed heptachlor for two months, the highest levels of heptachlor epoxide were found in fat, with lower levels in liver, kidney and muscle and none in brain (Radomski and Davidow, 1953). There is evidence to show that the efficiency of conversion to the epoxide in humans is less than in the rat (Tashiro and Matsumura, 1978). Various researchers have found that heptachlor epoxide is more toxic to mammals than the parent compound (U.S. EPA, 1979). There is an approximate ten to fifteen-fold increase in heptachlor residues found in body fat, milk butterfat, and in the fat of poultry, eggs, and livestock as compared to residue levels found in their normal food rations (U.S. EPA, 1976).

Heptachlor and its epoxide pass readily through the placenta (U.S. EPA, 1979). The epoxide can be found in over 90 percent of the U.S. population at approximate mean levels of 0.08 to 0.09 mg/kg (Kutz, et al. 1977).

C. Excretion

Elimination of non-stored heptachlor and its metabolites occurs within the first five days, chiefly in the feces and to a lesser extent in the urine (Mizyukova and Kurchatov, 1970). In addition, a primary route for excretion in females is through lactation, mostly as the epoxide. Levels can be as high as 2.05 mg/l (Jonsson, et al. 1977).

IV. EFFECTS

A. Carcinogenicity

The studies on rats have generated much controversy, especially for doses around 10 mg/kg/day. However, heptachlor and/or heptachlor epoxide (1 to 18 mg/kg/day of unspecified purities) have induced hepatocellular carcinomas in mice during three chronic feeding studies. Heptachlor epoxide (also of unspecified purity) has produced the same response in rats in one study (Epstein, 1976; U.S. EPA, 1977). Clearly, studies with chemicals of specified purity still need to be performed to establish if contaminants or species differences are responsible for the observed effects.

B. Mutagenicity

Heptachlor has been reported to be mutagenic in mammalian assays but not in bacterial assays. Heptachlor (1 to 5 mg/kg) caused dominant lethal changes in male rats as demonstrated by the number of resorbed fetuses in intact pregnant rats (Cerey, et al. 1973). Bone marrow cells of the treated animals showed increases in the incidence of abnormal mitoses, chromatid abnormalities, pulverization, and translocation. Both heptachlor and heptachlor epoxide induced unscheduled DNA synthesis in SV-40 transformed

human cells (VA-4) in culture with metabolic activation (Ahmed, et al. 1977). Neither heptachlor nor heptachlor epoxide was mutagenic for Salmonella typhimurium in the Ames test (Marshall, et al. 1976).

C. Teratogenicity

In long-term feeding studies with heptachlor, cataracts developed in the parent rats and in the offspring shortly after their eyes opened (Mestitzova, 1967).

D. Other Reproductive Effects

In long-term feeding studies in rats, heptachlor caused a marked decrease in litter size and a decreased lifespan in suckling rats (Mestitzova, 1967). However, newborn rats were less susceptible to heptachlor than adults (Harbison, 1975).

E. Chronic Toxicity

Little information on chronic effects is available. When administered to rats in small daily doses over a prolonged period of time, heptachlor induced alterations in glucose homeostasis which were thought to be related to an initial stimulation of the cyclic AMP-adenylate cyclase system in liver and kidney cortex (Kacew and Singhal, 1973, 1974; Singhal and Kacew, 1976).

F. Other Relevant Information

Heptachlor is a convulsant (St. Omer, 1971). Rats fed protein-deficient diets are less susceptible to heptachlor and have lower heptachlor epoxidase activities than pair-fed controls (Webb and Miranda, 1973; Miranda, et al. 1973; Miranda and Webb, 1974). Phenobarbital potentiates the toxicity of heptachlor in newborn rats (Harbison, 1975). Many liver and brain enzymes are affected by heptachlor down to 2 mg/kg doses in pigs (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

Numerous studies on the acute toxicity of heptachlor to freshwater fish and invertebrate species have been conducted. Many of these studies on heptachlor have used technical grade material. Available data suggest that toxicity of the technical material is attributable to the heptachlor and its degradation product, heptachlor epoxide, and that toxicities of these compounds are similar (Schimmel, et al. 1976). In addition, during toxicity testing with heptachlor, there is apparently an appreciable loss of heptachlor by volatilization due to aeration or mixing, leading to variability of static and flow-through results (Schimmel, et al. 1976; Goodman, et al. 1978).

Fish are less sensitive to heptachlor than are invertebrate species. Ninety-six hour LC_{50} values for fish range from 7.0 µg/l for the rainbow trout, Salmo gairdneri, (Macek, et al. 1969) to 320 µg/l for the goldfish (Carassius auratus). Ten days after a dose of 0.868 µg/g ^{14}C-heptachlor to goldfish, 91.2 percent was unchanged, 5.4 percent was heptachlor epoxide, 1 percent was hydroxychlordene, 1.1 percent was 1-hydroxy-2,3-epoxychlordene and 1.2 percent was a conjugate (Feroz and Khan, 1979). Reported values for invertebrate species range from 0.9 µg/l for the stonefly, Pteronarcella badia, (Sanders and Cope, 1968) to 80 µg/l for the cladoceran (Simocephalus serrulatis). These data indicate that heptachlor is generally highly toxic in acute exposures.

The relative toxicity of heptachlor to its common degradation product, heptachlor epoxide, is 52 µg/l to 120 µg/l as determined in a 26-hour LC_{50} Daphnia magna bioassay (Frear and Boyd, 1967).

Heptachlor has been shown to be acutely toxic to a number of saltwater fish and invertebrate species. The 96-hour LC_{50} values derived from flow-through tests on four fish species range from 0.85 to 10.5 µg/l (Hansen and Parrish, 1977; Korn and Earnest, 1974; Schimmel, et al. 1976). Results of static exposures of eight fish species are from 0.8 to 194 µg/l (Eisler, 1970; Kutz, 1961). The commercially valuable pink shrimp (Penaeus duorarum) is especially sensitive, with reported 96-hour values as low as 0.03 µg/l (Schimmel, et al. 1976). Other species such as the blue crab, Callinectes sapidus, and American oyster, Crassostrea virginica, are 2,100 and 950 times less sensitive, respectively, than the pink shrimp (Butler, 1963).

B. Chronic Toxicity

In a 40-week life cycle test with fathead minnows (Pimephales promelas), the determined no-adverse-effect concentration was 0.86 µg/l. All fish exposed to 1.84 µg/l were dead after 60 days (Macek, et al. 1976). Valid chronic test data are not available for any aquatic invertebrate species.

In a 28-day exposure starting with sheepshead minnow embryo (Cyprinodon variegatus) growth of fry was significantly reduced at 2.04 µg/l, the safe dose being at 1.22 µg/l (Goodman, et al. 1978). In an 18-week partial life cycle exposure with this same species, egg production was significantly decreased at 0.71 µg/l (Hansen and Parrish, 1977).

C. Plant Effects

In the only study available, a concentration of 1,000 µg/l caused a 94.4 percent decrease in productivity of a natural saltwater phytoplankton community after a 4-hour exposure to heptachlor (Butler, 1963).

D. Residues

The amount of total residues, heptachlor and heptachlor epoxide, accumulated by fathead minnows after 276 days of exposure was found to be

20,000 times the concentration in water (Macek, et al. 1976). Heptachlor epoxide constituted 10-24 percent of the total residue. Adult sheepshead minnows exposed to technical grade material for 126 days accumulated heptachlor and heptachlor epoxide 37,000 times over the concentration of ambient water (Hansen and Parrish, 1977). Juvenile sheepshead minnows exposed in two separate experiments for 28 days bioconcentrated heptachlor 5,700 and 7,518 times the concentration in the water (Hansen and Parrish, 1977; Goodman, et al. 1976).

VI. EXISTING GUIDELINES AND STANDARDS

The issue of the carcinogenicity of heptachlor in humans is being reviewed; thus, it is possible that the human health criterion will be changed.

A. Human

Based on the data for the carcinogenicity of heptachlor epoxide in mice (Davis, 1965), and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of heptachlor/heptachlor epoxide 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	0.0023 ng/l	0.023 ng/l	0.23 ng/l
Consumption of fish and shellfish only.	0	0.0023 ng/l	0.023 ng/l	0.23 ng/l

Existing Guidelines and Standards

Agency	Published Standard	Reference
Occup. Safety Health Admin.	500 $\mu g/m^3$* on skin from air	Natl. Inst. Occup. Safety Health, 1977
Am. Conf. Gov. Ind. Hyg. (TLV)	500 $\mu g/m^3$ inhaled	Am. Conf. Gov. Ind. Hyg., 1971
World Health Org.	0.5 µg/kg/day acceptable daily intake in diet	Natl. Acad. Sci., 1977

U.S. Publ. Health Serv. Adv. Comm.	Recommended drinking water standard (1968) 18 µg/l of heptachlor and 18 µg/l of heptachlor epoxide	Natl. Acad. Sci., 1977

*Time weighted average

B. Aquatic

For heptachlor the draft criterion to protect freshwater aquatic life is 0.0015 µg/l as a 24-hour average, not to exceed 0.45 µg/l at any time. To protect saltwater aquatic life, the draft criterion is 0.0036 µg/l as a 24-hour average, not to exceed 0.05 µg/l at any time (U.S. EPA, 1979).

HEPTACHLOR

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No. 109

Heptachlor Epoxide

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.

HEPTACHLOR EPOXIDE

SUMMARY

Heptachlor epoxide is the principal metabolite of heptachlor in microorganisms, soil, plants, animals, and probably man, and is more acutely toxic than the parent compound. Its intrinsic effects are difficult to gauge since most of the relevant data in the literature is a side product of the effects of technical heptachlor. Heptachlor epoxide (mostly of unspecified purity) has induced liver cancer in mice and rats and was mutagenic in a mammalian assay system, but not in a bacterial system. Pertinent information on teratogenicity and chronic toxicity could not be located in the available literature. Heptachlor epoxide accumulates in adipose tissue.

The chronic value for the compound derived from a 26-hour exposure of Daphnia magna is reported to be 120 µg/l, approximately the same value obtained for heptachlor.

Fathead minnows bioconcentrated heptachlor and its biodegradation product, heptachlor expoxide, 20,000 times after 276 days of exposure. Heptachlor epoxide constituted between 10 and 24 percent of the total residue.

HEPTACHLOR EPOXIDE

I. INTRODUCTION

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

Heptachlor epoxide is the principal metabolite of heptachlor in microorganisms, soil, plants, and mammals, although the conversion in man may be less efficient (Tashiro and Matsumura, 1978). Since much of the data has been obtained as a side-product of the effects of technical heptachlor and the purity of the epoxide is often unspecified, there is a paucity of reliable literature on its biological effects (U.S. EPA, 1979a).

Heptachlor epoxide is relatively persistent in the environment but has been shown to undergo photodecomposition to photoheptachlor epoxide (Graham, et al. 1973). Photoheptachlor epoxide has been reported to exhibit greater toxicity than heptachlor epoxide (Ivie, et al. 1972). Heptachlor epoxide will bioconcentrate in numerous species and will accumulate in the food chain (U.S. EPA, 1979a).

II. EXPOSURE

A. Water

Heptachlor epoxide has been detected by various investigators in the major river basins of the United States (U.S. EPA, 1979a) at levels ranging from 0.001 to 0.020 µg/l (Breidenbach, et al. 1967).

B. Food

The FDA showed in their market basket survey (1974-1975) of 20 different cities that 3 of 12 food classes con-

tained residues of heptachlor epoxide ranging from 0.0006 to 0.003 ppm (Johnson and Manske, 1977). Heptachlor epoxide residues greater than 0.03 mg/kg were found in 14 to 19 percent of red meat, poultry, and dairy products during the period 1964-1974. Average daily intake was estimated to be between 0.3 to 3 µg from 1965 to 1974 (Nisbet, 1977). Heptachlor and/or heptachlor epoxide were found in 32 percent of 590 fish samples obtained nationally, with whole fish residues containing 0.01 to 8.33 mg/kg (Henderson, et al. 1969). Human milk can be contaminated with heptachlor epoxide; 63 percent of samples in 1975-1976 contained 1 to 2,050 µg/l (fat adjusted) (Savage, 1976). Levels of 5 ng/l have been reported in evaporated milk. Cooking did not reduce the residue level in poultry meat by more than one-half (Ritcey, et al. 1972).

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for heptachlor to be 5,200 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the measured steady-state bioconcentration studies in three species of fish. Since heptachlor epoxide is the primary metabolite of heptachlor and shows greater persistence in body fat (U.S. EPA, 1976), it may be assumed that heptachlor epoxide is bioconcentrated to at least the same extent as heptachlor.

C. Inhalation

Heptachlor epoxide is present in ambient air to a lesser extent than heptachlor and is not thought to con-

tribute substantially to human exposure except in areas near sprayed fields, where concentrations of up to 9.3 $\mu g/m^3$ may be encountered (Nisbet, 1977).

D. Dermal

Gaines (1960) found rat dermal LD_{50} values of 195 and 200 mg/kg for males and females, respectively, compared with oral LD_{50}'s of 100 and 162 mg/kg, respectively, for technical heptachlor. Thus, it is likely that dermal exposure in humans can be important under certain conditions.

III. PHARMACOKINETICS

A. Absorption

Heptachlor epoxide is readily absorbed from the gastrointestinal tract (U.S. EPA, 1979a).

B. Distribution

Studies dealing directly with exposure to heptachlor epoxide could not be located in the available literature. After oral administration of heptachlor to experimental animals, high concentrations of heptachlor epoxide have been found in fat, with much lower levels in liver, kidney, and muscle, and none in brain (Radomski and Davidow, 1953). Another study (Mizyukova and Kurchatav, 1970) also demonstrated the persistence of heptachlor epoxide in fat. Levels in fatty tissues stabilize after three to six months after a single dose. The U.S. EPA (1979a) states that there is approximately 10- to 15-fold increase in heptachlor residues found in body fat, milk butterfat, and in the fat of poultry eggs and livestock as compared to residue levels found in their normal food rations. "Heptachlor residues"

probably refers primarily to heptachlor epoxide. Heptachlor epoxide passes readily through the placenta (U.S. EPA, 1979a) and could be found in over 90 percent of the U.S. population at average levels of around 90 ng/kg (Kutz, et al. 1977).

C. Metabolism and Elimination

Heptachlor epoxide accumulates in adipose tissue, as discussed in the "Distribution" section. The primary route for excretion is fecal (Mizyukova and Kurchatav, 1970). When heptachlor epoxide was fed to rats over a period of 30 days, approximately 20 percent of the administered dose (approximately 5 mg heptachlor epoxide/rat/30 day) was excreted in the feces, primarily as 1-exo-hydroxyheptachlor epoxide and 1,2-dihydroxydihydrochlordene (Matsumura and Nelson, 1971; Tashiro and Matsumura, 1978). In females, a primary route for excretion is via lactation, usually as the epoxide. Levels can be as high as 2.05 mg/l (Jonasson, et al. 1977).

IV. EFFECTS

A. Carcinogenicity

Heptachlor epoxide of unspecified purity induced hepatocellular carcinoma in a chronic feeding study with mice and in one study with rats (Epstein, 1976; U.S. EPA, 1977).

B. Mutagenicity

Heptachlor epoxide induced unscheduled DNA synthesis in SV-40 transformed human cells (VA-4) in culture when metabolically activated (Ahmed, et al. 1977), but was

not mutagenic for Salmonella typhimurium in the Ames test (Marshall, et al. 1976).

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature.

D. Other Relevant Information

Heptachlor epoxide is more acutely toxic than heptachlor (U.S. EPA, 1979a). It inhibits synaptic calcium magnesium dependent ATPases in rats (Yamaguchi, et al. 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity data could not be located in the available literature relative to the effects of heptachlor epoxide on fish or invertebrates.

B. Chronic Toxicity

In the only reported chronic study, the 26-hour LC_{50} for heptachlor epoxide in Daphnia magna was 120 µg/l (Frear and Boyd, 1967). In the same test, the corresponding value for heptachlor was 52 µg/l.

C. Plant Effects

Data on the toxicity of heptachlor epoxide to plants could not be located in the available literature.

D. Residues

Macek, et al. (1976) determined the bioconcentration factor of 20,000 for heptachlor and heptachlor epoxide in fathead minnows after 276 days' exposure. Heptachlor epoxide residues were reported as constituting 10 to 24 percent of the total residue. The geometric mean bioconcen-

tration factor for heptachlor in all species of fish tested is 11,400 (U.S. EPA, 1979a). As explained in the "Distribution" section of this text, the bioconcentration factor for heptachlor epoxide would be as least as great as that for heptachlor.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The existing guidelines and standards for heptachlor and heptachlor epoxide are:

AGENCY/ORG.	STANDARD	REFERENCE
Occup. Safety Health Admin.	500 $\mu g/m^3$* on skin from air	Natl. Inst. Occup. Safety Health, 1977
Am. Conf. Gov. Ind. Hyg. (TLV)	500 $\mu g/m^3$ inhaled	Am. Conf. Gov. Ind. Hyg., 1971
Fed. Republic Germany	500 $\mu g/m^3$ inhaled	Winell, 1975
Soviet Union	10 $\mu g/m^3$ ceiling value inhaled	Winell, 1975
World Health Organ.**	0.5 µg/kg/day acceptable daily intake in diet	Natl. Acad. Sci., 1977
U.S. Pub. Health Serv. Adv. Comm.	Recommended drinking water standard (1968) 18 µg/l of heptachlor and 18 µg/l heptachlor epoxide	Natl. Acad. Sci., 1977

* Time weighted average

** Maximum residue limits in certain foods can be found in Food Agric. Organ./World Health Organ. 1977, 1978

The U.S. EPA (1979a) is in the process of establishing ambient water quality criteria for heptachlor and heptachlor epoxide. Based on potential carcinogenicity of heptachlor epoxide, the draft criterion is calculated on the esti-

mate that 0.47 ng/man/day would result in an increased additional lifetime cancer risk of no more than 1/100,000. Based on this lifetime carcinogenicity study of heptachlor epoxide at 10 ppm in the diet of C3Heb/Fe/J strain mice, the recommended draft criterion is calculated to be 0.233 ng/l.

B. AQUATIC

No existing guidelines are available for heptachlor epoxide. However, since heptachlor epoxide is a biodegradation product of heptachlor, the hazard profile on heptachlor should be consulted (U.S. EPA, 1979b).

HEPTACHLOR EPOXIDE

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No. 110

Hexachlorobenzene

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

HEXACHLOROBENZENE

Summary

Hexachlorobenzene is ubiquitous in the environment and has an extremely slow rate of degradation. Ingested hexachlorobenzene is absorbed readily when associated with lipid material and, once absorbed, is stored for long periods of time in the body fat. Chronic exposures can cause liver and spleen damage and can induce the hepatic microsomal mixed functional oxidase enzyme. Hexachlorobenzene can pass the placental barrier and produce toxic or lethal effects on the fetus. Hexachlorobenzene appears to be neither a teratogen nor a mutagen; however, this compound has produced tumors in both rats and mice.

In the only steady-state study with hexachlorobenzene, the pinfish, *Lagodon rhoimboides*, bioconcentrated this compound 23,000 times in 42 days of exposure. The concentration of HCB in muscle of pinfish was reduced only 16 percent after 28 days of depuration, a rate similar to that for DDT in fish.

HEXACHLOROBENZENE

I. INTRODUCTION

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

Hexachlorobenzene (HCB; C_6Cl_6; molecular weight 284.79) is a colorless solid with a pleasant aroma. Hexachlorobenzene has a melting point of 230°C, a boiling point of 322°C, a density of 2.044 g/ml, and is virtually insoluble in water. Hexachlorobenzene is used in the control of fungal diseases in cereal seeds intended solely for planting, as a plasticizer for polyvinyl chloride, and as a flame retardant (U.S. EPA, 1979).

Commercial production of hexachlorobenzene in the U.S. was discontinued in 1976 (Chem. Econ. Hdbk., 1977). However, even prior to 1976, most hexachlorobenzene was produced as a waste by-product during the manufacture of perchloroethylene, carbon tetrachloride, trichloroethylene, and other chlorinated hydrocarbons. This is still the major source of hexachlorobenzene in the U.S., with 2,200 kg being produced by these industries during 1972 (Mumma and Lawless, 1975).

II. EXPOSURE

A. Water

Very little is known regarding potential exposure to hexachlorobenzene as a result of ingestion of contaminated water. Hexachlorobenzene has been detected in specific bodies of water, particularly near points of industrial discharge (U.S. EPA, 1979). Hexachlorobenzene has been detected in the polluted waters of the Mississippi River (usually below 2 ng/kg) and in the clean waters of Lake Superior (concentrations not quantitatively measured). Hexachlorobenzene was detected in drinking water supplies at

three locations, with concentrations ranging from 6 to 10 ng/kg, and in finished drinking water at two locations, with concentrations ranging from 4 to 6 ng/kg (U.S. EPA, 1975).

B. Food

Ingestion of excessive amounts of hexachlorobenzene has been a consequence of carelessness, usually from feeding seed grains to livestock. Foods high in animal fat (e.g., meat, eggs, butter, and milk) have the highest concentrations of hexachlorobenzene. The daily intake of hexachlorobenzene by infants from human breast milk in part of Australia was 39.5 µg per day per 4 kg baby. This exceeded the acceptable daily intake recommended by the FAO/WHO of 2.4 µg/kg/day (1974). The dietary intake by young adults (15 to 18-year old males) was estimated to be 35 µg hexachlorobenzene per person per day (Miller and Fox, 1973). The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for hexachlorobenzene to be 12,000 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of hexachlorobenzene.

C. Inhalation

Hexachlorobenzene enters the air by various mechanisms, such as release from stacks and vents of industrial plants, volatilization from waste dumps and impoundments, intentional spraying and dusting, and unintentional dispersion of hexachlorobenzene-laden dust from manufacturing sites (U.S. EPA 1979). No data is given on the concentrations of hexachlorobenzene in ambient air. Significant occupational exposure can occur particularly to pest control operators (Simpson and Chandar, 1972).

D. Dermal

Hexachlorobenzene may enter the body by absorption through the skin as a result of skin contamination (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

To date, only absorption of hexachlorobenzene from the gut has been examined in detail. Hexachlorobenzene in aqueous suspensions is absorbed poorly in the intestines of rats (Koss and Koransky, 1975); however, cotton seed oil (Albro and Thomas, 1974) or olive oil (Koss and Koransky, 1975) facilitated the absorption. Between 70 and 80 percent of doses of hexachlorobenzene ranging from 12 mg/kg to 180 mg/kg were absorbed. Hexachlorobenzene in food products will selectively partition into the lipid portion, and hexachlorobenzene in lipids will be absorbed far better than that in an aqueous milieu (U.S. EPA, 1979).

B. Distribution

The highest concentrations of hexachlorobenzene are found in fat tissue (Lu and Metcalf, 1975). In rats receiving a single intraperitoneal (i.p.) injection or oral dose of hexachlorobenzene in olive oil, adipose tissue contained about 120-fold more hexachlorobenzene than muscle tissue; liver, 4-fold; brain, 2.5-fold; and kidney, 1.5-fold (Koss and Koransky, 1975). Adipose tissue serves as a reservoir for hexachlorobenzene, and depletion of fat deposits results in mobilization and redistribution of stored hexachlorobenzene. However, excretion is not increased, and the total body burden is not lowered (Villeneuve, 1975).

C. Metabolism

Hexachlorobenzene is metabolized after i.p. administration in the rat to pentachlorophenol, tetrachlorohydroquinone and pentachlorothiophenol (Koss, et al. 1976). In another study using rats in which the metabolic products were slightly different, only a small percentage of the metabolites were present as glucuronide conjugates (Engst, et al. 1976). Hexachlorobenzene appears to be an inducer of the hepatic microsomal enzyme system in rats (Carlson, 1978). It has been proposed that both the phenobarbital type and the 3-methylcholanthrene type microsomal enzymes are induced (Stonard, 1975; Stonard and Greig, 1976).

D. Excretion

Hexachlorobenzene is excreted mainly in the feces and, to some extent, in the urine in the form of several metabolites which are more polar than the parent compound (U.S. EPA, 1979). In the rat, 34 percent of the administered hexachlorobenzene was excreted in the feces, mostly as unaltered hexachlorobenzene. Fecal excretion of unaltered hexachlorobenzene is presumed to be due to biliary secretion. Five percent of the administered HCB was excreted in the urine (Koss and Koransky, 1975).

IV. EFFECTS

A. Carcinogenicity

Carcinogenic activity of hexachlorobenzene was assessed in hamsters fed 4.8 or 16 mg/kg/day for life (Cabral, et al. 1977). Whereas 10 percent of the unexposed hamsters developed tumors, 92 percent of the hamsters fed 16 mg/kg/day, 75 percent fed 8 mg/kg/day, and 56 percent fed 4 mg/kg/day developed tumors. The tumors were hepatomas, haemangioendotheliomas and thyroid adenomas. In a study on mice fed 6.5, 13 or 26 mg/kg/day for life, the only increase in tumors was in hepatomas (Cabral, et al. 1978). How-

ever, the incidence of lung tumors in strain A mice treated three times a week for a total of 24 injections of 40 mg/kg each was not significantly greater than the incidence in control mice (Theiss, et al. 1977). Also, ICR mice fed hexachlorobenzene at 1.5 or 7.0 mg/kg/day for 24 weeks showed no induced hepatocellular carcinomas (Shirai, et al. 1978).

B. Mutagenicity

Hexachlorobenzene was assayed for mutagenic activity in the dominant lethal assay. Rats were administered 60 mg/kg/day hexachlorobenzene orally for ten days; there was no significant difference in the incidence of pregnancies (Khera, 1974).

C. Teratogenicity

Hexachlorobenzene does not appear to be teratogenic for the rat (Khera, 1974). CD-1 mice receiving 100 mg/kg/day hexachlorobenzene orally on gestational days 7 to 11 showed a small increase in the incidence of abnormal fetuses per litter (Courtney, et al. 1976). However, the statistical significance was not mentioned, and the abnormalities appeared in both the exposed and unexposed groups.

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 as in the adult, with the highest concentration in fatty tissue.

E. Chronic Toxicity

In one long-term study where rats were given 50 mg/kg hexachlorobenzene every other day for 53 weeks, an equilibrium between intake and elimination was achieved after nine weeks. Changes in the histology of the

liver and spleen were noted (Koss, et al. 1978). On human exposure for an undefined time period, porphyrinuria has been shown to occur (Cam and Nigogosyan, 1963).

F. Other Relevant Information

At doses far below those causing mortality, hexachlorobenzene enhances the capability of animals to metabolize foreign organic compounds. This type of interaction may be of importance in determining the effects of other concurrently encountered xenobiotics (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. No pertinent information is available on acute and chronic toxicity or plant effects.

B. Residues

Hexachlorobenzene (HCB) is bioconcentrated from water into tissues of saltwater fish and invertebrates. Bioconcentration factors (BCF) in short 96-hour exposures are as follow (Parrish, et al. 1974): grass shrimp, Palaeomonetes pugio, - 4,116 µg/l; pink shrimp, Penaeus duorarum, - 1,964 µg/l; sheepshead minnow, Cyprinodon variegatus, - 2,254 µg/l. In a 42-day exposure, the pinfish, Lagodon rhomboides, BCF was 23,000. The concentration of HCB in pinfish muscle was reduced only 16 percent after 28 days of depuration; this slow rate is similar to that for DDT in fish.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

The 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 at 0.3 mg/kg (U.S. EPA, 1976). The FAO/WHO recommendations for residues in foodstuffs are 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 bioassay 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 Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.0125 ng/l	0.125 ng/l	1.25 ng/l
Consumption of fish and shellfish only.	0	0.0126 ng/l	0.126 ng/l	1.26 ng/l

B. Aquatic

Pertinent information concerning aquatic criteria could not be located in the available literature.

HEXACHLOROBENZENE

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No. 111

Hexachlorobutadiene

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

HEXACHLOROBUTADIENE

SUMMARY

Hexachlorobutadiene (HCBD) is a significant by-product of the manufacture of chlorinated hydrocarbons. HCBD has been found to induce renal neoplasms in rats (Kociba, et al., 1971). The mutagenicity of HCBD has not been proven conclusively, but a bacterial assay by Taylor (1978) suggests a positive result. Two studies on the possible teratogenic effects of HCBD produced conflicting results.

Ninety-six hour LC_{50} values for the goldfish, snail, and sowbug varied between 90 and 210 µg/l in static renewal tests. Measured bioconcentration factors after varying periods of exposure are as follows: crayfish, 60; goldfish, 920-2,300; Scuyemouth bass, 29; and an alga, 160.

HEXACHLOROBUTADIENE

I. INTRODUCTION

Hexachlorobutadiene (HCBD) is produced in the United States as a significant by-product in the manufacture of chlorinated hydrocarbons such as tetrachloroethylene, trichloroethylene, and carbon tetrachloride. This secondary production in the U.S. ranges from 7.3 to 14.5 million pounds per year, with an additional 0.5 million pounds being imported (U.S. EPA, 1975).

HCBD is used as an organic solvent, the major domestic users being chlorine producers. Other applications include its use as an intermediate in the production of rubber compounds and lubricants. HCBD is a colorless liquid with a faint turpentine-like odor. Its physical properties include: boiling point, 210-220°C vapor pressure, 0.15 mm Hg; and water solubility of 5 μg/l at 20°C (U.S. EPA, 1979).

Environmental contamination by HCBD results primarily during the disposal of wastes containing HCBD from chlorinated hydrocarbon industries (U.S. EPA, 1976). It has been detected in a limited number of water samples. HBCD appears to be rapidly adsorbed to soil and sediment from contaminated water, and concentrates in sediment from water by a factor of 100 (Leeuwangh, et al., 1975).

II. EXPOSURE

A. Water

HCBD contamination of U.S. finished drinking water supplies does not appear to be widespread. The problem is localized in areas with raw water sources near industrial

plants discharging HBCD. From its physical and chemical properties, HBCD removal from water by adsorption into sediment should be rapid (Laseter, et al., 1976). Effluents from various industrial plants were found to contain HCBD levels ranging from 0.04 to 240 µg/l (Li, et al., 1976). An EPA study of the drinking water supply of ten U.S. cities revealed that HCBD was detected in one of the water supplies, but the concentration was less than 0.01 µg/l (U.S. EPA, 1975).

B. Food

Since the air, soil and water surrounding certain chlorohydrocarbon plants have been shown to be contaminated with HCBD (Li, et al., 1976), food produced in the vicinity of these plants might contain residual levels of HCBD. A survey of foodstuffs produced within 25 miles of tetrachloroethylene and trichloroethylene plants did not detect measurable levels of HCBD. Freshwater fish caught in the lower Mississippi contained HBCD residues in a range from 0.01 to 1.2 mg/kg. Studies on HCBD contamination of food in several European countries have measured levels as high as 42 µg/kg in certain foodstuffs (Kotzias, et al., 1975).

The U.S. EPA (1979) has estimated a HCBD bioconcentration factor of 870 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in goldfish.

C. Inhalation

The levels of HCBD detected in the air surrounding chlorohydrocarbon plants are generally less than 5 µg/m^3,

although values as high as 460 $\mu g/m^3$ have been measured (Li, et al. 1976).

III. PHARMACOKINETICS

A. Absorption

Pertinent data were not found on the absorption of HCBD in the available literature.

B. Distribution

HCBD did not have a strong tendency to accumulate in fatty tissue when administered orally with other chlorinated hydrocarbons. Some of the chlorinated hydrocarbons were aromatic compounds and accumulated significantly in fat (Jacobs, et al. 1974).

C. Metabolism

Pertinent data were not found in the available literature.

D. Excretion

Pertinent data were not found in the available literature.

IV. EFFECTS ON MAMMALS

A. Carcinogenicity

Kociba, et al. (1977) administered dietary levels of HCBD ranging from 0.2 mg/kg/day to 20.0 mg/kg/day for two years to rats. In males receiving 20 mg/kg/day, 18 percent (7/39) had renal tubular neoplasms which were classified as adenocarcinomas; 7.5 percent (3/40) of the females on the high dose developed renal carcinomas. Metastasis to the lung was observed in one case each for both male and female rats.

No carcinomas were observed in controls, however, a nephroblastoma developed in one male and one female.

A significant increase in the frequency of lung tumors was observed in mice receiving intraperitoneal injections of 4 mg/kg or 8 mg/kg of HCBD, three times per week until totals of 52 mg and 96 mg, respectively, were administered (Theiss, et al. 1977).

B. Mutagenicity

Taylor (1978) tested the mutagenicity of HCBD on S. typhimurium TA100. A dose dependent increase in reversion rate was noted, but the usual criterion for mutagenicity of double the background rate was not reached.

C. Teratogenicity

Poteryaeva (1966) administered HCBD to nonpregnant rats by a single subcutaneous injection of 20 mg/kg. After mating, the pregnancy rate for the dosed rats was the same as that of controls. The weights of the young rats from the dosed mothers were markedly lower than the controls. Autopsies at 2-1/2 months revealed gross pathological changes in internal organs including glomerulonephritis of the kidneys. Degenerative changes were also observed in the red blood cells.

D. Other Reproductive Effects

Schwetz, et al. (1977) studied the effects of dietary doses of HCBD on reproduction in rats. Males and females were fed dose levels of 0.2 to 20 mg/kg/day HCBD starting 90 days prior to mating and continuing through lactation. At the two highest doses, adult rats suffered weight loss,

decreased food consumption and alterations of the kidney cortex, while the only effect on weanlings consisted of a slight increase in body weight at 21 days of age at the 20 mg/kg dose level. Effect on survival of the young was not effected.

E. Chronic Toxicity

The kidney appears to be the organ most sensitive to HCBD. Possible chronic effects are observed at doses as low as 2 to 3 mg/kg/day (Kociba, et al., 1971, 1977; Schwetz, et al., 1977). Single oral doses as low as 8.4 mg/kg have been observed to have deleterious effects on the kidney (Schroit, et al. 1972). Neurotoxic effects in rats have been reported at a dose of 7 mg/kg and effects may occur at even lower dose levels (Poteryaeva, 1973; Murzakaev, 1967). HCBD at 0.004 mg/kg gave no indication of neurotoxicity. Acute HCBD intoxication affects acid-base equilibrium in blood and urine (Popovich, 1975; Poteryaeva, 1971). Some investigators report a cumulative effect for HCBD during chronic dosing by dermal (Chernokan, 1970) or oral Poteryaeva, 1973) routes. An increase in urinary coproporphyrin was observed in rats receiving 2 mg/kg/day and 20 mk/kg/day HCBD for up to 24 months (Kociba, 1977).

F. Other Relevant Information

The possible antagonistic effect of compounds containing mercapto (-SH) groups on HCBD have been suggested by two studies. Murzokaev (1967) demonstrated a reduction in free -SH groups in cerebral cortex homogenate and blood serum following HCBD injection in rats. Mizyukova, et al. (1973) found thiols (-SH compounds) and amines to be effective anti-

dotes against the toxic effects of HCBD when administered prior to or after HCBD exposure.

V. AQUATIC TOXICITY

A. Acute Toxicity

Goldfish, (Carassius auratus), had an observed 96-hour LC_{50} of 90 µg/l in a static renewal test (Leeuwangh, et al. 1975). A snail, (Lymnaea stagnalis), and a sowbug, (Asellus aquaicus), were both exposed for 96-hours to HCBD resulting in EC_{50} values of 210 and 130 µg/l, respectively (Leeuwangh, et al., 1975). No acute studies with marine species have been conducted.

B. Chronic Toxicity

Pertinent information was not found in the available literature.

C. Plant Effects

Pertinent data was not found in the available literature.

D. Residues

Measured bioconcentration factors are as follows: crayfish, Procambaeus clarhi, 60 times after 10 days exposure; goldfish, Caressius auretus, 920-2,300 times after 49 days exposure; large mouth bass, Microptorus salmoides, 29 times after 10 days exposure; and a freshwater alga, Oedogonium cardiacum, 160 times after 7 days exposure (Laseter, et al., 1976). Residue data on saltwater organisms are not available.

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

Standards or guidelines for exposure to HCBD are not available.

The draft ambient water quality criteria for HCBD have been calculated to reduce the human carcinogenic risk levels to 10^{-5}, 10^{-6}, and 10^{-7} (U.S. EPA, 1979). The corresponding criteria are 0.77 µg/l, 0.077 µg/l, 0.0077 µg/l, respectively.

B. Aquatic

Draft freshwater or saltwater criterion for hexachlorobutadiene have not been developed because of insufficient data (U.S. EPA, 1979).

HEXACHLOROBUTADIENE

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No. 112

Hexachlorocyclohexane

Health and Environmental Effects

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

APRIL 30, 1980

-1310-

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

HEXACHLOROCYCLOHEXANE

Summary

Hexachlorocyclohexane (HCH), a broad spectrum insecticide, is a mixture of five configurational isomers. HCH is no longer used in the United States; however, its gamma-isomer, commonly known as lindane, continues to have significant commercial use. Technical HCH, alpha-HCH, beta-HCH, and lindane (gamma-HCH) have all been shown to induce liver tumors in mice. Most of the studies on hexachlorocyclohexanes deal only with lindane. Evidence for mutagenicity of lindane is equivocal. Lindane was not teratogenic for rats, although it reduced reproductive capacity in rats in a study of four generations. Chronic exposure of animals to lindane caused liver enlargement and, at higher doses, some liver damage and nephritic changes. Humans chronically exposed to HCH suffered liver damage. Chronic exposure of humans to lindane produced irritation of the central nervous system. HCH and lindane are convulsants. The U.S. EPA (1979) has estimated the ambient water concentrations of hexachlorocyclohexanes corresponding to a lifetime cancer risk for humans of 10^{-5} as follows: 21 ng/l for technical HCH, 16 ng/l for alpha-HCH, 28 ng/l for beta-HCH, and 54 ng/l for lindane (gammaHCH).

Lindane has been studied in a fairly extensive series of acute studies for both freshwater and marine organisms. Acute toxic levels as low as 0.17 ng/l have been reported for marine invertebrate species.

HEXACHLOROCYCLOHEXANE

INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Hexachlorocyclohexane (U.S. EPA, 1979). 1,2,3,4,5,6-Hexachlorocyclohexane ($C_6H_6Cl_6$; molecular weight 290.0) is a brownish-to-white crystalline solid with a melting point of 65°C and a solubility in water of 10 to 32 mg/l. It is a mixture of five configurational isomers and is commonly referred to as BHC or benzene hexachloride. Lindane is the common name for the gamma isomer of 1,2,3,4,5,6-hexachlorocyclohexane (U.S. EPA, 1979).

Technical grade hexachlorobenzene (HCH) contains the hexachlorocyclohexane isomers in the following ranges: alpha-isomer, 55 to 70 percent; beta-isomer, 6 to 8 percent; gamma-isomer, 10 to 18 percent; delta-isomer, 3 to 4 percent; epsilon-isomer, trace amounts. Technical grade HCH may also contain 3 to 5 percent of other chlorinated derivatives of cyclohexane, primarily heptachlorocyclohexane and octachlorocyclohexane (U.S. EPA, 1979).

Hexachlorocyclohexane (HCH) is a broad spectrum insecticide of the group of cyclic chlorinated hydrocarbons called organochlorine insecticides. Since the gamma-isomer (lindane) has been shown to be the insecticidally active ingredient in technical grade HCH, technical grade HCH has had limited commercial use except as the raw material for production of lindane. Use of technical HCH has been banned in the U.S., but significant commercial use of lindane continues. Lindane is used in a wide range of applications including treatment of animals, buildings, man (for ectoparasites), clothes, water (for mosquitoes), plants, seeds, and soils (U.S. EPA, 1979).

No technical grade HCH or lindane is currently manufactured in the U.S.; all lindane used in the U.S. is imported (U.S. EPA, 1979).

Lindane has a low residence time in the aquatic environment. It is removed by sedimentation, metabolism, and volatilization. Lindane contributes less to aquatic pollution than the other hexachlorocyclohexane isomers (Henderson, et al. 1971).

Lindane is slowly degraded by soil microorganisms (Mathur and Saha, 1975; Tu, 1975, 1976) and is reported to be isomerized to the alpha and/or delta isomers in microorganisms and plants (U.S. EPA, 1979), though this is controversial (Tu, 1975, 1976; Copeland and Chadwick, 1979; Engst, et al. 1977). It is not isomerized in adipose tissues of rats, however (Copeland and Chadwick, 1979).

II. EXPOSURE

A. Water

The contamination of water has occurred principally from direct application of technical hexachlorocyclohexane (HCH) or lindane to water for control of mosquitoes, from the use of HCH in agriculture and forestry, and, to a lesser extent, from occasional contamination of wastewater from manufacturing plants (U.S. EPA, 1979).

In the finished water of Streator, Illinois, lindane has been detected at a concentration of 4 μg/l (U.S. EPA, 1975).

B. Food

The daily intake of lindane has been reported to be 1 to 5 μg/kg body weight and the daily intake of all other HCH isomers to be 1 to 3 μg/kg body weight (Duggan and Duggan, 1973). The chief sources of HCH residues in the human diet are milk, eggs, and other dairy products (U.S. EPA, 1979), and carrots and potatoes (Lichtenstein, 1959). Seafood is usually a minor

source of HCH, probably because of the relatively high rate of dissipation of HCH in the aquatic environment (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for lindane to be 780 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration in bluegills.

C. Inhalation

Traces of HCH have been detected in the air of central and suburban London (U.S. EPA, 1979). No further pertinent information could be found in the available literature.

D. Dermal

Lindane has been used to eradicate human ectoparasites and few adverse reactions have been reported (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

The rapidity of lindane absorption is enhanced by lipid mediated carriers. Compared to other organochlorine insecticides, HCH and lindane are unusually soluble in water, which contributes to rapid absorption and excretion (Herbst and Bodenstein, 1972; U.S. EPA, 1979). Intraperitoneal injection of lindane resulted in 35 percent absorption (Koransky, et al. 1963). Lindane is absorbed after oral and dermal exposure (U.S. EPA, 1979).

B. Distribution

After administration to experimental animals, lindane was detected in the brain at higher concentrations than in other organs (Laug, 1948; Davidow and Frawley, 1951; Koransky, et al. 1963; Huntingdon Res. Center,

1972). At least 75 percent of an intraperitonial dose of ^{14}C-labeled lindane was consistently found in the skin, muscle, and fatty tissue (Koransky, et al. 1963). Lindane enters the human fetus through the placenta; higher concentrations were found in the skin than in the brain and never exceeded the corresponding values for adult organs (Poradovsky, et al. 1977; Nishimura, et al. 1977).

C. Metabolism

Lindane is metabolized to gamma-3,4,5,6-tetrachlorocyclohexene in rat adipose tissue, but is not isomerized (Copeland and Chadwick, 1979); other metabolites are 2,3,4,5,6-pentachloro-2-cyclohexene-1-ol, two tetrachlorophenols, and three trichlorophenols (Chadwick, et al. 1975; Engst, et al. 1977). These are commonly found in the urine as conjugates (Chadwick and Freal, 1972). Lindane metabolic pathways are still matters of some controversy (Engst, et al. 1977; Copeland and Chadwick, 1979). Hexachlorocyclohexane isomers other than lindane are metabolized to trichlorophenols and mercapturic acid conjugates (Kurihara, 1979). Both free and conjugated chlorophenols are far less toxic than the parent compounds (Natl. Acad. Sci., 1977).

D. Excretion

HCH and lindane appear to be eliminated primarily as conjugates in the urine. Elimination of lindane appears to be rapid after administration ceases. Elimination of beta-HCH is much slower (U.S. EPA, 1979). In females, HCH is excreted in the milk as well as in the urine. The beta-isomer usually accounts for above 90 percent of the HCH present in human milk (Herbst and Bodenstein, 1972).

IV. EFFECTS

A. Carcinogenicity

An increased incidence of liver tumors was reported in male and/or female mice of various strains fed technical hexachlorocyclohexane (Goto, et al. 1972; Hanada, et al. 1973; Nagasaki, et al. 1972), alpha-HCH (Goto, et al. 1972; Hanada, et al. 1973; Ito, et al. 1973, 1975), beta-HCH (Goto, et al. 1972; Thorpe and Walker, 1973) and lindane (gamma-HCH) (Goto, et al. 1972; Hanada, et al. 1973; Natl. Cancer Inst., 1977a; Thorpe and Walker, 1973). Male rats fed alpha-HCH also developed liver tumors (Ito, et al. 1975). A mixture containing 68.7 percent alpha-HCH, 6.5 percent beta-HCH and 13.5 percent lindane in addition to other impurities (hepta- and octa-chlorocyclohexanes), administered orally (100 ppm in the diet, or 10 mg/kg body weight by intubation), caused tumors in liver and in lymph-reticular tissues in male and female mice after 45 weeks. Application by skin painting had no effect (Kashyap, et al. 1979). A review by Reuber (1979) suggests that lindane is carcinogenic on uncertain evidence.

B. Mutagenicity

Evidence for the mutagenicity of lindane is equivocal. Some alterations in mitotic activity and the karyotype of human lymphocytes cultured with lindane at 0.1 to 10 μg/ml have been reported (Tsoneva-Maneva, et al. 1971). Lindane was not mutagenic in a dominant-lethal assay (U.S. EPA, 1973) or a host-mediated assay (Buselmair, et al. 1973).

Gamma-HCH was found to be mutagenic in microbial assays using Salmonella typhimurium with metabolic activation, the host-mediated assay, and the dominant lethal test in rats. Other reports indicate that it does not have significant mutagenic activity (U.S. EPA, 1979).

C. Teratogenicity

Lindane given in the diet during pregnancy at levels of 12 or 25 mg/kg body weight/day did not produce teratogenic effects in rats (Mametkuliev, 1978; Khera, et al. 1979).

D. Other Reproductive Effects

Chronic lindane feeding in a study of four generations of rats increased the average duration of pregnancy, decreased the number of births, increased the proportion of stillbirths, and delayed sexual maturation in F_2 and F_3 females. In addition, some of the F_1 and F_2 animals exhibited spastic paraplegia (Petrescu, et al. 1974).

In rats and rabbits, lindane given in the diet during pregnancy increased postimplanation death of embryos (Mametkuliev, 1978; Palmer, et al. 1978). Testicular atrophy has been observed for lindane in rats and mice (National Cancer Institute, 1977b; Nigam, et al. 1979).

E. Chronic Toxicity

Irritation of the central nervous system, with other toxic side effects (nausea, vomiting, spasms, weak respiration with cyanosis and blood dyscrasia), was reported after prolonged or improper use of Hexicid (1 percent lindane) for the treatment of scabies on humans (Lee, et al. 1976). Production workers exposed to technical HCH exhibited symptoms including headache, vertigo, irritation of the skin, eyes, and respiratory tract mucosa. In some instances, there were apparent disturbances of carbohydrate and lipid metabolism and dysfunction of the hypothalamo-pituitary-adrenal system (Kazahevich, 1974; Besuglyi, et al. 1973). A study of persons occupationally exposed to HCH for 11 to 23 years revealed biochemical manifestations of toxic hepatitis (Sasinovich, et al. 1974).

In chronic studies with rats given lindane in oil, liver cell hypertrophy (fat degeneration and necrosis) and nephritic changes were noted at higher doses (Fitzhugh, et al. 1950; Lehman, 1952). Rats inhaling lindane (0.78 mg/m^3) for seven hours, five days a week for 180 days showed liver cell enlargement, but showed no toxic symptoms or other abnormalities (Heyroth, 1952). The addition of 10 ppm lindane to the diet of rats for one or two years decreased body weight after five months of treatment and altered ascorbic acid levels in urine, blood, and tissues (Petrescu, et al. 1974). Dogs chronically exposed to lindane in the diet had slightly enlarged livers (Rivett, et al. 1978).

F. Other Relevant Information

Hexachlorocyclohexane is a convulsant.

Lindane is the most acutely toxic isomer of HCH. The toxic effects of lindane are antagonized by pretreatment with phenobarbital (Litterst and Miller, 1975) and by treatment with silymarin (Szpunar, et al. 1976) and various tranquilizers (Ulmann, 1972).

V. AQUATIC TOXICITY

A. Acute Toxicity

Among 16 species of freshwater fish, LC_{50} values from one flow-through and 24 static bioassays for the gamma isomer of hexachlorocyclohexane ranged from 2 µg/l for the brown trout (Salmo trutta) (Macek and McAllister, 1970) to 152 µg/l for the goldfish (Carassius auratus) (Henderson, et al. 1959). In general, the salmon tended to be more sensitive to the action of lindane than did warm water species. Zebrafish (Brachydanio rerio) showed a lindane LC_{50} value of 120 ng/l, but rainbow trout (Salmo gairdneri) evidenced respiratory distress at 40 ng/l (Slooff, 1979). Technical grade HCH was much less toxic than pure lindane; LC_{50}

values obtained for lindane in 96-hour studies of the freshwater goldfish (Carassius auratus) ranged from 152 µg/l for 100 percent lindane to 8,200 µg/l for BCH (13.5 percent gamma isomer) (Henderson, et al. 1959). Static tests on freshwater invertebrates revealed a range of LC_{50} values of from 4.5 µg/l (96-hour test) (Sanders and Cope, 1968) for the stonefly (Pteronarcys californica) to 880 µg/l (48-hour test) (Sanders and Cope, 1968) for the clado- ceran (Simocephalus serralatus) for lindane. Canton and Slooff (1977) re- ported an LC_{50} value for the pond snail (Lymnaea stagnalis) of 1,200 µg/l for alpha-HCH in a 48-hour static test.

Among seven species of marine fish tested for the acute effects of lindane, static test LC_{50} values ranged from 9.0 µg/l for the Atlantic silversides (Menidia menidia) to 66.0 µg/l for the striped mullet (Mugil cephalus) (Eisler, 1970). The results of six flow-through assays on five species of marine fish produced LC_{50} values from 7.3 µg/l for the striped bass (Morone saxatilis) (Korn and Earnest, 1974) to 240 µg/l for the long nose killifish (Fundulus similis) (Butler, 1963). A single species, the pinfish (Lagodon rhomboides), tested with technical grade hexachlorocyclohexane, produced a 96-hour flow-through LC_{50} value of 86.4 µg/l (Schimmel, et al. 1977). Acute tests on marine invertebrates showed six species to be quite sensitive to lindane, with LC_{50} values from both static and flow-through assays ranging from 0.17 µg/l for the pink shrimp (Panaeus duorarum) (Schimmel, et al. 1977) to 10.0 µg/l for the grass shrimp (Palaemonetas vulgaris) (U.S. EPA, 1979). An LC_{50} value of 0.34 µg/l was obtained for technical grade hexachlorocyclohexane for the pink shrimp (Schimmel, et al. 1977). The American oyster had an EC_{50} of 450 µg/l based on shell decomposition (Butler, 1963).

B. Chronic

A chronic value of 14.6 µg/l for lindane was obtained in a life-cycle assay of the freshwater fathead minnow (Pimephales promelas). For three species of freshwater invertebrates tested with lindane, chronic values of 3.3, 6.1, and 14.5 µg/l were obtained for Chironomus tentans, Gammarus fasciatus, and Daphnia magna (Macek, et al. 1976). No chronic marine data for any of the hexachlorobenzenes were available.

C. Plant Effects

Concentrations causing growth inhibition of the freshwater alga, Scenedesmus acutus were reported to be 500, 1,000, 1,000, and 5,000 µg/l for alpha-HCH, technical grade HCH, lindane, and beta-HCH, respectively (Krishnakumari, 1977). In marine phytoplankton communities, an effective concentration value of 1,000 µg/l (resulting in decreased productivity) was reported for lindane; and for the alga, Acetabularia mediterranea an effective concentration of 10,000 µg/l was obtained for lindane-induced growth inhibition. No effect in 48 hours was observed for the algae Chlamydomonas sp. exposed to lindane at the maximum solubility limit. Irreparable damage to Chlorella sp. occurred at lindane concentrations of more than 300 µg/l (Hansen, 1979).

D. Residues

Bioconcentration factors for lindane ranging from 35 to 938 were reported for six species of freshwater organisms (U.S. EPA, 1979; Sugiura, et al. 1979a). In marine organisms, bioconcentration factors (after 28 days) for 39 percent lindane of 130, 218, and 617 were obtained for the edible portion of the pinfish (Lagodon rhomboides), the American oyster

(Crassostrea virginica), and offal tissue of the pinfish (Schimmel, et al. 1977). Sugiura, et al. (1979a) found alpha-, beta-, and gamma-HCH had accumulation factors of 1,216, 973 and 765 in golden orfe (Leuciscusidus melanotus); 330, 273, and 281 in carp (Cyprinus carpio); 605, 658, and 442 in brown trout (Salmo trutta fario); and 588, 1,485, and 938 in guppy (Poecila reticula), respectively. Further, these accumulation factors were proportional to the lipid content of the fish. Accumulation occurred in the adipose tissues and the gall bladder, with the alpha and beta-HCH being more persistent (Sugiura, et al. 1979b).

Equilibrium accumulation factors of 429 to 602 were observed at days 2 to 6 after exposure of Chlorella sp. to 10 to 400 μg/l of lindane in aqueous solution (Hansen, 1979).

VI. EXISTING STANDARDS AND GUIDELINES

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 the induction of liver tumors in male mice, and using the "one-hit" model, the U.S. EPA (1979) has estimated the following levels of technical hexachlorocyclohexane and its isomers in ambient water which will result in specified risk levels of human cancer.

The water concentrations of technical HCH corresponding to a lifetime cancer risk for humans of 10^{-5} is 21 ng/l, based on the data of Nagasaki, et al. (1972).

The water concentrations of alpha-HCH corresponding to a lifetime cancer risk for humans of 10^{-5} is 16 ng/l, based on the data of Ito, et al. (1975).

The water concentrations of beta-HCH corresponding to a lifetime cancer risk for humans of 10^{-5} is 28 ng/l, based on the data of Goto, et al. (1972).

The water concentrations of lindane (gamma-HCH) corresponding to a lifetime cancer risk for humans of 10^{-5} is 54 ng/l, based on the data of Thorpe and Walker (1973).

Data for the delta and epsilon isomers are insufficient for the estimation of cancer risk levels (U.S. EPA, 1979).

An ADI of 1 µg/kg for HCH has been set by the Food and Agricultural Organization and the World Health Organization (U.S. EPA, 1979).

Tolerance levels set by the EPA are as follows: 7 ppm for animal fat, 0.3 ppm for milk, 1 ppm for most fruits and vegetables, 0.004 pm for finished drinking water, and 0.5 $\mu g/m^3$ (skin) for air (U.S. EPA, 1979).

B. Aquatic

For lindane, freshwater criteria have been drafted as 0.21 µg/l with 24-hour average concentration not to exceed 2.9 µg/l. For marine organisms, criteria for lindane have not been drafted. No criteria for mixtures of isomers of hexachlorocyclohexane (benzene hexachloride) were drafted for freshwater or marine organisms because of the lack of data.

HEXACHLOROCYCLOHEXANE

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No. 113

gamma-Hexachlorocyclohexane

Health and Environmental Effects

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

APRIL 30, 1980

-1330-

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.

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GAMMA-HEXACHLOROCYCLOHEXANE (Lindane)

Summary

Gamma-1,2,3,4,5,6-hexachlorocyclohexane, commonly known as lindane, can induce liver tumors in mice. Evidence for mutagenicity of lindane is equivocal. Lindane was not teratogenic for rats, although it reduced reproductive capacity over four generations. Chronic exposure of animals to lindane caused liver enlargement and, at higher doses, some liver damage and nephritic changes. Humans chronically exposed to HCH suffered liver damage. Chronic exposure of humans to lindane produced irritation of the central nervous system. Lindane is a convulsant.

Lindane has been extensively studied in a number of freshwater and marine acute studies. Levels as low as 0.17 µg/l are toxic to marine invertebrate species.

GAMMA-HEXACHLOROCYCLOHEXANE (Lindane)

I. INTRODUCTION

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

Gamma-1,2,3,4,5,6-hexachlorocyclohexane or lindane ($C_6H_6Cl_6$; molecular weight 290.0) is a crystalline solid with a melting point of 112.8°C, a vapor pressure of 0.003 mm Hg at 20°C (U.S. EPA, 1979), a solubility in water at 25°C of 7.8 mg/l (Hansen, 1979), and a solubility in ether of 20.8 g/100 g at 20°C (U.S. EPA, 1979). Other trade names include Jacutin, Lindfor 90, Lindamul 20, Nexit-Staub, Prodactin, gamma-HCH, gamma-BHC, and purified BHC (U.S. EPA, 1979). Technical grade hexachlorocyclohexane contains 10 to 18 percent lindane.

Lindane is a broad spectrum insecticide, and is a member of the cyclic organo-chlorinated hydrocarbons. It is used in a wide range of applications including treatment of animals, buildings, man (for ectoparasites), clothing, water (for mosquitoes), plants, seeds, and soil. Lindane is not currently manufactured in the U.S.; all lindane used in the U.S. is imported (U.S. EPA, 1979).

Lindane has a low residence time in the aquatic environment. It is removed by sedimentation, metabolism, and volatilization. Lindane contributes less to aquatic pollution than the other hexachlorocyclohexane isomers (Henderson, et al. 1971).

Lindane is slowly degraded by soil microorganisms (Mathur and Saha, 1975; Tu, 1975, 1976) and is reported to be isomerized to the alpha- and/or delta- isomers in microorganisms and plants (U.S. EPA, 1979), but not in rats (Copeland and Chadwick, 1979). The metabolic pathway in microorganisms is still controversial (Tu, 1975, 1976; Copeland and Chadwick, 1979).

II. EXPOSURE

A. Water

The contamination of water has occurred principally from direct application of technical hexachlorocyclohexane (HCH) or lindane to water for control of mosquitoes or from the use of HCH in agriculture and forestry; and to a lesser extent from occasional contamination of wastewater from manufacturing plants (U.S. EPA, 1979).

Lindane has been detected in the finished water of Streator, Illinois, at a concentration of 4 µg/l (U.S. EPA, 1975).

B. Food

The daily intake of lindane has been reported at 1 to 5 µg/kg body weight and the daily intake of all other HCH isomers at 1 to 3 µg/kg body weight (Duggan and Duggan, 1973). The chief sources of HCH residues in the human diet are milk, eggs, and other dairy products (U.S. EPA, 1979) and carrots and potatoes (Lichtenstein, 1959). Seafood is usually a minor source of HCH, probably because of the relatively high rate of dissipation of HCH in the aquatic environment (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for lindane to be 780 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

Traces of HCH have been detected in the air of central and suburban London (Abbott, et al. 1966). Uptake of lindane by inhalation is estimated at 0.002 µg/kg/day (Barney, 1969).

D. Dermal

Lindane has been used to eradicate human ectoparasites, a few adverse reactions have been reported (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

The rapidity of lindane absorption is enhanced by lipid-mediated carriers. Compared to other organochlorine insecticides, lindane is unusually soluble in water which contributes to its rapid absorption and excretion (Herbst and Bodenstein, 1972; U.S. EPA, 1979). Intraperitoneal injections of lindane resulted in 35 percent absorption (Koransky, et al. 1963). Lindane is also absorbed after oral and dermal exposure (U.S. EPA, 1979).

B. Distribution

After administration to experimental animals, lindane was detected in the brain at higher concentrations than in other organs (Laug, 1948; Davidow and Frawley, 1951; Koransky, et al. 1963; Huntingdon Research Center, 1971). At least 75 percent of an intraperitoneal dose of ^{14}C-labeled lindane was consistently found in the skin, muscle, and fatty tissue (Koransky, et al. 1963). Lindane enters the human fetus through the placenta; higher concentrations were found in the skin than in the brain, but never exceeded the corresponding values for adult organs (Poradovsky, et al. 1977; Nishimura, et al. 1977).

C. Metabolism

Copeland and Chadwick (1979) found that lindane did not isomerize in adipose tissues in rats, but noted dechlorination to γ-3,4,5,6-tetrachlorocyclohexene. Some other metabolites reported have been 2,3,4,5,6-pentachloro-2-cyclohexene-1-ol, pentachlorophenol, tetrachlorophenols, and three trichlorophenols (Chadwick, et al. 1975; Engst, et al. 1977), all of which were found in the urine as conjugates (Chadwick and Freal, 1972). Lindane metabolic pathways are still matters of some controversy (Engst, et

al. 1977; Copeland and Chadwick, 1979). Both free and conjugated chlorophenols with the possible exception of pentachlorophenol (Engst, et al. 1977) are far less toxic than lindane (Natl. Acad. Sci., 1977).

D. Excretion

Metabolites of lindane appear to be eliminated primarily as conjugates in the urine. Very little unaltered lindane is excreted (Laug, 1948). Elimination of lindane appears to be rapid after administration ceases (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

Nagasaki, et al. (1972b) fed α, β, γ, and δ isomers separately in the diet to mice at levels of 100, 250, and 500 ppm. At termination of the experiment after 24 weeks, multiple liver tumors, some as large as 2.0 centimeters in diameter were observed in all animals given α-HCH at the 500 ppm level. The 250 ppm α-HCH level resulted in smaller nodules, while no lesions were found at levels of 100 ppm. The various dosages did not produce any tumors with respect to the other isomers. Pathomorphological investigations by Didenko, et al. (1973) established that the γ isomer did not induce tumors in mice given intragastric administration at doses of 25 mg/kg twice a week for five weeks.

Hanada, et al. (1973) fed six-week-old mice a basal diet of 100, 300, and 600 ppm t-HCH and the α, β, γ isomers for a period of 32 weeks. After 38 weeks, liver tumors were found in 76.5 percent of the males and 43.5 percent of the females fed t-HCH, indicating males were more highly susceptible to HCH-induced tumors than females. Multiple nodules were found in the liver, although no peritoneal invasion or distinct metastasis was found. The β-isomer-treated animals had no tumors.

Goto, et al. (1972) essentially confirmed the findings of the above study using diets containing 600 ppm levels over a 26 week period. The combination of β-, γ-, or δ-HCH with the highly carcinogenic action of α-HCH revealed no synergistic or antagonistic effect on the production of tumors by α-HCH for dd strains of mice (Ito, et al. 1973). Kashyap, et al. (1979) found that γ-HCH (14 percent lindane) at 100 ppm levels in the diet or at 10 mg/kg/day caused liver and lymphoreticular tissue tumors in both male and female mice after 45 weeks. Application by skin painting had no effect.

The National Cancer Institute conducted a bioassay for the possible carcinogencity of δ-HCH to Osborne-Mendel rats and B6C3F1 mice. Administration continued for 80 weeks at two dose levels: time-weighted average dose for male rats was 236 and 472 ppm; for female rats, 135 and 275 ppm; and for all mice, 80 and 160 ppm. No statistically significant incidence of tumor occurrence was noted in any of the experimental rats as compared to the controls. At the lower dose concentration in male mice, the incidence of hepatocellular carcinoma was significant when compared to the controls, but not significant in the higher dose males. "Thus, the incidence of hepatocellular carcinoma in male mice cannot clearly be related to treatment." The incidence of hepatocellular carcinoma among female mice was not significant. Consequently, the carcinogenic activity of γ-HCH in mice is questionable (Natl. Cancer Inst., 1977).

B. Mutagenicity

Some alterations in mitotic activity and the karyotype of human lyphocytes cultured with lindane at 0.1 to 10 mg/ml have been reported (Tsoneva-Maneva, et al. 1971). γ-HCH was mutagenic in assays using <u>Salmonella typhimurium</u> with metabolic activation, the host-mediated assay, and the

dominant lethal assay in rats. Other reports indicate that it does not have significant mutagenic activity (U.S. EPA, 1979; Buselmair, et al. 1973).

C. Teratogenicity

Lindane given in the diet during pregnancy at levels of 12 or 25 mg/kg body weight/day did not produce teratogenic effects in rats (Mametkuliev, 1978; Khera, 1979).

D. Other Reproductive Effects

Chronic lindane feeding in a study of four generations of rats increased the average duration of pregnancy, decreased the number of births, increased the proportion of stillbirths, and delayed sexual maturation in F2 and F3 females. In addition, some of the F1 and F2 animals exhibited spastic paraplegia (Petrescu, et al. 1974).

In rats and rabbits, lindane given in the diet during pregnancy increased postimplantation death of embryos (Mametkuliev, 1978; Palmer, et al. 1978). Testicular atrophy has been observed in rats and mice (National Cancer Institute, 1977; Nigam, et al. 1979).

E. Chronic Toxicity

Irritation of the central nervous system with other toxic side effects (nausea, vomiting, spasms, weak respiration with cyanosis and blood dyscrasia) have been reported after prolonged or improper use of Hexicid (1 percent lindane) for the treatment of scabies on humans (Lee, et al. 1976).

In chronic studies with rats given lindane in oil, liver cell hypertrophy (fat degeneration and necrosis) and nephritic changes were noted at higher doses (Fitzhugh, et al. 1950; Lehman, 1952a,b). Rats inhaling lindane (0.78 mg/m^3) for 7 hours, 5 days a week for 180 days showed liver cell enlargement but showed no clinical symptoms or other abnormalities (Heyroth, 1952). The addition of 10 ppm lindane to the diet of rats for one

or two years decreased body weight after five months of treatment and altered ascorbic acid levels in urine, blood, and tissues (Petrescu, et al. 1974). Dogs chronically exposed to lindane in the diet had friable and slightly enlarged livers (Rivett, et al. 1978).

F. Other Relevant Information

Lindane is a convulsant and is the most acutely toxic isomer of hexachlorocyclohexane. The toxic effects of lindane are antagonized by pretreatment with phenobarbitol (Litterst and Miller, 1975) and by treatment with silymarin (Szpunar, et al. 1976), and various tranquilizers (Ulmann, 1972).

V. AQUATIC TOXICITY

A. Acute Toxicity

The range of adjusted LC_{50} values for one flow-through and 24 static bioassays for lindane in freshwater fish ranged from 1 µg/l for the brown trout Salmo trutta (Macek, et al. 1970) to 83 µg/l for the goldfish (Carassius auratus), and represents the results of tests on 16 freshwater fish species (U.S. EPA, 1979). Zebrafish (Brachydanio rerio) showed an LC_{50} value of 120 µg/l but rainbow trout (Salmo gairdneri) exhibited respiratory distress at 40 µg/l (Slooff, 1979). Among eight species of freshwater invertebrates studied with lindane, stoneflies (Pteronarcys californica) and three species of crustaceans: scuds (Gammarus lacustris and G. faciatus) and sowbugs (Ascellus brevicaudus) were most sensitive, with adjusted LC_{50} values ranging from 4 to 41 µg/l. Three species of cladocerans (Daphnia pulex, D. magna and Simocephalus serralatus) were most resistant with LC_{50} values of 390 to 745 µg/l. The midge (Chironomus tentans) was intermediate in sensitivity with LC_{50} values of 175 µg/l (U.S. EPA, 1979).

Among eight species of marine fish tested in static bioassays with lindane, the Atlantic silversides (Menidia menidia) was most sensitive, with an acute LC_{50} of 9 µg/l (Eisler, 1970), while the striped mullet (Mugil cephalus) was reported as having an acute static LC_{50} of 66.0 µg/l (U.S. EPA, 1979). The results of six flow-through assays on five species of marine fish revealed that the striped bass (Morone saxatilis) was most sensitive with an acute LC_{50} of 7.3 µg/l (Korn and Earnest, 1974); and the longnose killifish (Fundulus similis) was most resistant with a reported LC_{50} of 240 µg/l. Acute studies with six species of marine invertebrates showed these organisms to be extremely sensitive to lindane, with LC_{50} values ranging from 0.17 µg/l for the pink shrimp, Panaeus duorarum (Schimmel, et al. 1977), to 8.5 µg/l for the grass shrimp (Palaemonetes vulgaris).

B. Chronic

A chronic value of 14.6 µg/l was obtained for lindane in a life-cycle assay of the freshwater fathead minnow (Pimephales promelas). Chronic values of 3.3, 6.1, and 14.5 µg/l were obtained for three freshwater invertebrates, Chironomus tentans, Gammarus fasciatus, and Daphnia magna (Macek, et al. 1976). No marine chronic studies were available.

C. Plant Effects

For freshwater algae, Scenedesmus acutus, the effective concentration for growth inhibition was 1,000 µg/l. Effective concentrations for marine phytoplankton communities and the algae, Acetabularia mediterranea, were 1,000 and 10,000 µg/l, respectively. Irreparable damage to Chlorella spec. occurred at concentrations greater than 300 µg/l (Hansen, 1979).

D. Residues

Bioconcentration factors for lindane ranging from 35 to 938 have been obtained for six species of freshwater fish and invertebrates. No bioconcentration factors for lindane have been determined for marine organisms

(U.S. EPA, 1979; Sugiura, et al. 1979). Equilibrium accumulation factors of 429 to 602 were observed at days 2 to 6 after exposure of Chlorella spec. to 10 to 400 µg/l of lindane in aqueous solution (Hansen, 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

Using the "one-hit" model, the U.S. EPA (1979) has estimated that the water concentration of lindane (gamma-HCH) corresponding to a lifetime cancer risk for humans of 10^{-5} is 54 ng/l, based on the data of Thorpe and Walker (1973) for the induction of liver tumors in male mice.

Tolerance levels set by the U.S. EPA are as follows: 7 ppm for animal fat; 0.3 ppm for milk; 1 ppm for most fruits and vegetables; 0.004 ppm for finished drinking water; and 0.5 mg/m^3 (skin) for air (U.S. EPA, 1979). It is not clear whether these levels are for hexachlorocyclohexane or for lindane.

B. Aquatic

The criterion has been drafted to protect freshwater organisms as a 0.21 µg/l 24-hour average concentration not to exceed 2.9 µg/l. Data are insufficient to draft criterion for the protection of marine life from gamma-hexachlorocyclohexane (lindane).

GAMMA-HEXACHLOROCYCLOHEXANE (LINDANE)

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No. 114

Hexachlorocyclopentadiene

Health and Environmental Effects

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

APRIL 30, 1980

-1349-

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.

HEXACHLOROCYCLOPENTADIENE

Summary

Hexachlorocyclopentadiene (HEX) is used as a chemical intermediate in the manufacture of chlorinated pesticides. Evidence is not sufficient to categorize this compound as a carcinogen or non-carcinogen; HEX was not mutagenic in either short-term *in vitro* assays or a mouse dominant lethal study. Teratogenic effects were not observed in rats receiving oral doses of HEX during gestation.

The reported 96-hour LC_{50} value for the fathead minnow under static and flow-through conditions using larval and adult fish ranges from 7.0 µg/l to 104 µg/l. The chronic value for fish in an embryo-larval test is 2.6 µg/l.

HEXACHLOROCYCLOPENTADIENE

I. INTRODUCTION

Hexachlorocyclopentadiene (HEX; C_5Cl_6) is a pale to greenish-yellow liquid. Other physical properties include: molecular weight, 272.77; solubility in water, 0.805 mg/l; and vapor pressure, 1 mm Hg at 78-79°C. HEX is a highly reactive compound and is used as a chemical intermediate in the manufacture of chlorinated pesticides (Kirk-Othmer, 1964). Recent government bans on the use of chlorinated pesticides have restricted the use of HEX as an intermediate to the endosulfan and decachlorobi-2,4-cyclopentadiene-1-yl industries. Currently, the major use of HEX is as an intermediate in the synthesis of flame retardants (Sanders, 1978; Kirk-Othmer, 1964). Production levels of HEX approximate 50 million pounds per year (Bell, et al. 1978).

Environmental monitoring data for HEX are lacking, except for levels measured in the vicinity of industrial sites. The most likely route of entry of HEX into the environment arises from its manufacture or the manufacture of HEX-containing products. Small amounts of HEX are present as impurities in pesticides made from it; some HEX has undoubtedly entered the environment via this route.

HEX appears to be strongly adsorbed to soil or soil components, although others have reported its volatilization from soil (Rieck, 1977a, 1977b). HEX degrades rapidly by photolysis, giving water-soluble degradation products (Natl. Cancer Inst., 1977). Tests on its stability towards hydrolysis at ambient temperature indicated a half-life of about 11 days at pH3-6, which was reduced to 6 days at pH 9.

II. EXPOSURE

A. Water

HEX has been detected in water near points of industrial discharge at levels ranging from 0.156 to 18 mg/l (U.S. EPA, 1979). Other than this, there is little information concerning HEX concentrations in surface or drinking waters. Due to its low solubility, photolability, and tendency to volatize, one would not expect HEX to remain in flowing water.

B. Food

HEX has been identified in a few samples of fish taken from waters near the Hooker Chemical Plant in Michigan (Spehar, et al. 1977). No reports concerning HEX contamination of other foods could be located.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of HEX for the edible portions of fish and shellfish consumed by Americans to be 3.2. This estimate is based on measured steady-state bioconcentration studies in fathead minnows.

C. Inhalation

The most significant chronic exposure to HEX occurs among persons engaged directly in its manufacture and among production workers fabricating HEX-containing products. Inhalation is the primary mode of exposure to HEX in the event of accidental spills, illegal discharges, or occupational situations.

III. PHARMACOKINETICS

A. Absorption

Kommineni (1978) found in rats that HEX is absorbed through the squamous epithelium of the nonglandular part of the stomach, causing necrotic changes, and that the major route of elimination of HEX is through the lungs. This information is based on morphological changes in rats

administered HEX by gavage. Further study with guinea pigs showed that HEX was absorbed through the skin; but, unlike the rat stomach, the squamous epithelium of these animals did not undergo necrotic changes.

B. Distribution

The tissues of four rats administered single oral doses of HEX retained only trace amounts of the compound after 7 days (Mehendale, 1977). For example, approximately 0.5 percent of the total dose was retained in the kidney and less than 0.5 percent in the liver. Other organs and tissues - fat, lung, muscle, blood, etc. - contained even less HEX. Tissue homogenates from rats receiving injections of ^{14}C-HEX showed that 93 percent of the radioactivity in the kidney and 68 percent in the liver were associated with the cytosol fraction (Mehendale, 1977).

C. Metabolism

At least four metabolites were present in the urine of rats administered HEX (Mehendale, 1977). Approximately 70 percent of the metabolites were extractable using a hexane:isopropanol mixture.

D. Excretion

Mehendale (1977) found that approximately 33 percent of the total dose of HEX administered to rats via oral intubation was excreted in the urine after 7 days. About 87 percent of that (28.7 percent of the total dose) was eliminated during the first 24 hours. Fecal excretion accounted for 10 percent of the total dose; nearly 60 percent of the 7 day fecal excretion occurred during the first day. These findings suggest that elimination of HEX may occur by routes other than urine and feces, and it has been postulated that a major route of excretion may be the respiratory tract.

Whitacre (1978) did not agree with the study by Mehendale (1977). This recent study of HEX excretion from mice and rats showed that excretion was mainly by the fecal route with no more than 15 percent in the urine.

Approximately nine percent of an injected dose of HEX was excreted in the bile in one hour (Mehendale, 1977). Because this quantity is equivalent to that excreted in the feces over seven days, enterohepatic circulation of this compound is probable.

IV. EFFECTS

A. Carcinogenicity

Only one *in vitro* test of HEX for carcinogenic activity could be located. Litton Bionetics (1977) reported the results of a test to determine whether HEX could induce malignant transformation in BALB/3T3 cells. HEX was found to be relatively toxic to cells, but no significant carcinogenic activity was reported with this assay.

The National Cancer Institute (1977) concluded that toxicological studies conducted thus far have not been adequate for evaluation of the carcinogenicity of HEX. Because of this paucity of information and HEX's high potential for exposure, HEX has been selected for the NCI's carcinogenesis testing program.

B. Mutagenicity

HEX has been reported to be non-mutagenic in short-term *in vitro* mutagenic assays (Natl. Cancer Inst., 1977; Industrial Bio-Test Laboratories, 1977; Litton Bionetics, 1978a) and in a mouse dominant lethal assay (Litton Bionetics, 1978b).

C. Teratogenicity

International Research and Development Corporation (1978) studied the effect of oral doses of up to 300 mg/kg/day of HEX administered to rats on days 6 through 15 of gestation. Teratogenic effects were not reported at doses up to 100 mg/kg/day; the highest dosage (300 mg/kg/day) resulted in the death of all rats by day ten of gestation. In this study, elimination via the respiratory tract did not appear to be significant.

D. Other Reproductive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

There are very few studies concerning the chronic toxicity of HEX in laboratory animals. Naishstein and Lisovskaya (1965) found that daily administration of 1/30 the median lethal dose (20 mg/kg) for 6 months resulted in the death of two of ten animals. The investigators judged the cumulative effects of HEX to be weak; no neoplasms or other abnormalities were reported. Naishstein and Lisovskaya (1965) applied 0.5 to 0.6 ml of a solution of 20 ppm HEX daily to the skin of rabbits for 10 days and found no significant adverse effects from exposure. Treon, et al. (1955) applied 430-6130 mg/kg HEX to the skin of rabbits. Degenerative changes of the brain, liver, kidneys, and adrenal glands of these animals were noted, in addition to chronic skin inflammation, acanthosis, hyperkeratosis, and epilation. Further study by Treon, et al. (1955) revealed slight degenerative changes in the liver and kidney of guinea pigs, rabbits, and rats exposed to 0.15 ppm HEX for daily seven-hour periods over approximately seven months. Four of five mice receiving the same dosage died within this period.

There is virtually no information regarding the human health effects of chronic exposure to HEX. According to Hooker's material safety data sheet for HEX, (1972) acute exposure to the compound results in irritation of the eyes and mucous membranes, causing lacrimation, sneezing, and salivation. Repeated contact with the skin can cause blistering and burns, and inhalation can cause pulmonary edema. Ingestion can cause nausea, vomiting, diarrhea, lethargy, and retarded respiration.

V. AQUATIC TOXICITY

A. Acute Toxicity

The reported 96-hour LC_{50} values for the fathead minnow (Pimephales promelas) under static and flow-through conditions with larval and adult fish range from 7.0 µg/l to 104 µg/l. The effect of water hardness is minimal (Henderson 1956; U.S. EPA, 1978). There are no reports of studies of the acute toxicity of HEX on saltwater organisms.

B. Chronic Toxicity

In the only chronic study reported, the lowest chronic value for the fat- head minnow (embryo-larval) is 2.6 µg/l (U.S. EPA, 1978).

C. Plant Effects

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

The Occupational Safety and Health Administration has not set a standard for occupational exposure to HEX. The American Conference of Governmental Industrial Hygienists has adopted a threshold limit value (TLV) of 0.01 ppm (0.11 mg/m^3) and a short term exposure limit of 0.03 ppm (0.33 mg/m^3) (ACGIH, 1977).

The draft ambient water quality criterion for HEX is 1.0 µg/l (U.S. EPA, 1979).

B. Aquatic

For HEX, the draft criterion to protect freshwater aquatic life is 0.39 µg/l as a 24-hour average, not to exceed 7.0 µg/l at any time (U.S. EPA, 1979). Criteria have not been proposed for saltwater species because of insufficient data.

HEXACHLOROCYCLOPENTADIENE

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No. 115

Hexac[illegible]roethane

Health and Environmental Effects

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

APRIL 30, 1980

-1361-

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.

HEXACHLOROETHANE

SUMMARY

Results of a National Cancer Institute (NCI) carcinogenesis bioassay showed that hexachloroethane produced an increase in hepatocellular carcinoma incidence in mice.

Testing of hexachloroethane in the Ames *Salmonella* assay showed no mutagenic effects. No teratogenic effects were observed following oral or inhalation exposure of rats to hexachloroethane, but some toxic effects on fetal development were observed.

Toxic symptoms produced in humans following hexachloroethane exposure include central nervous system depression and liver, kidney, and heart degeneration.

Hexachloroethane is one of the more toxic of the chlorinated ethanes reviewed for aquatic organisms with marine invertebrates appearing to be the most sensitive organisms studied. This chlorinated ethane also had the greatest bioconcentration factor, 139 for bluegill sunfish, observed in this class of compounds.

HEXACHLOROETHANE

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 are replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. Hexachloroethane (Perchloroethane; M.W. 236.7) is a solid at room temperature with a boiling point of 186°C, specific gravity of 2.091; and is insoluble 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. Hexachloroethane does not appear to be commercially produced in the U.S., but 730,000 kg were imported in 1976. (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 are present in raw and finished waters due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water or treatment of sewage. Air levels are produced by evaporation of volatile chloroethanes.

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). Information on the levels of hexachloroethane in foods is not available.

U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for hexachloroethane to be 320 for the edible portion of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

III. PHARMOKINETICS

Pertinent data could not be located in the available literature on hexachloroethane 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 through the body; enzymatic dechlorination and oxidation to the alcohol and ester forms; and excretion of the chloroethanes primarily in the urine and in expired air.

IV. EFFECTS

A. Carcinogencitiy

Results of an NCI carcinogenensis bioassay for hexachloroethane showed that oral administration of the compound produced an increase in the incidence of hepatocellular carcinoma in mice. No statistically significant tumor increase was seen in rats.

B. Mutagenicity

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

C. Teratogenicity

Teratogenic effects were not observed in pregnant rats exposed to hexachloroethane by inhalation or intubation (Weeks, et al. 1979).

D. Other Reproductive Effects

Hexachloroethane administered orally to pregnant rats decreased the number of live fetuses per litter and increased the fetal resorption rate (Weeks, et al. 1979).

E. Chronic Toxicity

Toxic symptoms produced in humans following hexachloroethane exposure include liver, kidney, and heart degeneration, and central nervous system depression (U.S. EPA, 1979a).

Animal studies have shown that chronic exposure to hexachloroethane produces both hepatotoxicity and nephrotoxicity (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

A. Acute Toxicity

Among freshwater organisms, the bluegill sunfish (Lepomis macrochirus) was reported to have the lowest sensitivity to hexachloroethane, with a 96-hour static LC_{50} value of 980 µg/l. The 48-hour static LC_{50} value of the freshwater Cladoceran (Daphnia magna) was reported as 8,070 µg/l (U.S. EPA, 1978). For the marine fish, the sheepshead minnow (Cyprinodon variegatus), a 96-hour LC_{50} value of 2,400 µg/l was reported from a static assay. The marine mysid shrimp (Mysidopsis bahia) was the most sensitive aquatic organism tested, with a 96-hour static LC_{50} value of 940 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

Pertinent data could not be located in the available literature.

C. Plant Effects

For the freshwater algae, Selenastrum capricornutum, the 96-hour EC_{50} effective concentrations based on chlorophyll and cell number were 87,000 and 93,200 µg/l for chlorophyll a production and cell growth, respectively. The marine algae, Skeletonema costatum, was much more sensitive, with effective concentrations from 7,750 to 8,570 µg/l being reported.

D. Residues

A bioconcentration factor of 139 was obtained for the freshwater bluegill sunfish (U.S. EPA, 1979a).

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

By applying a linear, non-threshold model to the data from the NCI bioassay for carcinogenesis, the U.S. EPA (1979a) has estimated the level of hexachloroethane in ambient water that will result in an additional risk of 10^{-5} to be 5.9 µg/l.

The eight-hour TWA exposure standard established by OSHA for hexachloroethane is 1 ppm.

B. Aquatic Toxicity

The proposed criterion to protect freshwater aquatic life is 62 µg/l as a 24-hour average and should not exceed 140 µg/l at any time. The drafted criterion for saltwater aquatic life is a 24-hour average concentration of 7 µg/l not to exceed 16 µg/l at any time.

HEXACHLOROETHANE

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No. 116

Hexachlorophene

Health and Environmental Effects

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

APRIL 30, 1980

-1369-

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.

HEXACHLOROPHENE

Summary

Oral, dermal, and subcutaneous administration of hexachlorophene in animal studies has failed to show significant carcinogenic effects.

Mutagenic effects of hexachlorophene exposure have been reported in one study which indicated increased chromosome aberrations in rats. Testing of hexachlorophene in the host mediated assay or the dominant lethal assay did not produce positive effects.

Several reports have indicated that hexachlorophene may produce some teratogenic and embryotoxic effects. A three generation feeding study in rats failed to show any teratogenic activity. Hexachlorophene has shown some adverse effects on male reproductive performance.

Chronic administration of hexachlorophene has produced central nervous system effects and muscular paralysis.

I. INTRODUCTION

Hexachlorophene ($C_{13}H_6O_2CL_6$, molecular weight 406.9) is a white powder which melts between 166°C and 167°C. The compound is practically insoluble in water but is soluble in ethanol, ether, and other organic solvents. Under alkaline conditions, hexachlorophene forms water-soluble salts (IARC, 1979).

The principle uses of hexachlorophene have been for the manufacture of germicidal soaps, as a topical anti-infective agent for humans, as a veterinary anti-helminthic, for disinfection of hospital equipment, and as a broad-spectrum soil fungicide (IARC, 1979). Limitation of drugs and cosmetics containing hexachlorophene was instituted by the FDA in 1972.

Commercial hexachlorophene produced from 2,4,5-trichlorophenol contains less than 15 µg/kg of 2,3,7,8-tetrachlorodibenzo-para-dioxin (IARC, 1979).

II. EXPOSURE

There are no available estimates on daily exposure levels of humans to hexachlorophene from air, water, or food.

Water monitoring studies have detected hexachlorophene in two finished drinking water samples (Shackelford and Keith, 1976) and in effluents of sewage treatment plants at levels of 3.2 to 44.3 µg/l (Sims and Pfaender, 1975), as well as in creek sediments (9.3 to 377 µg/kg).

Data on hexachlorophene levels in aquatic organisms indicate that the compound is bioaccumulated (Sims and Pfaender, 1975).

Hexachlorophene has been detected in human milk at levels up to 9 µg/l (West, et al. 1975). Blood levels of the compound in users of soap containing hexachlorophene have been reported (0.02 to 0.14 mg/l blood) (Butcher, et al. 1973); blood levels fall after use is discontinued.

A 1974 survey by NIOSH indicated that exposure to hexachlorophene was primarily in hospitals, sanitariums, and convalescent homes (IARC, 1979).

III. PHARMACOKINETICS

A. Absorption

Systemic toxicity following dermal application or ingestion of hexachlorophene indicates that the compound is absorbed through the skin and the gastrointestinal tract (AMA Drug Evaluations, 1977).

B. Distribution

Whole-body autoradioigraphs of the murine fetus during late gestation following administration of labelled hexachlorophene indicate an even distribution pattern of the compound . The compound crosses the placenta; fetal retention increases during the course of pregnancy (Brandt, et al. 1979). Hexachlorophene has been detected in human adipose samples at levels of 0.80 μg/kg (Shafik, 1973).

C. Metabolism

Hexachlorophene is metabolized by the liver, producing a glucuronide conjugate. The clearance of blood hexachlorophene is dependent on this hepatic activity (Klaassen, 1979).

D. Excretion

Within three hours of hexachlorophene administration to rats, 50 percent of the initial dose was excreted in the bile (Klaassen, 1979). Oral administration of the compound to a cow resulted in excretion of 63.8 percent of the initial dose in the feces and 0.24 percent in the urine (St. John and Lisk, 1972).

IV. EFFECTS

A. Carcinogenicity

The lifetime dermal application of 25-percent and 50-percent solutions of hexachlorophene to mice failed to produce significant carcinogenic effects (Stenback, 1975); the levels of compound used caused high toxicity. Rudali and Assa (1978) were unable to produce carcinogenic effects in mice by lifetime feeding or subcutaneous injection at birth of hexachlorophene. Oral lifetime feeding of hexachlorophene to rats (17 to 150 ppm) also failed to show carcinogenic effects (NCI, 1978).

B. Mutagenicity

Single intraperitoneal injections of 2.5 or 5.0 mg/kg hexachlorophene failed to induce dominant lethal mutations in mice (Arnold, et al. 1975).

Desi, et al. (1975) have reported that hexachlorophene administered to rats produced chromosome aberrations (dose and route not specified).

C. Teratogenicity

Kennedy, et al. (1975a) reported that the fetuses of pregnant rats exposed to hexachlorophene at 30 mg/kg on days 6 to 15 of gestation show a low frequency of eye defects and skeletal abnormalities (angulated ribs). Fetuses of rabbits exposed to this compound at 6 mg/kg on days 6 to 18 of gestation showed a low incidence of skeletal irregularities, but no soft tissue anomalies (Kennedy, et al. 1975a). A three-generation feeding study of hexachlorophene to rats at levels of 12.5 to 50 ppm did not show teratogenic effects (Kennedy, et al. 1975b).

A single retrospective Swedish study on infants born to nurses regularly exposed to antiseptic soaps containing hexachlorophene has suggested that the incidence of malformations in this infant population is increased (Halling, 1979).

D. Other Reporductive Effects

Gellert, et al. (1978) have reported that male neonatal rats washed for eight days with three percent hexachlorophene solutions showed as adults a decreased fertility due to inhibited reflex ejaculation.

Oral administration of hexachlorophene to rats has been reported to produce degeneration of spermatogenic cells (Casaret and Doull, 1975). Subcutaneous injection of hexachlorophene to mice at various periods of gestation produced increased fetal resorptions (Majundar, et al. 1975).

E. Chronic Toxicity

Administration of hexachlorophene by gavage (40 mg/kg) produced hind leg paralysis and growth impairment after two to three weeks (Kennedy and Gordon, 1976). Histological examination showed generalized edema or status spongiosus of the white matter of the entire central nervous system. These gross effects and histopathological lesions have been reported to be reversible (Kennedy, et al. 1976).

Central nervous system effects in humans following chronic exposure to hexachlorophene include diplopia, irritability, weakness of lower extremities, and convulsions (Sax, 1975).

V. AQUATIC TOXICITY

A. Acute and Chronic Toxicity and Plant Effects

Pertinent data were not found in the available literature.

B. Residues

Sims and Pfaender (1975) found levels of hexachlorophenol in aquatic organisms ranging from 335 ppb in sludge worms to 27,800 ppb in water boatman (Sigara spp.).

VI. EXISTING GUIDELINES

A. Human

Hexachlorophene is permitted as a preservative in drug and cosmetic products at levels up to 0.1 percent (USFDA, 1972).

B. Aquatic

Pertinent data were not found in the available literature.

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No. 117

Hydrofluoric Acid

Health and Environmental Effects

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

APRIL 30, 1980

-1378-

DISCLAIMER

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HYDROFLUORIC ACID

Summary

Hydrofluoric acid (HF) has produced mutagenic effects in plants and Drosophila, and lymphocyte chromosome aberrations in rats. Chromosome effects were not observed in mice following sub-chronic inhalation exposure to the compound.

No data are avilable on the possible carcinogenic or teratogenic effects of HF.

Chronic exposure to the compound has produced skeletal fluorosis, dental mottling and pulmonary function impairment.

One short-term bioassay test demonstrated that a concentration of 50,000 µg/l HF was lethal to bluegill sunfish in one hour.

HYDROFLUORIC ACID

I. INTRODUCTION

Hydrofluoric acid (CAS registry number 7664-39-3) (HF) is a colorless, clear, fuming corrosive liquid made by treating fluorspar (CaF_2) with sulfuric acid. An unusual property of HF is that it will dissolve glass or any other silica-containing material. It has the following physical and chemical properties (Windholz, 1976; Hawley, 1971; Weast, 1972):

	Pure	Constant Boiling
Formula:	HF	HF/H_2O
Molecular Weight:	20.01	---
Melting Point:	-83.55°C	---
Boiling Point:	19.51°C	---
Density:	0.987	1.15 - 1.18
Vapor Pressure:	1 atm @ 19.51°C	
Solubility:	Very soluble in water; soluble in many organic solvents, e.g., benzene, toluene, xylene, etc.	

HF is used in the aluminum industry, for the production of fluorocarbons, for uranium processing, for petroleum alkylation, for the production of fluoride salts, and as a pickling agent for stainless steel. It has many other minor uses (CMR, 1978).

II. EXPOSURE

A. Water

Other than occasional leaks and spills, very small amounts of HF are released into water from manufacturing and production facilities (Union Carbide, 1977; U.S. EPA, 1977a). HF is released into the air from coal

fires (U.S. EPA, 1977b) and from manufacturing and production facilities (Union Carbide, 1977). HF released into the air has a high affinity for water, and it is expected that it will rain out (Fisher, 1976). The amounts of HF in water and the extent of its presence could not be determined from the available literature. Under alkaline conditions, HF will form aqueous salts.

B. Food

Pertinent data were not found in the available literature.

C. Inhalation

HF occurs in the atmosphere from coal fires and from manufacturing and production facilities (see above), as well as from the photochemical reaction of CCL_2F_2 with NO and humid air (Saburo, et al. (1977). It is present the stratosphere (Zander, et al. 1977; Drayson, et al. 1977; Farmer and Raper, 1977). The extent and amounts of HF in the atmosphere could not be determined from the available literature.

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

The major route of HF absorption is by the respiratory system; penetration of liquefied anhydrous HF through the skin has been reported (Burke, et al. 1973). Fatal inhalation of HF fumes resulted in a blood fluoride level of 0.4 mg/100 ml (Greendyke and Hodge, 1964), while skin penetration of anhydrous HF produced a maximum blood fluoride concentration of 0.3 mg/100 ml (Burke, et al. 1973). These levels are 100-fold higher

than normal serum fluoride levels (Hall et al. 1972). Forty-five percent of fluoride present in the air in gaseous or particulate form is absorbed on inhalation (Dinman, et al. 1976).

B. Distribution

Absorbed fluoride is deposited mainly in the skeleton and teeth; it is also found in soft tissues and body fluids (NAS, 1971; NIOSH, 1975; NIOSH, 1976). Fluoride reaches fetal circulation via the placenta and is deposited in the fetal skeleton (NAS, 1971).

Fluoride deposition in bone is not irreversible (NAS, 1971). However, laboratory animals chronically exposed to HF gas retained abnormally high levels of fluoride in the skeleton for up to 14 months after exposure (Machle and Scott, 1935).

C. Metabolism

The physiological or biochemical basis of fluoride toxicity has not been established, although it appears that enzymes involved in vital functions are inhibited by fluoride (NAS, 1971). Examination of the data of Collins, et al. (1951) indicates that metabolism of absorbed fluoride is the same whether it is inhaled as a particulate inorganic or gas (as HF) (NIOSH, 1976).

D. Excretion

Fluoride is excreted in the urine, feces and sweat, and in trace amounts in milk, saliva, hair and probably tears. Data are lacking regarding loss of fluoride by expired breath (NAS, 1971).

The primary route of fluoride elimination is through the urine. The urinary fluroide concentration is influenced by factors such as total absorption, the form of fluoride absorbed, frequency of exposure and general

health (NAS, 1971). It is recognized that urinary fluoride levels are directly related to the concetration of absorbed fluoride (NAS, 1971).

In a relatively unexposed person, about one-half of an acute dose of fluoride is excreted within 24 hours in the urine, and about one-half is deposited in the skeleton (NAS, 1971).

IV. EFFECTS

A. Carcinogenicity

Pertinent data were not found in the available literature.

B. Mutagenicity

Mohamed (1968) has reported various aberrations in second generation tomato plants following parenteral treatment with HF at 3 $\mu g/m^3$. These results could not be duplicated by Temple and Weinstein (1976).

Rats inhaling 0.1 mg HF/m^3 chronically for two months were reported to develop lymphocyte chromosomal aberrations; aberrations could not be detected in sperm cells of mice administered the same levels of HF (Voroshilin, et al. 1973).

Weak mutagenic effects in the offspring of Drosophila exposed to air bubbled through 2.5 percent HF have been reported (Mohamed, 1971).

C. Teratogenicity

Pertinent data were not found in the available literature.

D. Other Reproductive Effects

Reduced fertility in Drosophila and decreased egg hatch have been reported following exposure to 2.9 ppm HF (Gerdes, et al. 1971).

E. Chronic Toxicity

Among the adverse physiologic effects of long-term exposure to HF are skeletal fluorosis, dental mottling and pulmonary impairment (NAS, 1971; NIOSH, 1975; NIOSH, 1976). Skeletal fluorosis is characterized by increased

bone density, especially in the pelvis and spinal column, restricted spinal motion, and ossification of ligaments. Nasal irritation, asthma or shortness of breath, and in some cases pulmonary fibrosis are associated with HF-induced pulmonary distress (NIOSH, 1976). Digestive disturbances have also been noted (NIOSH, 1976). Fluoride-induced renal pathology has not been firmly established in man (Adler, et al. 1970). Causal relationships in industrial exposures are difficult to determine because exposure often involves other compounds in addition to fluorides (NIOSH, 1976).

Laboratory animals chronically exposed to 15.2 mg HF/m^3 developed pulmonary, kidney and hepatic pathology (Machle and Kitzmiller, 1935; Machle, et al. 1934), while animals exposed to 24.5 mg HF/m^3 developed lung edema (Stokinger, 1949). Testicular pathology was also observed in dogs at 24.5 mg HF/m^3 (Stokinger, 1949). Several animal studies have demonstrated that inhalation of HF increased fluoride deposition in the bones (NIOSH, 1976).

F. Other Relevant Information

Fluoride has anticholinesterase character which, in conjunction with the reduction in plasma calcium observed in fluoride intoxication, may be responsible for acute nervous system effects (NAS, 1971). The severe pain accompanying skin injury from contact with 10 percent HF has been attributed to immobilization of calcium, resulting in potassium nerve stimulation (Klauder, et al 1955).

Inhibition of enolase, oxygen uptake, and tetrazolium reductase activity has been demonstrated <u>in vitro</u> from application of HF to excised guinea pig ear skin (Carney, et al. 1974).

V. AQUATIC TOXICITY

A. Acute Toxicity

McKee and Wolf (1963) reported that HF was toxic to fish (unspecified at concentrations ranging from 40,000 to 60,000 μg/l. Bonner and Morgan (1976) observed that 50,000 μg/l HF was lethal to bluegill sunfish (Lepomis macrochirus) in one hour.

B. Chronic Toxicity, Plant Effects, and Residue

Pertinent data were not found in the available literature.

C. Other Relevant Information

Bonner and Morgan (1976) observed a marked increase in the opercular "breathing" rate of bluegill sunfish exposed to a concentration of 25,000 ug/l for four hours. The fish recovered within three days.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

In 1976, NIOSH proposed a workplace environmental limit for HF of 2.5 mg/m^3 (3 ppm) as a time-weighted average to provide protection from the effects of HF over a working lifetime (NIOSH, 1976). A ceiling limit of 5 mg HF/m^3 based on 15-minute exposures was also recommended to prevent acute irritation from HS (NIOSH, 1976).

B. Aquatic

Pertinent data were not found in the available literature.

HYDROFLUORIC ACID

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No. 118

Hydrogen Sulfide

Health and Environmental Effects

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

APRIL 30, 1980

-1390-

DISCLAIMER

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Hydrogen Sulfide

Summary

Pertinent information could not be located on the carcinogenicity, mutagenicity, or teratogenicity of H_2S.

Hydrogen sulfide is very toxic to humans via inhalation and has been reported to cause death at concentrations of 800 to 1000 ppm.

Hydrogen sulfide is reported to be very toxic to fish with toxic effects resulting from 1 to 100 ppm.

I. INTRODUCTION

Hydrogen sulfide (H_2S; CAS No. 7783064) is a colorless flammable gas with a rotten egg odor. It has the following physical properties:

Formula	H_2S
Molecular Weight	34.08
Melting Point	-85.5°C
Boiling Point	-60.4°C
Density	1.539 gram per liter at 0°C
Vapor Pressure	20 atm. at 25.5°C

Hydrogen sulfide is soluble in water, alcohol, and glycerol (ITII, 1976). Hydrogen sulfide is a flammable gas and the vapor may travel considerable distance to a source of ignition and flash back.

Hydrogen sulfide and other sulfur compounds occur to some extent in most petroleum and natural-gas deposits. Very substantial quantities of this gas are liberated in coking operations or in the production of manufactured gases from coal (Standen, 1969). Hydrogen sulfide is used to produce substantial tonnages of elemental sulfur, sulfuric acid, and a variety of other chemicals. Completely dry hydrogen sulfide, whether gaseous or liquid, has no acidic properties. Aqueous solutions, however, are weakly acidic (Standen, 1969). In 1965, some 5.2 million metric tons of H_2S was recovered from fossil fuels (Standen, 1969).

II. EXPOSURE

A. Water

Bacterial reduction of sulfates accounts for the occurrence of H_2S in numerous bodies of water, such as the lakes near El Agheila, Libya. Hydrogen sulfide is familiarly formed as a bacterial decomposition product of protein matter, particularly of animal origin (Standen, 1969) and this gas can be found in most sewage treatment plant and their piping systems.

B. Food

H_2S may be formed within the gastrointestinal tract after the ingestion of inorganic sulfide salts or elemental sulfur due to the actions of gastric acid and of colonic bacteria. (Division of Industrial Hygiene, 1941).

C. Inhalation

Wherever sulfur is deposited, pockets of hydrogen sulfide may be encountered, thus it is found at coal, lead, gypsum, and sulfur mines. Crude oil from Texas and Mexico contain toxic quantities of H_2S (Yont and Fowler, 1926). The decay of organic matter gives rise to the production of H_2S in sewers and waste from industrial plants where animals products are handled. Thus, there has been accidental poisoning from H_2S in tanneries, glue factories, fur-dressing and felt-making plants, abattoirs, and beet-sugar factories; for example, in Lowell, Massachusetts five men were poisoned (three died) when sent to repair a street sewer which drained waste from a tannery (Hamilton and Hardy, 1974).

Hydrogen sulfide is formed in certain industrial processes such as the production of sulfur dyes, the heating of rubber containing sulfur compounds, the making of artificial silk or rayon by viscose process (Hamilton and Hardy, 1974).

D. Dermal

Pertinent information could not be found in the available literature.

III. PHARMACOKINENTICS

A. Absorption

By far the greatest danger presented by hydrogen sulfide is through inhalation, although absorption through the skin has been reported (Patty, 1967).

B. Distribution

Pertinent information could not be found in the available literature.

C. Metabolism and Excretion

Evidence has been obtained for the presence of a sulfide oxidase in mammalian liver (Baxter and Van Reen, 1958; Sörbo, 1960), but important nonenxymatic mechanisms for sulfide detoxication are also recognized. Sulfide tends to undergo spontaneous oxidation to non-toxic products such as polysulfides, thiosulfates or sulfates (Gosselin, 1976).

When free sulfide exists in the circulating blood a certain amount of hydrogen sulfide is excreted in the exhaled breath, this is sufficient to be detected by odor, but the greater portion, however, is excreted in the urine, chiefly as sulfate, but some as sulfide (Patty, 1967).

IV. EFFECTS

A. Carcinogenicity

Pertinent information could not be found in the available literature.

B. Mutagenicity

Pertinent information could not be found in the available literature.

C. Teratogenicity

Pertinent information could not be found in the available literature.

D. Other Reproductive Efforts

Pertinent information could not be found in the available literature.

E. Chronic Toxicity

At low concentrations of hydrogen sulfide (e.g., 50 to 200 ppm) the toxic symptoms are due to local tissue irritation rather than to systemic actions. The most characteristic effect is on the eye, where superficial injury to the conjunctiva and cornea is known to workers in tunnels, caissons, and sewers as "gas eye" (Grant, 1972). More prolonged or intensive exposures may lead to involvement of the respiratory tract with cough, dyspnea and perhaps pulmonary edema. Evidence of severe pulmonary edema has been found at autopsy and in survivors of massive respiratory exposures (Gosselin, 1976). The irritating action has been explained on the basis that H_2S combines with alkali present in moist tissues to form sodium sulfide, a caustic (Sax, 1979). Chronic

poisoning results in headache, inflammation of the conjunctivae and eyelids, digestive disturbances, loss of weight, and general debility (Sax, 1979).

F. Other Relevant Information

Hydrogen sulfide is reported with a maximum safe concentration of 13 ppm (Standen, 1969), although at first this concentration can be readily recognized by its odor, H_2S may partially paralyze the olfactory nerve to the point at which the presence of the gas is no longer sensed. Hamilton and Hardy (1974) report that at a concentration of 150 ppm, the olfactory nerve is paralyzed.

Exposures of 800-1000 ppm may be fatal in 30 minutes, and high concentrations are instantly fatal (Sax, 1979). There are reports of exceptional cases of lasting injury, after recovery from acute poisoning, which point to an irreversible damage to certain cells of the body resulting from prolonged oxygen starvation (Hamilton and Hardy, 1974). Hydrogen sulfide has killed at concentrations as low as 800 ppm (Verschueren, 1974).

V. AQUATIC TOXICITY

A. Acute Toxicity

Verschueren (1974) has reviewed the effects of H_2S on several aquatic organisms. Goldfish have been reported to die at a concentration of 1 ppm after long time exposure in hard water. Verschueren (1974) reports a 96-hour LC50 value of 10 ppm for goldfish. Verschueren also reports on a large number of fresh water fish with toxic effects resulting from exposure

to H_2S at concentrations ranging from 1 to 100 ppm.

Verschueren (1974) reports median threshold limit values for Arthropoda: Asellus, 96-hour at 0.111 mg/l; Crangonyx, 96 hour at 1.07 mg/l; and Gammarus, 96-hour at 0.84 mg/l.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent information could not be located in the available literature.

C. Other Relevant Information

Verschueren (1974) reports that sludge digestion is inhibited at 70-200 mg/l of H_2S in wastewater treatment plants.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The 8-hour, time-weighted average occupational exposure limit for H_2S has been set in a number of countries and are tabled below (Verschueren, 1974):

T.L.V.:	Russia	7 ppm
	U.S.A.	20 ppm "peak"
	Federal German Republic	10 ppm

H_2S is a Department of Transportation flammable and poisonous gas and must be labelled prior to shipment.

B. Aquatic

Maximum allowable concentration of 0.1 mg/l for Class I and Class II waters has been established in Romania and Bulgaria for H_2S (Verschueren, 1974).

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No. 119

Indeno (1,2,3-cd)pyrene

Health and Environmental Effects

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

APRIL 30, 1980

-1400-

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 indeno(1,2,3-c,d)pyrene and has found sufficient evidence to indicate that this compound is carcinogenic.

INDENO[1,2,3-cd]PYRENE

Summary

Indeno[1,2,3-cd]pyrene (IP) is a member of the polycyclic aromatic hydrocarbon (PAH) class. Several compounds in the PAH class are well known to be potent animal carcinogens. However, IP is generally regarded as only a weak carcinogen to animals or man. There are no reports available concerning the chronic toxicity of IP. Exposure to IP in the environment occurs in conjunction with exposure to other PAH; it is not known how these compounds may interact in human systems.

There are no reports available concerning standard acute or chronic toxicity tests of this chemical in aquatic organisms.

I. INTRODUCTION

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

Indeno[1,2,3-cd]pyrene (IP; $C_{22}H_{12}$) is one of the family of polycyclic aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Its physical and chemical properties have not been well-characterized.

PAH, including IP, are ubiquitous in the environment. They have been identified in ambient air, food, water, soils, and sediments (U.S. EPA, 1979b). The PAH class contains several potent carcinogens (e.g., benz[b]fluoranthene), weak carcinogens (benz[a]anthracene), and cocarcinogens (e.g., fluoranthene), as well as numerous non-carcinogens (U.S. EPA, 1979b).

PAH which contain more than three rings (such as IP) are relatively stable in the environment and may be transported in air and water by adsorption to particulate matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment. The reader is referred to the PAH Hazard Profile for a more general discussion of PAH (U.S. EPA, 1979c).

II. EXPOSURE

A. Water

Basu and Saxena (1977, 1978) have conducted monitoring surveys of U.S. drinking water for the presence of six representative PAH, including IP. They found the average total level of the six PAH (fluoranthene, benzo[k]fluoranthene, benzo[j]fluoranthene, benzo[a]pyrene, benzo[g,h,i]-perylene, and indeno[1,2,3-cd]pyrene) to be 13.5 ng/l.

B. Food

Levels of IP are not routinely monitored in food, but it has been detected in foods such as butter and smoked fish (U.S. EPA, 1979a). However, the total intake of all types of PAH through the diet has been estimated at 1.6 to 16 µg/day (U.S. EPA, 1979b). The U.S. EPA (1979a) has estimated the bioconcentration factor of IP to be 15,000 for the edible portion of fish and shellfish consumed by Americans. This estimate is based upon the octanol/water partition coefficient for IP.

C. Inhalation

There are several studies in which IP has been detected in ambient air (U.S. EPA, 1979a). Measured concentrations ranged from 0.03 to 1.34 ng/m^3 (Gordon, 1976; Gordon and Bryan, 1973). Thus, the human daily intake of IP by inhalation of ambient air may be in the range of 0.57 to 25.5 ng, assuming that a human breathes 19 m^3 of air per day.

III. PHARMACOKINETICS

There are no data available concerning the pharmacokinetics of IP, or other PAH, in humans. Nevertheless, some experimental animal results were published on several other PAH, particularly benzo[a]pyrene.

A. Absorption

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

B. Distribution

Based on an extensive literature review, data on the distribution of IP in mammals were not found. However, it is known (U.S. EPA, 1979a) that other PAH are widely distributed throughout the body following their absorption in experimental rodents. Relative to other tissues, PAH tend to localize in body fat and fatty tissues (e.g., breast).

C. Metabolism

The metabolism of IP in animals or man has not been directly studied. However, IP, like other PAH, is most likely metabolized by the microsomal mixed-function oxidase enzyme system in mammals (U.S. EPA, 1979b). Metabolic attack on one or more of the aromatic rings leads to the formation of phenols and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed-function oxidases to yield diol epoxides, compounds which are known to be biologically reactive intermediates for certain PAH. Removal of activated intermediates by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

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

IV. EFFECTS

A. Carcinogenicity

IP is regarded as only a weak carcinogen (U.S. EPA, 1979b). LaVoie and coworkers (1979) reported that IP had slight activity as a tumor initiator and no activity as a complete carcinogen on the skin of mice which is known to be highly sensitive to the effects of carcinogenic PAH.

B. Mutagenicity

LaVoie and coworkers (1979) reported that IP gave positive results in the Ames Salmonella assay.

C. Teratogenicity and Other Reproductive Effects

There are no data available concerning the possible teratogenicity or other reproductive effects as a result of exposure to IP. Other related PAH are apparently not significantly teratogenic in mammals (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have not gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

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

for coke oven emissions, coal tar products, and coal tar pitch volatiles, all of which contain large amounts of PAH, including IP (U.S. EPA, 1979a).

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

B. Aquatic

There are no standards or guidelines concerning allowable concentrations of IP in aquatic environments.

INDENO[1,2,3-cd]PYRENE

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No. 120

Isobutyl Alcohol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

-1410-

DISCLAIMER

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Isobutyl Alcohol

I. Introduction

Isobutyl alcohol (2-methyl-1-propanol, $C_4H_{10}O$; molecular weight 74.12) is a flammable, colorless, refractive liquid with an odor like of amyl alcohol, but weaker. Isobutyl alcohol is used in the manufacture of esters for fruit flavoring essences, and as a solvent in paint and varnish removers. This compound is soluble in approximately 20 parts water, and is miscible with alcohol and ether.

II. Exposure

No data were readily available.

III. Pharmacokinetics

A. Absorption

Isobutyl alcohol is absorbed through the intestinal tract and the lungs.

B. Distribution

No data were readily available.

C. Metabolism

Isobutyl alcohol is oxidized to isobutyraldehyde and isobutyric acid in the rabbit, with further metabolism proceeding to acetone and carbon dioxide. Some conjugation with glucuronic acid occurs in the rabbit and dog.

D. Elimination

Approximately 14% of isobutyl alcohol is excreted as urinary conjugates in the rabbit.

IV. Effects

A. Carcinogenicity

Rats receiving isobutyl alcohol, either orally or subcutaneously, one to two times a week for 495 to 643 days showed liver carcinomas and

sarcomas, spleen sarcomas and myeloid leukemia (Gibel, et al., Z. Exp. Chir. Chir. Forsch. 7: 235 (1974).

B. Teratogenicity

No data were readily available.

C. Other Reproductive Effects

No data were readily available.

D. Chronic Toxicity

Ingestion of one molar solution of isobutyl alcohol in water by rats for 4 months did not produce any inflammatory reaction of the liver. On ingestion of two molar solution for two months rats developed Mallory's alcoholic hyaline bodies in the liver, and were observed to have decreases in fat, glycogen, and RNA in the liver.

E. Other Relevent Information

Acute exposure to isobutyl alcohol causes narcotic effects, and irritation to the eyes and throat in humans exposed to 100 ppm for repeated 8 hour periods. Formation of facuoles in the superficial layers of the cornea, and loss of appetite and weight were reported among workers subjected, to an undetermined, but apparently high concentration of isobutyl alcohol and butyl acetate. The oral LD_{50} of isobutyl alcohol for rates if 2.46 g/kg (Smith et al., Arch. Ind. Hyg. Occup. Med. 10: 61, 1954).

V. Aquatic Toxicity

A. Acute Toxicity

The LC_{50} of isobutyl alcohol for 24-hour-old Daphnia magna is between 10-1000 mg/l.

VI. Existing Guidelines and Standards

OSHA - 100 ppm
NIOSH - None
ACGIH - 50 ppm

VII. Information Sources

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No. 121

Lead

Health and Environmental Effects

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

APRIL 30, 1980

-1415-

DISCLAIMER

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LEAD

SUMMARY

The hazards of human exposure to lead have been well-recognized for centuries. The hematopoietic system is the most sensitive target organ for lead in humans, although subtle neurobehavioral effects are suspected in children at similar levels of exposure. The more serious health effects of chronic lead exposure, however, involve neurological damage, irreversible renal damage, and adverse reproductive effects observed only at higher levels of lead exposures. Although certain inorganic lead compounds are carcinogenic to some species of experimental animals, a clear association between lead exposure and cancer development has not been shown in human populations.

The effects of lead on aquatic organisms have been extensively studied, particularly in freshwater species. As with other heavy metals, the toxicity is strongly dependent on the water hardness. Unadjusted 96-hour LC_{50} values with the common fathead minnow, Pimephales promelas, ranged from 2,400-7,480 µg/l in soft water to 487,000 µg/l in hard water. Toxicity is also dependent on the life stage of the organism being tested. Chronic values ranged from 32 µg/l to 87 µg/l for six species of freshwater fish. Lead at 500 µg/l can reduce the rate of photosynthesis by 50 percent in freshwater algae. Lead is bioconcentrated by all species tested - both marine and freshwater - including

fish, invertebrates, and algae. The mussel, *Mytilus edulis*, concentrated lead 2,568 times that found in ambient water. Two species of algae concentrated lead 900-1000-fold.

LEAD

I. INTRODUCTION

This hazard profile is based primarily upon the Ambient Water Quality Criteria Document for Lead (U.S. EPA, 1979). A number of excellent comprehensive reviews on the health hazards of lead have also been recently published. These include the U.S. EPA Ambient Air Quality Criteria Document for Lead and the lead criteria document of the National Institute for Occupational Safety and Health (1978).

Lead (Pb, At. No. 82) is a soft gray acid-soluble metal used in electroplating, metallurgy, and the manufacture of construction materials, radiation protection devices, plastics, electronics equipment, storage batteries, gasoline antiknock additives, and pigments (NIOSH, 1978). The solubility of lead compounds in water depends heavily on pH and ranges from about 10^6 µg/l at pH 5.5 to 1 µg/l at pH 9.0 (U.S. EPA, 1979). Inorganic lead compounds are most stable in the +2 valence state, while organolead compounds are more stable in the +4 valence state (Standen, 1967).

Lead comsumption in the United States has been fairly stable from year to year at about 1.3×10^6 metric tons annually. Consumption of lead as an antiknock additive to gasoline (20 percent annual production) is expected to decrease steadily. Since lead is an element, it will remain indefinitely once released to the environment (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Lead is ubiquitous in nature, being a natural constituent of the earth's crust. Most natural groundwaters have concentrations ranging from 1 to 10 µg/l.

Lead does not move readily through stream beds because it easily forms insoluble lead sulfate and carbonate. Moreover, it binds tightly to organic ligands of the dead and living flora and fauna of stream beds. However, lead has been found at high concentrations in drinking water (i.e., as high as 1000 µg/l), due primarily to conditions of water softness, storage, and transport (Beattie, et al. 1972).

The magnitude of the problem of excessive lead in drinking water is not adequately known. In one recent survey of 969 water systems, 1.4 percent of all tap water samples exceeded the 50 µg/l standard (McCabe, 1970). The U.S. EPA (1979) has not estimated a bioconcentration factor for lead in aquatic organisms.

B. Food

It is generally believed that food constitutes the major source of lead absorption in humans. The daily dietary intake of lead has been estimated by numerous investigators, and the results are generally consistent with one another. This dietary intake is approximately 241 µg/day for adults (Nordman, 1975; Kehoe, 1961). For children (ages 3 months to 8.5 years) the dietary intake is 40 to 210 µg of lead per day (Alexander, et al. 1973).

C. Inhalation

A great deal of controversy has been generated regarding the contribution of air to total daily lead absorption. Unlike the situation with food and water, ambient air lead concentrations vary greatly. In metropolitan areas, average air lead concentrations of 2 $\mu g/m^3$, with excursions of 10 $\mu g/m^3$ in areas of heavy traffic or industrial point sources, are not uncommon (U.S. EPA, 1979). In non-urban areas average air lead concentrations are usually on the order of 0.1 $\mu g/m^3$ (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

The classic studies of Kehoe (1961) on lead metabolism in man indicate that on the average and with considerable day-to-day excursions, approximately eight percent of the normal dietary lead (including beverages) is absorbed. More recent studies have confirmed this conclusion (Rabinowitz, et al. 1974). The gastrointestinal absorption of lead is considerably greater in children than in adults (Alexander, et al. 1973; Ziegler, et al. 1978).

It has not been possible to accurately estimate the extent of absorption of inhaled lead aerosols. To varying degrees, depending on their solubility and particle size, lead aerosols will be absorbed across the respiratory epithelium or cleared from the lung by mucociliary action and subsequently swallowed.

Very few studies concerning dermal absorption of lead in man or experimental animals are available. A

recent study by Rastogi and Clausen (1976) indicates that lead is absorbed through intact skin when applied at high concentrations in the form of lead acetate or naphthenate.

B. Distribution

The general features of lead distribution in the body are well known, both from animal studies and from human autopsy data. Under circumstances of long-term exposure, approximately 95 percent of the total amount of lead in the body (body burden) is localized in the skeleton after attainment of maturity (U.S. EPA, 1979). By contrast, in children only 72 percent is in bone (Barry, 1975). The amount in bone increases with age but the amount in soft tissues, including blood, attains a steady state early in adulthood (Barry, 1975; Horiuchi and Takada, 1954).

The distribution of lead at the organ and cellular level has been studied extensively. In blood, lead is primarily localized in the erythrocytes (U.S. EPA, 1979). The ratio of the concentration of lead in the cell to lead in the plasma is approximately 16:1. Lead crosses the placenta readily, and its concentration in the blood of the newborn is quite similar to maternal blood concentration.

C. Excretion

There are wide interspecies differences concerning routes of excretion for lead. In most species biliary excretion predominates in comparison to urinary excretion, except in the baboon (Eisenbud and Wrenn, 1970). It also appears that urinary excretion predominates in man (Rabino-

witz, et al. 1973). This conclusion, however, is based on very limited data.

IV. EFFECTS

A. Carcinogenicity

At least three studies have been published which report dose-response data for lead-induced malignancies in experimental animals (Roe, et al. 1965; Van Esch, et al. 1962; Zollinger, 1953; Azar, et al. 1973). These studies established that lead caused renal tumors in rats.

Several epidemiologic studies have been conducted on persons occupationally exposed to lead (Dingwall-Fordyce and Lane, 1963; Nelson, et al. 1973; Cooper and Gaffey, 1975; Cooper, 1978). These reports do not provide a consistent relationship between lead exposure and cancer development.

B. Mutagenicity

Pertinent information could not be located in the available literature concerning mutagenicity of lead. However, there have been conflicting reports concerning the occurrence of chromosomal aberrations in lymphocytes of lead-exposed workers (O'Riordan and Evans, 1974; Forni, et al. 1976).

C. Teratogenicity

In human populations exposed to high concentrations of lead, there is evidence of embryotoxic effects although no reports of teratogenesis have been published (U.S. EPA, 1979). In experimental animals, on the other hand, lead has repeatedly produced teratogenic effects (Cat-

zione and Gray, 1941; Karnofsky and Ridgway, 1952; McClain and Becker, 1975; Carpenter and Ferm, 1977; Kimmel, et al. 1976). Positive results were shown by injection into the yolk sac of chick embryos and by intravenous and intraperitoneal injection in rats and hamsters. Chronic administration of lead in the drinking water of pregnant rats at concentrations up to 250 µg/l resulted in delayed fetal development and fetal resorption without teratologic effects (Kimmel, et al. 1976).

D. Other Reproductive Effects

Lead has caused miscarriages and stillbirths among women working in the lead trades (Lane, 1949; Nogaki, 1958). In addition, decreased sperm quality in lead-exposed human males (Lancranjan, et al. 1975) and reduced fertility in animals of both sexes (Stowe and Goyer, 1971; Jacquet, et al. 1975) have been reported.

E. Other Chronic Toxicity

There is considerable information in man concerning the renal effects of lead in both adults and children (Clarkson and Kench, 1956; Chisolm, 1968; Cramer, et al. 1974; Wedeen, et al. 1975). Two distinctive effects on the kidney occur with lead absorption. One is reversible proximal tubular damage, which is seen mainly with short-term exposure. The other effect is reduced glomerular filtration, which has generally been considered to be of a slow, progressive nature. Human exposures to high concentrations of lead have also been associated with cerebrovascular disease (Dingwall-Fordyce and Lane, 1963), heart failure

(Kline, 1960), electrocardiographic abnormalities (Kosmider and Pentelenz, 1962), impaired liver function (Dodic, et al. 1971), impaired thyroid function (Sandstead, et al. 1969), and intestinal colic (Beritic, 1971).

V. AQUATIC TOXICITY

A. Acute Toxicity

The available data base on the toxic effects of lead to freshwater organisms is quite large and clearly demonstrates the relative sensitivity of freshwater organisms to lead. The data base shows that the different lead salts have similar LC_{50} values, and that LC_{50} values for lead are greatly different in hard and soft water. Between soft and hard water, the LC_{50} values varied by a factor of 433 times for rainbow trout, 64 times for fathead minnows, and 19 times for bluegills (Davies, et al. 1976; Pickering and Henderson, 1966).

Some 96-hour LC_{50} values for freshwater fish are 2,400 to 7,480 µg/l for fathead minnows in soft water (Tarzwell and Henderson, 1960; Pickering and Henderson, 1966), 482,000 for fathead minnows in hard water (Pickering and Henderson, 1966), 23,800 µg/l for bluegills in soft water (Pickering and Henderson, 1966), and 442,000 µg/l for bluegills in hard water (Pickering and Henderson, 1966).

For invertebrate species, Whitely (1968) reported 24-hour LC_{50} values of 49,000 and 27,500 µg/l for sludge worms (Tubifex sp.) obtained from tests conducted at pH

levels of 6.5 and 8.5, respectively. The effects of water hardness on toxicity of lead to invertebrates could not be located in the available literature.

The acute toxicity data base for saltwater organisms is limited to static tests with invertebrate species. The LC_{50} values ranged from 2,200 to 3,600 µg/l for oyster larvae in a 48-hour test (Calabrese, et al. 1973) to 27,000 µg/l for adult soft shell clams (Eisler, 1977) in a 96-hour test.

B. Chronic Toxicity

Chronic tests in soft water have been conducted with lead on six species of fish. The chronic values ranged from 32 µg/l for lake trout (Sauter, et al. 1976) to 87 µg/l for the white sucker (Sauter, et al. 1976), both being embryo-larval tests.

Only one invertebrate chronic test result was found in the literature. This test was with Daphnia magna in soft water, and the resulting chronic value was 55 µg/l, about one-eighth the acute value of 450 µg/l (Biesinger and Christensen, 1972).

Life cycle or embryo-larval tests conducted with lead on saltwater organisms could not be located in the available literature.

C. Plant Effects

Fifteen tests on eight different species of aquatic algae are found in the literature. Most studies measured the lead concentration which reduced $^{14}CO_2$ fixation by 50 percent. These values range from 500 µg/l for Chlorella

sp. (Monahan, 1976) to 28,000 for a diatom, Navicula (Malanchuk and Gruendling, 1973).

Pertinent data could not be located in the available literature on the effects of lead on marine algae.

D. Residue

The mayfly (Ephemerella grandis) and the stonefly (Pteronarcys californica) have been studied for their ability to bioconcentrate lead (Nehring, 1976). The bioconcentration factor for lead in the mayfly is 2,366 and in the stonefly 86, both after 14 days of exposure.

Schulz-Baldes (1972) reported that mussels (Mytilus edulis) could bioconcentrate lead 2,568-fold. Two species of algae bioconcentrate lead 933 and 1,0[illegible] fold (Schulz-Baldes, 1976).

VI EXISTING GUIDELINES AND STANDARDS

A. Human

As of February 1979, the U.S. Occupational Safety and Health Administration has set the permissible occupational exposure limit for lead and inorganic lead compounds at 0.05 mg/m^3 of air as an 8-hour time-weighted average. The U.S. EPA (1979) has also established an ambient airborne lead standard of 1.5 $\mu g/m^3$.

The U.S. EPA (1979) has derived a draft criterion for lead of 50 $\mu g/l$ for ambient water. This draft criterion is based on empirical observation of blood lead in human population groups consuming their normal amount of food and water daily.

B. Aquatic

For lead, the draft criterion to protect freshwater aquatic life is:

$$e^{(1.51 \ln (\text{hardness}) - 3.37}$$

as a 24-hour average, where e is the natural logarithm; the concentration should not exceed:

$$e^{(1.51 \ln (\text{hardness}) - 1.39)}$$

at any time (U.S. EPA, 1979).

For saltwater aquatic life, no draft criterion for lead was derived.

LEAD

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No. 122

Maleic Anhydride

Health and Environmental Effects

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

APRIL 30, 1980

-1434-

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.

MALEIC ANHYDRIDE

SUMMARY

Maleic anhydride is readily soluble in water where it hydrolyzes to form maleic acid. It is readily biodegraded by microorganisms and is not expected to bioconcentrate.

Maleic anhydride induced local tumors in rats following repeated subcutaneous injections. Maleic anhydride is an acute irritant and can be an allergen in sensitive individuals.

I. INTRODUCTION

A. Chemical Characteristics

Maleic anhydride ($C_4H_2O_3$; 2,5-furandione; CAS No. 108-31-6) is a white, crystalline solid with an acrid odor. The chemical has the following physical/chemical properties (Windholz, 1976):

Molecular Weight:	98.06
Boiling Point:	202.0°C
Melting Point:	52.80°C
Solubility:	Soluble in water and many organic solvents

A review of the production range (includes importation) statistics for maleic anhydride (CAS No. 108-31-6) which is listed in the initial TSCA Inventory (1979a) has shown that

between 200 million and 300 million pounds of this chemical were produced/imported in 1977. */

Maleic anhydride is used as a chemical intermediate in the production of unsaturated polyester resins, fumaric acid, pesticides, and alkyd resins (Hawley, 1977).

II. EXPOSURE

A. Environmental Fate

Maleic anhydride is readily soluble in water where it hydrolyzes to form maleic acid (Hawley, 1977; Windholz, 1976). Matsui et al. (1975) reported that maleic anhydride in wastewater is easily biodegraded by activated sludge.

B. Bioconcentration

Maleic anhydride is not expected to bioaccumulate (U.S. EPA, 1979b).

C. Environmental Occurrence

The major source of maleic anhydride emissions is associated with release of the chemical as a byproduct of phthalic anhydride manufacture. Emissions can also occur during the production and handling of maleic anhydride and its derivatives (U.S. EPA, 1976).

*/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).

III. PHARMACOKINETICS

No data were found. Nonetheless, it is expected that any maleic anhydride that is absorbed would be hydrolyzed to maleic acid and then neutralized to a maleate salt. Maleate should be readily metabolized to CO_2 and H_2O.

IV. HEALTH EFFECTS

A. Carcinogenicity

Dickens (1963) reported that local fibrosarcomas developed in rats after repeated subcutaneous injections of maleic anhydride suspended in arachis oil. Multiple injections of arachis oil alone or a hydrolysis product derived from maleic anhydride (sodium maleate) did not produce any tumors at the injection site.

A long term dietary study of maleic anhydride in rats for possible carcinogenicity is now in progress. Terminal necropsies are schedules for January, 1980 (CIIT, 1979).

B. Other Toxicity

Maleic anhydride vapors and dusts are acute irritants of the eyes, skin, and upper respiratory tract (ACGIH, 1971). Repeated exposures to maleic anhydride concentrations above 1.25 ppm in air have caused asthmatic responses in workers. Allergies have developed in which workers have become sensitive to even lower concentrations of the compound. An increased incidence of bronchitis and dermatitis has also been noted among workers with long-term exposure to maleic anhydride. One case of pulmonary edema in a worker has been reported (U.S. EPA, 1976).

V. AQUATIC EFFECTS

The 24 to 96-hr median threshold limit (TLm) for maleic anhydride in mosquito fish is 230-240 mg/l. The 24-hr TLm for bluegill sunfish is 150 mg/l (Verschueren, 1977).

VI. EXISTING GUIDELINES

The existing OSHA standard for maleic anydride is an 8-hour time weighted average (TWA) of 0.25 ppm in air (39CFR23540).

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No. 123

Malononitrile

Health and Environmental Effects

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

APRIL 30, 1980

-1441-

DISCLAIMER

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MALONONITRILE

Summary

Nitriles, as a group, are sources of the cyanide ion, which interferes with basic cellular oxidative mechanisms. Malononitrile has effects on the cardiovascular, renal, hepatic and central nervous systems. This compound can take effect after inhalation, dermal contact or ingestion. No carcinogenic, mutagenic or teratogenic effects have been reported.

Malononitrile has been used in the treatment of various forms of mental illness. A thorough documentation of the side effects of this compound exists. The only human toxicity data on malononitrile found in the available literature are those reported during clinical psychiatric use.

MALONONITRILE

I. INTRODUCTION

Malononitrile ($NCCH_2CH$), CAS registry number 109-77-3, is an odorless, yellow crystalline chemical with a molecular weight of 66.06 and a specific gravity of 1.049. Its melting point is between 30°C and 31°C. Malononitrile is soluble in water, acetone, alcohol and ether, but is insoluble in ethanol (Weast, 1974). When heated to decomposition, nitriles emit toxic fumes containing cyanides (Sax, 1968).

Malononitrile is used in the following applications: as a lubricating oil additive, for thiamine synthesis, for pteridine-type anti-cancer agent synthesis, and in the synthesis of photosensitizers, acrylic fibres, and dyestuffs (Eur. Chem. News, 1975; Lonza Inc., 1978).

Imports of malononitrile, which currently is not manufactured in the United States, were 60,000 pounds for 1976 (NIOSH, 1978).

II. EXPOSURE

A. Water and Food

Pertinent data were not found in the available literature.

B. Inhalation

Research by Panov (1969) indicates that malononitrile was readily absorbed by the lungs of animals. As test chamber temperatures increased, the mortality rate also increased, presumably due to higher absorption.

The major occupational exposure to nitriles occurs principally by inhalation of vapor or aerosols and by skin absorption. The likelihood of such exposure increases during the handling, transferring and quality control sampling of these compounds.

C. Dermal

Panov (1969) reported that malononitrile was readily absorbed through the eyes of rabbits. He also reported that mice and rabbits absorb the compound through the skin. Extreme irritation resulted from both modes of application.

III. PHARMACOKINETICS

A. Absorption

Animal studies indicated that malononitrile is absorbed through the lungs and by the skin (Panov, 1969).

B. Distribution

Hicks (1950) determined that, to some extent, malononitrile exerts tissue specificity (brain, liver, kidney, lung and thyroid) in its action.

The formation of thiocyanate *in vitro* from malononitrile and thiosulfate was highest in the presence of liver tissue, lowest with brain, and intermediate with kidney (Stern et al., 1952).

C. Metabolism

The dinitrile compounds (such as malononitrile) presumably can exert a greater toxic effect than the mononitriles due to the more rapid release of cyanide from the parent compound. Malononitrile released cyanide *in vivo* and was ultimately excreted as thiocyanate after oxidation (Ghiringhelli, 1955).

The C≡N group may be converted to a carboxylic acid derivative and ammonia, or may be incorporated into cyanocobalamine. Ionic cyanide also reacts with carboxyl groups and with disulfides (McKee et al., 1962).

Stern et al. (1952) found that *in vitro* respiration of brain, kidney, and liver slices was inhibited by 0.01 M malononitrile. The same investigators also demonstrated the formation of thiocyanate from malononitrile and thiosulfate in liver and kidney tissues *in vitro*. The release of cyanide from dinitriles suggests that their mechanism of acute toxicity may be similar to that of the mononitriles.

The enzyme rhodanase, which catalyzed the formation of thiocyanate from cyanide and thiosulfate, was ineffective in the catalysis of thiocyanate from malononitrile. *In vivo* thiocyanate formation apparently came from an intermediate metabolite and not the malononitrile molecule.

D. Excretion

After absorption, malononitrile may be metaboilized to an organic cyanide, which is oxidized to thiocyanate and excreted in the urine (McKee et al, 1962). No evidence of respiratory excretion was found in the available literature.

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity and Reproductive Effects

Pertinent data were not found in the available literature.

B. Chronic Toxicity

The only available human toxicity data on malononitrile are those reported during the clinical use of the compound in the treatment of mental illness.

Hyden and Hartelius (1948) reported on the clinical use of malononitrile during psychiatric treatment. Its intended purpose was to stimulate the production of proteins and nucleic acids in the pyramidal cells of the frontal cortices of psychiatric patients, particularly those who were depressed or schizophrenic. All patients experienced tachycardia 10 to 20

minutes after the infusion of malononitrile (1-6 mg/kg). Facial redness, headache, nausea, vomiting, shivering, cold hands and feet, muscle spasms and numbness were also reported with varying frequency. Similar results were also submitted by MacKinnon et al. (1949), Hartelius (1950), and Meyers et al. (1950) in the treatment of mental patients.

Hicks (1950) reported that malononitrile poisoning induced brain lesions in rats. The compound produced demyelinating lesions of the optic tract and nerve, the cerebral cortex, the olfactory bulb and the substantia nigra.

Panov (1969) found the repeated exposure to malononitrile (36 mg/m^3 for 2 hours per day for 35 days) was slightly toxic to rats. The exposure caused slight anaplasia of bone-marrow, i.e. a lower hemoglobin level and elevated reticulocyte count.

F. Acute Toxicity

Panov (1969) subjected mice to a single, 2-hour inhalation exposure to malononitrile. The mice showed signs of restlessness and increased respiration rate in the early post-treatment period followed by Lassitude, decreased respiration rate, cyanosis, noncoordination of movement, trembling, convulsions and eventual death of some animals. The exposure concentration was not noted.

Panov (1969) reported that liquified malononitrile applied to the eyes of rabbits caused tearing, blepharospasm. hyperemia of the conjunctiva, and swelling of the eyelids. Panov also applied malononitrile solution (concentration not stated) to the tails of mice. The animals showed signs of restlessness, rapid respiration and slight cyanosis of the extremities and the mucosa of the lips. He also observed trembling and skin irritation following dermal application of malononitrile to a rabbit.

Nuclear changes in neurons and satellite spiral ganglia were seen in rats administered single doses (6-8 mg/kg) of malononitrile (Van Breeman and Hiraoka, 1961).

V. AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Because malononitrile is about three times as toxic as isobutyronitrile, NIOSH recommends that employee exposure to malononitrile not exceed 3 ppm (8 mg/m^3) as a TWA limit for up to 10-hour workshift in a 40-hour work week (NIOSH, 1978).

B. Aquatic

Pertinent data were not found in the available literature.

MALONONITRILE

References

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No. 124

Mercury

Health and Environmental Effects

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

APRIL 30, 1980

-1451-

DISCLAIMER

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MERCURY

SUMMARY

Short chain alkyl mercurials represent a toxic species that distributes widely and accumulates in the liver, kidneys and other organs. These compounds are eliminated from the body at a slow rate. In humans, mercurials have been associated with neurological disorders, sensory impairment and tremors. Prenatal exposure has produced psychomotor disorders. Brain development is impaired by accumulation of mercurials, and lesions in the cerebral and cerebellar areas have been observed.

Methylmercury crosses the placental barrier and is secreted in milk. Methylmercury and mercuric chloride have been shown to produce teratogenic effects in animals. Reproductive effects in animals of alkyl mercury compounds involve reversible inhibition of spermatogonia and damage to unfertilized gametes. A high infant mortality rate has been reported in a study of mothers exposed to high levels of mercurials.

Mercurials have induced chromosome breakage in plant cells and point mutations in Drosophila. Mercurials have not been shown to produce carcinogenic effects other than non-specific injection site sarcomas. The U.S. EPA (1979) has calculated an Acceptable Daily Intake (ADI) for mercury of 200 μg/day.

Mercury can be bioconcentrated many-fold in fish and other aquatic organisms because of rapid uptake and the excretion of

mercury from their tissues. In general, the methylmercury compounds are more toxic than the inorganic forms of mercury. Toxicity varies widely among species. Concentrations as low as 0.1 μg/l have been shown to be toxic to freshwater crayfish.

MERCURY

I. INTRODUCTION

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

Mercury (Hg; atomic weight 200.59) is a silver-white metal, which is a liquid at room temperature. It has the following physical properties: melting point, -38.87°C; boiling point, 356-358°C; specific gravity, 13.546; and vapor pressure at 20°C, 0.0012 mm Hg (Stecher, 1968).

Mercury exists in three oxidation states: elemental (0), mercurous (+1), and mercuric (+2). The solubilities of some common mercuric salts are as follows: $HgCl_2$ (1 g/13.5 ml water), $Hg(NO_3)_2$ (soluble in a "small amount" of water), $Hg(CH_3COO)_2$ (1 g/2.5 ml water) (Stecher, 1968). Mercurous salts are much less soluble in water; Hg_2Cl_2 is practically insoluble in water (Stecher, 1968).

Major usage of mercury include the following: as a cathode in the electrolytic preparation of chlorine and caustic soda, in electrical apparatus, in industrial and control instruments, in general laboratory applications, in dental amalgams, in anti-fouling and mildew-proofing paints, and as a fungicide in treating seeds, bulbs, and plants. However, mercury is no longer registered by the U.S. EPA for this last application.

Elemental mercury can be oxidized to the mercuric form in water in the presence of oxygen (Stock and Cucuel, 1934); this transformation in water is facilitated by the presence of organic substances (Jensen and Jernelov, 1972). The mercuric

ion is a substrate for biomethylation reactions; both dimethyl and monomethyl mercury may be formed by bacteria present in sediments (Wood, 1976 and Cotton and Wilkinson, 1966). Considerable bacterial demethylation of methylmercury occurs in the environment, limiting the buildup of methylmercury (Tonomura and Konzaki, 1969). The degree of oxygenation, pH, and the presence of inorganic and organic ligands are determining factors regulating which state of mercury is present in water. On thermodynamic grounds, one would expect inorganic mercury to be present mainly as mercuric compounds in well-oxygenated water and, in an increasing fraction of total mercury, as the elemental form or the sulfide form under reducing conditions (NAS, 1978).

II. EXPOSURE

Mercury undergoes a global cycle of emission and deposition. Total entry of mercury into the atmosphere is approximately 40,000 to 50,000 metric tons per year, mainly from natural sources (NAS, 1978 and Korringa and Hagel, 1974). Deposition from the atmosphere into the ocean is estimated at about 11,000 tons per year (NAS, 1978). These waters represent a relatively large mercury pool that maintains a stable concentration (U.S. EPA, 1979).

Industrial release of mercury involves both organic and inorganic forms. These emissions are from the burning of fossil fuels, discharges of waste from the chloralkali industries, discharges of methylmercury from chemical manufacturers, and runoff from the use of ethyl and methylmercury fungicides (U.S. EPA, 1979).

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

Source	Adult - µg/day Minimum	Adult - µg/day Maximum	Predominant form
Air	0.3	0.8	elemental
Water	0.1	0.4	mercuric
Food	3.0	5.0	methylmercury
Total	3.4	6.2	

Fish and shellfish represent a source of high methylmercury intake. The U.S. EPA (1979) has estimated average bioconcentration factors of 1,700 for mercuric chloride and 6,200 for methylmercury in the edible portions of fish and shellfish consumed by Americans. This estimate is based on bioconcentration studies in several species, and on other factors.

III. PHARMACOKINETICS

A. Absorption

Inorganic mercury salts are absorbed poorly by the human gastrointestinal tract; less than 15 percent absorption was reported (Rahola, et al., 1971). Inhalation of mercuric oxide has been shown to produce pulmonary deposition and absorption of the compound, with 45 percent of the administered dose cleared within 24 hours (Morrow, et al., 1964). Dermal absorption of mercuric chloride has been reported in studies with guinea pigs (Friberg, et al., 1961; Skog and Vahlberg, 1964).

Metallic mercury is not absorbed significantly from the gastrointestinal tract. Friberg and Nordberg (1973) calculate that less than 0.01 percent of an orally administered dose is absorbed. Studies with human subjects reveal approximately 80

percent of inhaled mercury vapor is retained (Hursh, et al., 1976), with alveolar regions indicated as the probable site of absorption into the bloodstream (Berlin, et al., 1969). Animal studies indicate dermal absorption of metallic mercury can occur (Juliusberg, 1901; Schamberg, et al., 1918).

Methylmercury shows virtually complete absorption from the gastrointestinal tract (Aberg, et al., 1969; Miettinen, 1973). Inhalation of alkyl mercurials leads to high retention, perhaps as high as 80 percent (Task Group on Metal Accumulation, 1973). Severe poisoning of humans following topical methylmercury applications indicates some dermal absorption of the compound (U.S. EPA, 1979).

B. Distribution

Methylmercury, after absorption from the gastrointestinal tract, distributes readily to all tissues in the body (WHO Expert Committee, 1976), with the highest concentrations being found in the kidney cortex and red blood cells. Approximately five percent of an ingested dose is found in the blood compartment following tissue distribution. Human studies with a radioactively labeled compound have indicated that approximately ten percent of the body burden may be transferred to the head region following complete tissue distribution (Aberg, et al., 1969). The ratio of methylmercury in the brain to levels in the blood may be as high as 10:1 (U.S. EPA, 1979). In muscle tissue, analysis of the mercury present indicates that it is almost entirely methylmercury, while liver and kidney contain a substantial amount of demethylated, inorganic forms (Magos, et al., 1976).

Determination of methylmercury in cord blood and fetal red cells indicates that the compound is transported across placental membranes (Tejing, 1970; Suzuki, et al., 1971). Methylmercury is secreted in mother's milk and may average as much as five percent of the maternal blood level (Bakir, et al., 1973).

Mercury in the mercuric form concentrates in the kidneys following inhalation of mercury vapor. Animal studies show that up to 90 percent of an administered dose may localize at this site (Rothstein and Hayes, 1964). Experiments using radiolabeled mercury in human volunteers have shown approximately seven percent accumulation of the inhaled compound in the head region (Hursch, et al., 1976). Oxidation of absorbed elemental mercury to the mercuric form takes place *in vivo*, probably largely through the enzymatic activities of red blood cells (Clarkson, et al., 1978).

Mercury has been shown to be transferred into the fetus after maternal exposure. The rate of transfer of elemental mercury appears to be greater than ionic forms of mercury (Clarkson, et al., 1972).

Animal studies with inorganic mercury salts indicate the distribution pattern is similar to the pattern observed after exposure to mercury vapors (Friberg and Vostal, 1972); however, the ratio of mercuric ion in red cells to plasma levels is lower (Rahola, et al., 1971). The major site of mercuric ion accumulation is the kidney (U.S. EPA, 1979).

C. Metabolism

Methylmercury undergoes cleavage of the carbon mercury bond, resulting in the production of inorganic mercury *in vivo*.

Plasma, liver, and kidney all contain substantial amounts of inorganic mercury following administration of the organic form of the compound (Bakir, et al., 1973). Norseth and Clarkson (1971) have suggested that gut microflora may aid in this biotransformation. Bakir, et al. (1973) have determined a mean half-life value of 65 days for 16 hospital cases. However, a wide range of blood half-lives have been determined in human studies (U.S. EPA, 1979). Whole body half-life values for methylmercury appear to be in the same range (~52-93 days) as blood clearance half-lives (Miettinen, 1973).

Elemental mercury can undergo oxidation in the body to the mercuric form, which is then capable of interacting with many tissue ligands (Clarkson, et al., 1978). Limited experiments with subjects exposed to mercury vapor indicate a two component loss of mercury from the bloodstream. Clarkson (1978) has estimated half-lives of 2.4 days for the fast component and 14.9 days for the slow component following a brief exposure to mercury vapor. Hursh, et al. (1976) have estimated that the whole body half-life of elemental mercury is comparable with that of methyl mercury.

D. Excretion

The excretion of methylmercury occurs predominantly by the fecal route in humans. Less than ten percent of excretion occurs in the urine (U.S. EPA, 1979). Norseth and Clarkson (1971) have determined significant biliary secretion of methylmercury in animals, raising the possibility that biotransformation to the inorganic form might be affected by microflora in the gut.

Elemental mercury exposure has been shown to lead to mercury excretion predominantly through the feces and urine (Lovejoy, et al., 1974). As kidney levels of mercury increase, a greater urinary excretion of the compound occurs (Rothstein and Hayes, 1964). Urinary excretion values from 13 percent to 58 percent have been determined. Elimination of inhaled mercury has been observed in expired air (7 percent) (Cherian, et al., 1978) and in sweat (Lovejoy, et al., 1974).

Human studies with small ingested doses of mercuric salts have indicated that following excretion of the unabsorbed compound, urinary and fecal excretion of inorganic mercury were approximately equal (Rahola, et al., 1971).

IV. EFFECTS

A. Carcinogenicity

Intraperitoneal injection of metallic mercury into rats produced injection site sarcomas (Druckrey, et al., 1957).

Pertinent data could not be located in the available literature indicating that mercury is carcinogenic.

B. Mutagenicity

Methylmercury has been shown to block mitosis in plant cells and in human leukocytes treated *in vivo*, and human cells *in vitro*, as well as to induce chromosome breakage in plant cells and point mutations in *Drosophila* (Swedish Expert Group, 1971; Ramel, 1972).

No evidence for the mutagenic effects of elemental or inorganic mercury could be located in the available literature.

C. Teratogenicity

Oharazawa (1968) reported increased frequency of cleft palate in mice treated with an alkyl mercury compound. Embryotoxic effects without gross teratological effects were reported by Fujita (1969) in mice. Prenatal exposure to methylmercury has produced histological evidence of brain damage in several species (Matsumoto, et al., 1967; Nonaka, 1969; Morikawa, 1961). Spyker and Smithburg (1972) and Olson and Massaro (1977) have also reported anatomical malformations in animals exposed prenatally to methylmercury.

Teratological effects of mercuric chloride have been reported in animals (Gale and Ferm, 1971). However, data are not available on the teratogenicity of inorganic mercury in human populations.

Exposure of rats prenatally to mercury vapor produced fetal toxicity without evidence of teratological effects (Baranski and Szymczyk, 1973).

D. Other Reproductive Effects

A high mortality rate in infants born to women suffering mercury poisoning has been reported (Baranski and Szymczyk, 1973).

Methylmercury has been reported to interfere with reproductive capability in adult animals treated with this compound (Ramel, 1972; Suter, 1975). Khera (1973) has observed that administration of alkyl mercury compounds to rats may damage gametes prior to fertilization. Reversible inhibition of spermatogonial cells in mice treated with mercuric chloride has been reported (Lee and Dixon, 1975).

E. Chronic Toxicity

Chronic exposure to methylmercury has produced several outbreaks of poisoning, characterized by neurological symptoms following central nervous system damage (Nordberg, 1976; NAS, 1978). Adult exposure to methylmercury has produced symptoms of paresthesia of the extremities, impaired peripheral vision, slurred speech, and unsteadiness of gait and of limbs (U.S. EPA, 1979). Neuropathological investigation showed cerebellar atrophy and focal atrophy of the calcarine cortex (Hunter and Russell, 1954).

Prenatal exposure to methylmercury produced psychomotor brain abnormalities (Engleson and Herner, 1952; Harada, 1968). Brain development was shown to be disturbed, and both cerebral and cerebellar lesions were observed (U.S. EPA, 1979). An epidemiological study on school children in the Minamata Bay area has reported a higher incidence of neurological deficits, learning difficulties, neurological symptoms, and poor performance on intelligence tests for these residents of a high methylmercury exposure region (Med. Tribune, 1978).

An ethylmercury poisoning outbreak indicated renal and cardiac damage following this exposure (Jalili and Abbasi, 1961).

Mercury vapor poisoning may produce signs of mental disturbances, tremors, and gingivitis (U.S. EPA, 1979). Exposure to extremely high concentrations can damage lung tissue causing acute mercurial pneumonitis. Kidney dysfunction (proteinuria) in workers exposed to mercury vapor has also been reported (Kazantzis, et al., 1962; Joselow and Goldwater, 1967).

V. AQUATIC TOXICITY

A. Acute Toxicity

Observed LC_{50} values for three flow-through and two static-renewal assays for mercuric chloride with the rainbow trout as the test species ranged from 155 to 903 µg/l. The results of two flow-through and three static-renewal assays on rainbow and brook trout provide an LC_{50} range for methylmercuric compounds from 24 to 84 µg/l, with the rainbow trout being from three to five times as sensitive as the brook trout. For five other mercury compounds, LC_{50} values ranged from 5.1 for phenylmercuric acetate to 39,910 µg/l for merthiolate. Ethyl- and phenylmercury compounds generally were more toxic while merthiolate and pyridylmercuric acetate were less toxic. A total of 14 freshwater invertebrate species have been tested in static and static-renewal bioassays for acute toxicity to mercuric chloride and mercuric nitrate. LC_{50} values ranged from 0.02 to 2,100 µg/l (U.S. EPA, 1979). Heit and Fingerman (1977) and Beisinger and Christensen (1972) reported the more sensitive species to be the crayfish *Faxonella clypeata* and the daphnid, *Daphnia magna*, respectively. Warnick and Bell (1969) reported that the mayfly (*Ephemerella subvaria*), the stonefly (*Acroneuria lycorius*), and the caddisfly (*Hydropsyche betteni*) were among the most resistant freshwater invertebrates to mercuric chloride. Two static tests have produced 96-hour LC_{50} values of 800 and 2,000 µg/l for mercuric chloride to the marine fish, the mummichog (*Fundulus heteroclitus*). Among marine invertebrates exposed to mercuric chloride, LC_{50} values ranged from 3.6 to 32,000 µg/l for 21 species. Embryo

stages of the oyster (Crassostrea virginica), the hard-shell clam (Mercenaria mercenaria), and the mysid shrimp (Mysidopsis bahia), the latter in the only acute flow-through test reported, were the more sensitive species reported. Lockwood and Inman (1975) provide the only acute study for methylmercuric chloride with a adjusted 96-hour LC_{50} value of 150 µg/l.

B. Chronic Toxicity

McKim, et al. (1976) offered the single source reported for chronic effects to freshwater fish. Examining the long-term effects of methylmercury chloride on three generations of the brook trout (Salvelinus fontinalis), adverse effects were reported at 0.93 µg/l, but not at 0.29 µg/l. Brook trout were from three to four times more resistant than rainbow trout (Salmo gairderi). Sosnowski, et al. (1979) have examined the effects of mercuric chloride by a flow-through, life-cycle bioassay on the mysid shrimp, Mysidopsis bahia. The highest concentration producing no-observed-effect was 0.82 µg/l.

C. Plant Effects

A number of different parameters have been used to determine the toxic effects of mercury compounds on freshwater plants. Effective concentrations of mercuric chloride ranged from 60 to 2,590 µg/l. Blinn, et al. (1977) demonstrated altered photosynthetic activity in a summer assemblage of algal species at 60 µg/l. Two of these studies on the effects of methylmercury chloride to freshwater algae revealed enzyme inhibition at 1,598 µg/l in Anklstrodesmus braunii and 50 percent growth inhibition to Coelastrum microporum at concentrations of 2.4 to 4.8 µg/l. For other organomercury compounds, effective concentrations ranged

from less than 0.6 to 200.6 µg/l. Using 18 marine species, Berland, et al. (1976) measured growth inhibition at mercuric chloride concentrations from 5 to 15 µg/l and lethalities from 10 to 50 µg/l. Effective concentrations for the alga Isochrysis galbana ranged up to 2,000,000 µg/l, at which no growth was observed (Davies, 1976). For other organomercury compounds, effective concentrations ranged from 0.1 to less than 2,000 µg/l. Harriss, et al. (1970) reported reduced photosynthetic activity to methylmercury hexachlorophthalimine in the diatom, Nitzchia delictissima, at the level of 0.1 µg/l. Methylmercury chloride was reported by Overnell (1975) to reduce photosynthetic activity at concentrations of less than 2,000 µg/l.

D. Residues

Bioconcentration data for freshwater species for various mercury compounds can be summarized by the following bioconcentration factors: 33,800 for the algae Synedra ulna (Fujita and Hashizuma, 1972) exposed to mercuric chloride; 4,532 to 8,049 for juvenile rainbow trout exposed to methylmercury chloride (Reinert, et al., 1974); 12,000 to 20,000 for brook trout exposed to methylmercury chloride (McKin, et al., 1976); and 62,898 for the fathead minnow exposed to methylmercury chloride (Olson, et al., 1975). It should be noted that for the high bioconcentration value for the fathead minnow, the fish were allowed to forage on aquatic organisms growing within the mercury enriched exposure chambers; therefore, this measurement may more closely reflect actual field data. The trout were fed a pelleted diet. A variety of marine organisms have been used to demonstrate the rapid accumulation of inorganic and organic mercury compounds.

Bioconcentration values for marine algae ranged from 853 to 7,400, with exposure periods of two to eight days for mercuric chloride. A 30-day bioconcentration factor of 129 for the lobster, Homarus americanus, has been reported by Thurberg, et al. (1977), and a range of 2,800 to 10,000 reported for adult oysters, Crassostrea virginica, (both species for mercuric chloride). Kopfler (1974) reports a biomagnification value of 40,000 for the oyster C. virginica to methylmercury and phenyl-mercury chloride. The biological half-lives of rapidly accumulated mercuric compounds indicate that clearance is not rapid even after several months.

VI. EXISTING GUIDELINES

A. Human

The U.S. EPA has recommended a drinking water standard of 2 ug Hg/l to protect human health (U.S. EPA, 1973).

Calculation of an acceptable daily intake (ADI) of mercury by the U.S. EPA (1979) has produced a tentative criterion of 0.2 µg/l (with an uncertainty factor applied) for ambient water.

B. Aquatic

The criteria for mercury are divided into tentative recommendations for inorganic and organic mercury. Freshwater criteria have been drafted as follows: for inorganic mercury, the draft criterion is 0.064 µg/l for a 24-hour average exposure, not to exceed 3.2 µg/l at any time. For methylmercury, the draft criterion is 0.016 µg/l for a 24-hour average, not to exceed 8.8 µg/l at any time. To protect marine life from inorganic mercury, the draft criterion is 0.19 µg/l for a 24-hour average, not to exceed 1.0 µg/l at any time. For methylmercury, the tenta-

tive criterion is 0.025 µg/l as a 24-hour average not to exceed 2.6 µg/l at any time (U.S. EPA, 1979).

The above criteria have not yet gone through the process of public review; therefore, there is a possibility that the criteria may be changed.

MERCURY

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No. 125

Methomyl

Health and Environmental Effects

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

APRIL 30, 1980

-1475-

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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.

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METHOMYL

Summary

Methomyl is a toxic carbamate insecticide used on field crops and fruit. It is readily absorbed through inhalation or dermal exposure and is almost completely eliminated from the body within 24 hours. Chronic toxicity studies in rats and dogs show that no effects occur below 100 ppm. The threshold limit value for methomyl in air is 2.5 $\mu g/m^3$. Methomyl inhibits the activity of cholinesterase in the body. Studies have shown that methomyl is not carcinogenic in rats and dogs or mutagenic in the Ames bioassay. However, a different type of bioassay showed mutagenic activity at a methomyl concentration of 50 ppm. A potential product of the reaction of methomyl with certain nitrogen compounds in the environment or in mammalian systems is nitrosomethomyl, which is a potent mutagen, carcinogen, and teratogen.

Methomyl is toxic to many aquatic organisms with 96-hour LC_{50} levels ranging from 0.1 to 3.4 ppm.

METHOMYL

I. INTRODUCTION

Methomyl is a broad-spectrum insecticide used on many vegetables, field crops, certain fruit crops, and ornamentals (Serg, et al. 1977). Introduced by DuPont in 1966 as an experimental insecticide-nematacide (Martin and Worthing 1974), methomyl is now manufactured by DuPont and Shell (Stanford Research Institute 1974) and used commercially as a foliar treatment to control aphids, army worms, cabbage looper, tobacco budworm, tomato fruitworm, cotton leaf perforator, and ballworm (Martin and Worthing 1974). About three million pounds (1360 tonnes) of methomyl were produced in the United States in 1974 under the trade name Lannate® (Pest Control, 1975). Wastes associated with methomyl production may contain methylene chloride. Methomyl formulations may contain pyridine as a contaminant (Sittig, 1977). Methomyl is highly soluble in water. Its bioconcentration factor is 1.0; octanol/water coefficient, 2.0 (see Table 1).

II. EXPOSURE

A. Water

Methomyl is considered stable in ground water and decomposes at a rate of less than 10 percent in 5 days in a river environment. In a lake environment, methomyl decomposes at a rate of less than 85 percent per year (U.S. EPA 1980).

B. Food

After the application of methomyl from 0.25 to 0.50 kilograms per hectare (kg/ha) on tomatoes, plant residues were below 0.2 ppm. Application of 1 kg/ha left residues of 0.3, 0.13, and 0.06 ppm at 1, 2, and 3 days, respectively, after spraying (Love and Steven, 1974). Methomyl applied at a rate of 3 oz/acre (0.2 kg/ha) left a 17 ppm residue on rape plants immediate-

TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF METHOMYL

Synonyms: S-methyl N-(methylcarbamoyl)oxy)thioacetamidate; 1-(methylthio)ethylideneamino methylcarbamate; 1-(methylthio)acetaldehyde O-methylcarbamoyloxime; methyl N-(((methylamino)carbonyl)oxy)ethanimidothioate; CAS Registry No. (16752-77-5); DuPont 1179; Lannate; Mesomile; Nudrin

Chemical Formula: $(CH_3S)(CH_3)C{=}N{-}O(C{=}O)NHCH_3$

Molecular Weight: 162.2

Description: White crystal solid
Slight sulfurous odor
Soluble in organic solvents

Specific Gravity and/or Density $\frac{24}{4}$ d = 1.2946

Melting and/or Boiling Points: mp 78 to 79°C

Stability: Stable in aqueous solution
Subject to decomposition in moist soil
Overall degradation rate constant (0.01/day)

Half-life approximately 50 days

Solubility (water): 5.8 g/100 ml at 25°C

$$\frac{\text{sediment}}{H_2O} : \frac{.5}{1}$$

Vapor Pressure: 5×10^{-5} mm Hg at 25°C

Bioconcentration Factor (BCF) and/or
Octanol/water partition coefficient (K_{ow}): $K_{ow} = 2.0$
BCF = 1.0

Source: Martin and Worthing, 1974; Fairchild, 1977; Windholz, 1976, U.S. EPA, 1980.

ly after application. This concentration declined rapidly to 1.5, 1.0, 0.4, and 0.2 ppm, 1, 2, 5, and 9 days later, respectively. Methomyl residues were not detected (less than 0.02 ppm) in seed harvested 22 days after application. Rape plant leaves collected after the application of methomyl at 3 to 4 oz/acre (0.2-0.3 kg/ha) had 2.5 to 16 ppm residues (Lee, et al. 1972).

Methomyl has a half-life in plants of 3 to 7 days. Harvey (1975) detected methomyl residue, its oxime, and small polar fractions one month after application. Methomyl residue standards for crops are noted in the Existing Guidelines and Standards Section of this report.

C. Inhalation and Dermal

Data are not available indicating the number of people exposed to methomyl by inhalation or dermal contact. Most human exposure would appear to occur during production and application. The U.S. EPA (1976) listed the frequency of illness among occupational groups exposed to pesticides. In 1157 reported cases, most illnesses occurred among ground applicators (229) and mixer/ loaders (142). The lack of or refusal to use safety equipment was a major factor of this contamination. Other groups affected were gardeners (101), field workers exposed to pesticide residues (117), nursery and greenhouse workers (75), soil fumigators in agriculture (29), equipment cleaners and mechanics (28), tractor drivers and irrigators (23), workers exposed to pesticide drift (22), pilots (crop dusters) (17), and flaggers for aerial application (6). Most illnesses resulted from carelessness, lack of knowledge of the hazards, and/or lack of safety equipment. Under dry, hot conditions workers tended not to wear protective clothing. Such conditions also tended generally to increase pesticide levels and dust on the workers.

III. PHARMACOKINETICS

A. Absorption and Distribution

Methomyl is a highly water-soluble carbamate insecticide which can be absorbed readily by moist mucous membranes or through the skin (Guerzoni, et al. 1976). Methomyl applied to the skin is less toxic than methomyl administered orally (Kaplan and Sherman, 1977). Kaplan and Sherman (1977) noted that there was no buildup of methomyl in fish after a 30-day feeding study, indicating that methomyl was not distributed or retained in any one specific organ of the body. In another study, there was no cumulative oral toxicity in rats (Harvey, et al. 1975). The investigators measured a total clearance rate of less than 24 hours after oral administration of methomyl to rats.

B. Metabolism

Harvey, et al. (1973) administered ^{14}C-labeled methomyl to rats. The radioactive methomyl was eliminated in the form of carbon dioxide, acetonitrile, and urinary metabolites. They noted the absence of methomyl, S-methyl N-hydroxythioacetimidate, methyl S,S-dioxide, and conjugates of the former two compounds. Radiolabeled methomyl administered in the rat by Huhtanen and Dorough (1976) also was metabolized to carbon dioxide and acetonitrile. Carbon dioxide was also found in soils treated with methomyl (Heywood 1975), without the presence of sulfoxide or sulfone (Baron 1978).

Han (1975) investigated the formation of nitrosomethomyl from cured meats containing methomyl and residual sodium nitrite. The samples were incubated under simulated stomach conditions (pH^2) for 1 and 3 hours. Nitrosomethyl was not found in the test material; the detection limit was less than 1 ppb.

C. Excretion

Methomyl is eliminated primarily through the urinary system (Harvey, et al. 1975).

IV. EFFECTS

A. Carcinogenicity

No evidence of methomyl carcinogenicity was observed in tests with rats and dogs (Kaplan and Sherman, 1977). Lijinsky and Schmaehl (1978) concluded that if nitrosomethyl carbamates (nitrosomethomyl) were formed by the reaction of the parent insecticide (methomyl) with nitrite in the environment or in the stomach, the carcinogenic risk of the parent compound could increase.

In pesticide workers, two cases of embryonal cell carcinoma have been associated with exposure to methomyl and three other pesticides (carbaryl, paration, and dimethoate). One of the pesticide workers underwent surgery for a testicular mass; the second worker died of metastatic embryonal cell carcinoma. These cases led the authors to suggest that testicular cancer may be related to agricultural chemical exposure (Prabhakar and Fraumeni, 1978).

B. Mutagenicity

Blevins, et al. (1977) screened methomyl and its nitroso derivative for mutagenic activity. Using histidine auxotrophs of S. typhimurium derived by Ames, they noted that methomyl, unlike its nitroso derivative, did not cause a significant increase in the number of revertant colonies in any of the strains used. Thus, while nitrosomethomyl appeared to be a potent mutagen, they considered methomyl to be non-mutagenic.

Guerzoni, et al. (1976) tested methomyl for mutagenic activity on Saccharomyces cerevisiae. Methomyl was considered mutagenic at 50 ppm. The

authors noted, however, that the mutagenic effect depended on the S. cerevisiae strain.

C. Teratogenicity and Other Reproductive Effects

Methomyl was fed to pregnant New Zealand White rabbits on days 8 to 16 of gestation. Teratogenic effects were not found at any of three dietary levels, 0, 50, and 100 ppm (Kaplan and Sherman, 1977). The same authors also reported on a 3-generation, 6-litter reproduction study with rats with the same dietary levels. Methomyl did not have adverse effects on reproduction and lactation performance; in addition, pathological changes were not observed in the third-generation weanling pups. Using a model ecosystem, Howe (1978) did not see effects on quail egg production or egg fertility from a diet of 0, 40, and 80 ppm methomyl.

Blevins, et al. (1977) treated normal human skin cells with six insecticidal esters of N-methylcarbamic acid or their N-nitroso derivatives. The DNA of the cells was sedimented in alkaline sucrose gradients at various times after treatment. The insecticides used were aldicarb, baygon (propoxur), BUX-TEN® (bufencab), carbofuran, landrin, and methomyl. Numerous singlestrand breaks were apparent in the DNA of all the nitroso derivative-treated cells but not in the DNA of those treated with the parent insecticides. The effect of the nitroso derivatives on the DNA could be observed for at least 20 hours after removal of the chemical from the cultures. The duration of effect suggested that the DNA-repairing events normally occurring in human cells after damage initiated by these chemical agents were different from repairing events which follow UV-type DNA damage or ionizing-type DNA damage in human cells. These observations suggest that the human cellular DNA in vivo is irreversibly altered by nitrosated N-methyl carbamate insecticides, resulting in numerous alkali-sensitive bonds (Blevins, et al. 1977).

D. Chronic Toxicity

Rats of both sexes were fed nutritionally complete diets containing 0, 10, 50, 125, and 250 ppm of methomyl in a 90-day feeding study and 0, 50, 100, 200, and 400 ppm of methomyl in a 22-month feeding study. The weight gain for the high-dose males was significantly lower than that of controls. No clinical, hematological, biochemical, urinary, or pathologic evidence of toxicity was observed at 90 days. However, in the 22-month study, decreased Hb values were noted in the two higher-dose female test groups. A higher testis/body weight ratio was observed in the high-dose males. Histopathologic alterations were observed in kidneys of male and female rats receiving 400 ppm and in spleens of the female rats receiving 200 and 400 ppm of methomyl. Beagles of both sexes fed nutritionally complete diets containing 0, 50, 100, and 400 ppm of methomyl in 90-day and 2-year feeding studies showed no nutritional, clinical, urinary, or biochemical evidence of toxicity. In the 2-year study, an additional dietary level of 1000 ppm caused some clinical signs of toxicity and mortality. Similar to findings in the 22-month feeding study in rats, histopathologic changes were observed after 2 years in the kidney, spleen, and liver at the two higher feeding levels. Dogs receiving the high-level diet showed a compound-related anemia. Results of the long-term studies indicated that the no-effect level for rats and dogs was 100 ppm (Kaplan and Sherman, 1977).

E. Other Relevant Information

Several incidents of acute occupational exposure have been reported in the literature. In the first incident, four crews of field workers harvesting vegetables and fruits treated with pesticides including methomyl were studied. One crew had depressed blood cholinesterase activity

after harvesting corn treated with methomyl. Forty-eight percent of another crew had significant cholinesterase depression after harvesting treated citrus, tomatoes, and gladiolas (Owens, et al. 1978).

A second incident involved 120 grape pickers where 108 displayed symptoms suggesting pesticide poisoning. Methomyl and other cholinesterase-inhibiting pesticides, such as dimethorate and torak, were named in a legal complaint against the grower. The major symptoms claimed by the exposed workers were headache, dermatitis, vomiting, nausea, fatigue, and eye pain (McClure, 1976).

Kumagaya, et al. (1978) reported on two cases of poisoning from swallowing methomyl. The general symptoms were loss of consciousness, respiratory failure, miosis, myofibrillary twitching, increase in airway secretions, and reduced serum cholinesterase activity. Complications of pulmonary edema, hepatitis, and polyneuritis were also observed.

The oral LD_{50} values for rats, mice, ducks, and wild birds have been reported as 17, 10, 15, and 10 mg methomyl per kilogram body weight (mg/kg), respectively. The oral LD_{50} values for dogs, monkeys, guinea pigs, and chickens are reportedly 30, 40, 15, and 15 mg/kg, respectively. Inhalation LC_{50} values for rats, quails, and ducks are 77, 3680, and 1890 ppm, respectively. The dermal LD_{50} for rabbits is 5000 mg/kg. No adverse effects were noted when bobtail quail and albino rabbits were sprayed six times (at 5-day intervals) with 1.1 kg/ha of a 90 percent formulation of methomyl. Methomyl is relatively non-toxic to bees once the spray has dried (Fairchild, 1977; Martin and Worthing, 1974).

Carbamate pesticides, such as methomyl, have cholinergic properties similar to those of the organic phosphates, but of shorter duration. Methomyl inhibits both RBC and plasma cholinesterase activity. The period

of inhibition of the cholinesterases is approximately 1-2 hours, and recovery usually occurs between 24 and 48 hours after contact. Atropine administration is the treatment of choice (Simpson and Bermingham, 1977).

V. AQUATIC TOXICITY

A. Acute and Chronic Toxicity

Methomyl 24-hour TL_m (median toxic limit) values for carp (Cyprinus carpio) and tilapia fish range from 1.054 to 3.16 mg/l (El-Refai, et al. 1976). The LC_{50} (96-hour exposure) for rainbow trout (Salmo gainneri) was 3.4 ppm; for bluegill (Lepomis macrochirus), 0.87 ppm; and for goldfish (Carrasius auratus), greater than 0.1 ppm (Martin and Worthing, 1974). Following exposure (4-48 hours) of marine or estuarine fishes to carbamate pesticide, the acetylcholinesterase activity in the brain was inhibited by 77 to 89 percent (Coppage, 1977).

B. Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The threshold limit value for air is established at 2.5 mg/m^3 (Fairchild, 1977). The Office of Water and Waste Management is in the process of conducting preregulatory assessment of methomyl under the Safe Drinking Water Act. The Office of Toxic Substances has promulgated regulations for methomyl under Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act.

Methomyl residue concentrations in crops are regulated as follows: 0.1 ppm for lentils and pecans; 1 ppm for forage, hay, barley (grain), and oats (grain); 2 ppm for strawberries and avocados; 5 ppm for chinese cabbage; 6 ppm for blueberries, beets, collard, dandelions, kale,

mustard greens, parsley, swiss chard, turnip greens, and watercress; 10 ppm for wheat, rye, barley, and oats used as hay, straw, or forage; and 40 ppm for bermuda grass hay (Federal Register [43(98): 21700, 1978; 43 and (112): 25120, 1978; 44(63): 18972; 44(83): 24846; 44(129): 38844; 44(160): 47934, and 44(227): 67117, 1979]).

B. Aquatic -

Guidelines or standards to protect aquatic life could not be located in the available literature.

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No. 126

Methyl Alcohol

Health and Environmental Effects

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-1491-

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BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Methyl alcohol, CH_3OH, also called methanol, is the first member of a homologous series of monohydric aliphatic alcohols. At room temperature, methyl alcohol is a colorless, neutral liquid possessing a mild distinctive odor. [1] Additional chemical and physical properties of methyl alcohol are presented in Table XIII-1. [2,3,4]

The greater part of methyl alcohol manufactured in the US is produced synthetically. [5] One widely used synthetic process is the "medium pressure process" which involves the reduction of carbon monoxide (containing small amounts of carbon dioxide) with hydrogen. The reduction step is carried out at 250-400 C and at 100-600 atmospheres pressure using a catalyst. [1]

During the years 1968-73, synthetic methyl alcohol production in the US increased at an average annual rate of over 13.2%. In 1973, the production of synthetic methyl alcohol amounted to slightly over seven billion pounds, around one billion gallons. In addition, an estimated 10 million pounds (1.5 million gallons) of "natural" (eg, from wood distillation) methyl alcohol were produced. [5]

Methyl alcohol is used in a variety of industrial processes. The major use is in the production of formaldehyde which amounted to 39% of the methyl alcohol consumed in the US in 1973. [5] Other commercial uses of methyl alcohol are in the production of chemical derivatives, such as dimethyl terephthalate, methyl halides, methyl methacrylate, acetic acid, and methylamines, and because of its solvent properties, methyl alcohol is

also used in paints, varnishes, cements, and other formulations such as inks and dyes. [1,5] Table XIII-2 lists the consumption of methyl alcohol by product and quantity produced in the US for the year 1973. [5]

A number of occupations with potential exposure to methyl alcohol are listed in Table XIII-3. [6]

NIOSH estimates that approximately 175,000 workers in the US are potentially exposed to methyl alcohol.

EFFECTS ON HUMANS

Burk [26] attributed the toxic effects of methyl alcohol to formaldehyde and formic acid, indicating that both compounds were oxidation products of methyl alcohol. The author stated that the diagnosis of methyl alcohol poisoning is sometimes very difficult, and would be more easily verified by quantitative determinations of formic acid in the urine of persons suspected of being poisoned with methyl alcohol.

Percutaneous absorption of methyl alcohol can lead to serious consequences, including death. In 1968, Gimenez et al [27] reported an analysis of 19 cases of children, ranging in age from 1.5 months to 4 years, who were poisoned as a result of having cloths soaked in methyl alcohol applied to their abdomens to relieve gastrointestinal troubles or other unspecified complaints. There were 2 additional cases reviewed in which both methyl and ethyl alcohols had been employed in this way, making a total of 21 cases. Although absorption of methyl alcohol via the respiratory tract was possible in these cases, the fact that the cloths were held in place by rubber baby pants would favor percutaneous absorption of the alcohol as the significant route of exposure. The length of time between application and onset of symptoms of intoxication was 1-13 hours (7 1/4 hours average). The early signs of intoxication were described by the authors as central nervous system depression with 13 children having

exhibited severe respiratory depression and 11 of these having convulsions. Blood pH in the 21 patients ranged from 6.4 to 7.38 (normal: 7.36-7.41 [28]), indicating acidosis in most cases. Twelve of the 21 children died of cardiac or respiratory arrest 2-10 days after hospital admission. The survivors recovered without apparent permanent damage. Papilledema and ocular fundus bleeding were observed in 2 of the infants who subsequently died. Abdominal skin lesions were present in 5 patients, 3 of the erythematous type and 2 of the scaling type. The authors [27] commented that while there was no relationship between methyl alcohol blood levels as tested in 11 children (57-1,130 mg%) and prognosis, there was a relationship between the initial blood pH and the subsequent course of the illness. In general, treatment consisted of administering sodium bicarbonate, glucose, ethyl alcohol, fluids, and electrolytes. Other forms of treatment included peritoneal dialysis, exchange transfusion, mechanical respiration, and the administration of anticonvulsant drugs. It must be pointed out that the absorptive properties of the skin of infants are probably different from those of adults and consequently infant susceptibility to, and manifestations of, methyl alcohol intoxication may not parallel those seen in adults.

In 1952, Leaf and Zatman [30] reported on experiments in which 5 male volunteers ingested 2.5-7.0 ml of methyl alcohol diluted to 100 ml with water. These amounts of methyl alcohol corresponded to doses of 29-84 mg/kg. Two blood samples were taken from 3 subjects, 2-5 hours after the ingestion. Urine was collected frequently for 11-16 hours following methyl alcohol administration. Both the blood and urine samples were analyzed for methyl alcohol by a colorimetric method based on the oxidation of methyl alcohol to formaldehyde and formation of a colored complex with a modified Schiff's reagent. The results of this experiment indicated that under these conditions methyl alcohol was rapidly absorbed from the gastrointestinal tract. The maximum methyl alcohol concentration in the urine was achieved approximately one hour after ingestion and then decreased exponentially. The ratio of blood to urine methyl alcohol

concentrations remained almost constant for the 3 subjects in which it was determined, and the authors [30] concluded that the change in the concentration of methyl alcohol in the urine was an accurate indicator of the change in methyl alcohol concentration in the body. At the levels used in this experiment, the concentration of methyl alcohol in the urine declined to control values within 13-16 hours after ingestion. Leaf and Zatman [30] also stated that only 0.4-1.2% of the ingested methyl alcohol was eliminated unchanged in the urine.

In another experiment in the same study, [30] 2 male volunteers ingested 15 ml of ethyl alcohol and 4 ml of methyl alcohol simultaneously. They then ingested 10 ml of ethyl alcohol every hour for the next 7 hours. The same individuals served as their own controls in a previous experiment in which they ingested only 4 ml of methyl alcohol. Urine was collected hourly and analyzed for methyl alcohol. The maximum urinary methyl alcohol concentrations for those individuals who ingested both methyl alcohol and ethyl alcohol were 8.82 and 9.20 mg/100 ml, compared to values of 6.05 and 5.50 mg/100 ml when methyl alcohol alone was ingested. Moreover, the total amount of methyl alcohol excreted unchanged in the urine in the first 7 hours after ingestion was 107.1 mg and 125.5 mg (3.7 and 3.96% of the administered dose respectively) when both methyl alcohol and ethyl alcohol were ingested, whereas only from 18.2 to 30.8 mg (0.57-0.97% of the administered dose) was excreted unchanged in a similar time period after ingestion of 4 ml methyl alcohol alone. The authors [30] concluded that in humans ethyl alcohol interfered with the normal oxidation of methyl alcohol, causing more of it to be excreted unchanged in the urine. Moreover, according to the authors' conclusion, higher concentrations of methyl alcohol in the blood are maintained in the presence of ethyl alcohol at any given time after absorption, as compared to concentrations achieved in the absence of ethyl alcohol.

Ethyl alcohol may inhibit the oxidation of methyl alcohol in vivo by competing (competitive inhibition) for the alcohol dehydrogenase system. It is conceivable, therefore, that chronic alcoholics might exhibit measurable concentrations of methyl alcohol in the blood or urine even though they have not been exposed to methyl alcohol. [37]

In summary, an integration of in vitro [33-35] and in vivo studies [29-31,37] indicates that in humans methyl alcohol is oxidized primarily by alcohol dehydrogenase. The results discussed in the section on Animal Toxicity, however, suggest that in nonprimates methyl alcohol is oxidized primarily by the catalase-peroxidase system.

ANIMAL TOXICITY

Gilger and Potts [42] concluded from their studies that the results of oral administration of methyl alcohol to rats, rabbits, and dogs differed from those reported on humans in 4 important areas, namely, lethal dose, time course of development and signs of intoxication, eye effects, and acidosis. The authors also concluded that, following intoxication with methyl alcohol, the responses of primates more closely approximated human responses than did those of nonprimates. An extensive review of the literature dealing with the oral toxicity of methyl alcohol in humans and nonprimates was supportive of their conclusion. The authors concluded that the approximate lethal oral dose of methyl alcohol in humans (0.85-1.4 g/kg) was 1/3 the equivalent dose in monkeys and 1/9 the equivalent dose in rats. Moreover, nonprimates exhibited severe early intoxication with narcosis lasting until death whereas primates showed much less early intoxication followed by a symptomless latent period, then by sickness and death. The only eye changes observed with certainty in nonprimates were early pupillary changes and corneal opacities following exposure keratitis. Some monkeys, however, and many humans developed partial or complete

blindness accompanied by eyeground changes such as hyperemia of the optic discs and venous engorgement. Finally, humans and monkeys often developed severe acidosis (CO_2-combining capacity less than 20 volumes %) after methyl alcohol ingestion; this condition was rare in nonprimates and occurred only at near lethal or lethal doses.

Correlation of Exposure and Effect

Well-documented studies that correlate environmental levels of methyl alcohol with observed toxic effects have not been found in the literature, nor have any long-term epidemiologic studies of chronic low-level occupational exposure been found.

Effects seen from either of the 2 most common routes of occupational exposure (inhalation and percutaneous absorption) include: headache [14,16,17,39]; dizziness [13,19]; nausea [16,17,26]; vomiting [17]; weakness (unspecified) [16]; vertigo [17,26]; chills [13]; shooting pains in the lower extremities [13]; unsteady gait [17]; dermatitis [14]; multiple neuritis characterized by paresthesia, numbness, prickling, and shooting pain in the back of the hands and forearms, as well as edema of the arms [15]; nervousness [19]; gastric pain [19]; insomnia [19]; acidosis [19]; and formic acid in the urine. [26] Eye effects, such as blurred vision, [16,17] constricted visual fields, [17,19,25] blindness, [13,25] changes in color perception, [17] double vision, [19] and general visual

disturbances [17] have been reported. Eye examinations have shown sluggish pupils, [13,17] pallid optic discs, [13] retinal edema, [17] papilledema, [26] hyperemia of the optic discs with blurred edges and dilated veins. [17]

The study by Bennett et al [40] showed similar symptoms resulting from ingestion. These are acidosis, headache, visual disturbances, dizziness, nausea and vomiting, severe upper abdominal pain, dilated and nonreactive pupils. Eyeground examinations showed hyperemia of the optic discs and retinal edema. The eyeground changes were almost always found in acidotic patients. This finding is suggestive of a correlation between acidosis and visual disturbances. However, a number of patients, with and without acidosis, complained of visual disturbances. Additionally, blood tests showed elevated serum amylase levels in 14 of 21 patients. This finding in conjunction with complaints of upper abdominal pain and pancreatic necrosis seen at autopsy led the authors [40] to conclude that hemorrhagic pancreatitis resulted from acute methyl alcohol intoxication. However, reports of acute hemorrhagic pancreatitis by parenteral routes have not been found.

Direct skin contact with methyl alcohol has been said to cause dermatitis, [14] erythema, and scaling. [27] The reported variability in susceptibility [14] is probably largely because of variations in time of contact with methyl alcohol; it is evident that sufficient dermal contact with any lipid solvent such as methyl alcohol has the potential for causing skin irritation.

Basis for the Recommended Environmental Standard

Epidemiologic studies incorporating comprehensive environmental surveys, well-planned surveillance, a sufficient study population, and statistical analysis have not been found in the literature. It is therefore difficult to recommend an environmental limit based upon unequivocal scientific data.

TABLES AND FIGURE

TABLE XIII-1

PHYSICAL AND CHEMICAL PROPERTIES OF METHYL ALCOHOL

Molecular formula	CH3OH
Formula weight	32.04
Apparent specific gravity at 20 C	0.7910
Boiling point at 760 mmHg	64.5 C
Vapor pressure at 20 C	96 mmHg
Melting point	-97.6 C
Solubility in water	Miscible
Solubility in alcohols, ketones, esters, and halogenated hydrocarbons	Miscible
Flash point, Tag open cup	16 C
Flash point, Tag closed cup	12 C
Flammable limits (% in air)	6.72-36.50
Vapor density (air=1)	1.11
Corrosivity	Noncorrosive at normal atmospheric temperatures. Exceptions: lead and aluminum
Conversion factors (760 mmHg and 25 C)	1 ppm=1.310 mg/cu m 1 mg/cu m=.763 ppm

Adapted from ANSI Z37 [2], the Manufacturing Chemists Association [3], and the Handbook of Chemistry and Physics [4]