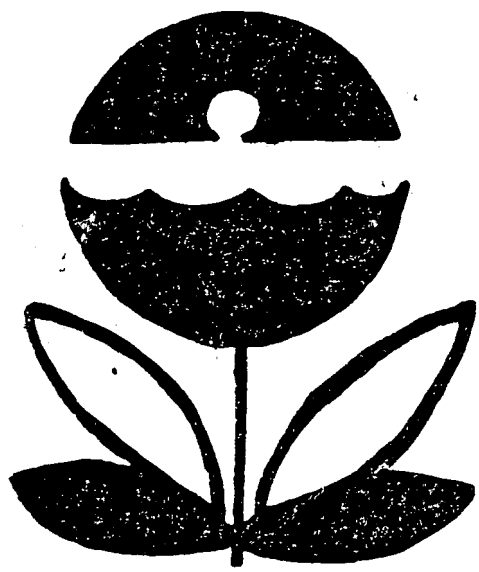
H E A L T H A N D E N V I R O N M E N T A L

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

2,4-DICHLOROPHENOL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for 2,4-dichlorophenol (U.S. EPA, 1979).

2,4-Dichlorophenol is a colorless, crystalline solid having the empirical formula $C_6H_4Cl_2O$ and a molecular weight of 163.0 (Weast, 1975). It has the following physical and chemical properties (Sax, 1975; Aly and Faust, 1965; Weast, 1975; Kirk and Othmer, 1964):

Melting Point:	45° C
Boiling Point:	210° C at 760 mm Hg
Vapor Pressure:	1.0 mm Hg at 53.0° C
Solubility:	slightly soluble in water at neutral pH; dissolves readily in ethanol and benzene

2,4-Dichlorophenol is a commercially produced, substituted phenol used entirely as an intermediate in the manufacture of industrial and agricultural products such as the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D), germicides, and miticides.

Little data exists regarding the persistence of 2,4-dichlorophenol in the environment. Its low vapor pressure and non-volatility from aqueous alkaline solutions would cause it to be only slowly removed from surface water via volatilization (U.S. EPA, 1979). Studies have indicated low absorption of 2,4-dichlorophenol from natural surface waters by various clays (Aly and Faust, 1964). 2,4-Dichlorophenol is photolabile in aqueous solutions (Aly and Faust, 1964; Crosby and Tutass, 1966) and can be degraded microbially to succinic acid in soils and aquatic environments (Alexander and Aleem, 1961; Ingols, et al., 1966; Loos, et al., 1967).

II. EXPOSURE

A. Water

Sources of 2,4-dichlorophenol in water are agricultural run-off (as a contaminant and metabolic breakdown product of biocides) and manufacturing waste discharges (U.S. EPA, 1979). Recent experiments under conditions simulating the natural environment have not demonstrated that 2,4-dichlorophenol is a significant product resulting from chlorination of phenol-containing wastes (Glaze, et al. 1978; Jolley, et al. 1978).

B. Food

Contamination of food with 2,4-dichlorophenol would probably result from use of the herbicide 2,4-D (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for 2,4-dichlorophenol to be 37 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

C. Inhalation

Pertinent information regarding direct evidence indicating that humans are exposed to significant amounts of 2,4-dichlorophenol through inhalation has not been found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Pertinent information regarding the absorption of 2,4-dichlorophenol in humans or animals was not found in the available literature, although data on toxicity indicate that 2,4-dichlorophenol is absorbed after oral administration (Deichmann, 1943; Kobayashi, et al. 1972). Due to its high lipid solubility and low ionization at physiological pH, 2,4-dichlorophenol is expected to be readily absorbed after oral administration (U.S. EPA, 1979).

B. Distribution

Pertinent information dealing directly with tissue distribution after 2,4-dichlorophenol exposure was not found in the available literature. Feeding of 2,4-D (300 - 2000 μg/g feed) to cattle and sheep (Clark, et al. 1975) and Nemacide (50 - 800 μg/g feed) to laying hens (Sherman, et al. 1972) did not produce detectible residues of 2,4-dichlorophenol in muscle or fat. Cattle and sheep had high levels of 2,4-dichlorophenol in kidney and liver; hens had detectible levels of 2,4-dichlorophenol in liver and yolk.

C. Metabolism

Pertinent information dealing directly with metabolism of administered 2,4-dichlorophenol was not found in the available literature. In mice, urinary metabolites of ^{14}C-labelled gamma or beta benzene hexachloride (hexachlorocyclohexane) included 2,4-dichlorophenol and its glucuronide and sulfate conjugates (as 4-6 percent of total metabolites) (Kurihara, 1975).

D. Excretion

Pertinent information dealing with excretion of administered 2,4-dichlorophenol was not found in the available literature. After oral administration of 1.6 mg Nemacide to rats over a 3-day period, 67 percent of that compound appeared in urine as 2,4-dichlorophenol within 3 days. With a dosage of 0.16 mg Nemacide, 70 percent of the compound appeared in urine as 2,4-dichlorophenol within 24 hours (Shafik, et al. 1973).

IV. EFFECTS

A. Carcinogenicity

Insufficient data exist to indicate that 2,4-dichlorophenol is a carcinogenic agent. The only study performed (Boutwell and Bosch, 1959) suggested that 2,4-dichlorophenol may promote skin cancer in mice after ini-

tiation with dimethylbenzanthracene and when repeatedly applied at a concentration high enough to damage the skin. An analysis of the data of Boutwell and Bosch using the Fisher Exact Test indicated that the incidence of papillomas in 2,4-dichlorophenol-treated groups was significantly elevated over controls, while the incidence of carcinomas was not (U.S. EPA, 1979).

B. Mutagenicity, Teratogenicity and Other Reproductive Effects

No studies addressing the mutagenicity, teratogenicity or other reproductive effects of 2,4-dichlorophenol in mammalian systems were found in the available literature. However, genotoxic effects of 2,4-dichlorophenol have been reported in plants. Exposure of flower buds or root cells of vetch, (Vicia fabia) to solutions of 2,4-dichlorophenol, 0.1M and 62.5 mg/l, respectively, caused meiotic and mitotic changes including alterations of chromosome stickiness, lagging chromosome anaphase bridges and fragmentation (Amer and Ali, 1968, 1969, 1974). The relationship of such changes in plant cells to potential changes in mammalian cells has not been established (U.S. EPA, 1979).

C. Chronic Toxicity

One report (Bleiberg, et al. 1964) suggested that 2,4-dichlorophenol was involved in inducing chloracne and porphyria in workers manufacturing 2,4-dichlorophenol and 2,4,5-trichlorophenol and exposed to acetic acid, phenol, monochloroacetic acid, and sodium hydroxide. Since various dioxins (including one associated with chloracne) have been implicated as contaminants of 2,4,5-trichlorophenol, the role of 2,4-dichlorophenol in causing chloracne and porphyria is not conclusive (Huff and Wassom, 1974).

In a study (Kobayaski, et al. 1972) in which male mice were fed 2,4-dichlorophenol at estimated daily doses of 45, 100 and 230 mg/kg body weight, no adverse effects were noted except for some microscopic nonspeci-

fic liver changes after the maximum dose. Parameters evaluated included body and organ weights and food consumption, as well as hematological and histological changes.

D. Other Relevant Information

2,4-Dichlorophenol appears to be a weak uncoupler of oxidative phosphorylation (Farquharson, et al. 1958; Mitsuda, et al. 1963). Values on odor threshold for 2,4-dichlorophenol in water range from 0.65 to 6.5 µg/l, depending on the temperature of water (Hoak, 1957).

V. AQUATIC TOXICITY

A. Acute Toxicity

Two 96-hour assays have been performed examining the acute effects of 2,4-dichlorophenol in freshwater fish. An LC_{50} value of 2,020 µg/l for the bluegill, Lepomis macrochirus, (U.S. EPA, 1978), and an LC_{50} value of 8,230 ug/l for the juvenile fathead minnow, Pimephales promelas, (Phipps, et al. manuscript), have been reported. Two studies on the freshwater cladoceran, Daphnia magna, have produced 48-hour static LC_{50} values of 2,610 and 2,600 µg/l (Kopperman, et al. 1974; U.S. EPA, 1978).

Only one marine fish or invertebrate species has been tested for the acute effects of 2,4-dichlorophenol. Hiatt, et al. (1953) observed only a moderate reaction to a concentration of 20,000 µg/l in mountain bass, a species endemic to Hawaii.

B. Chronic Toxicity

Data for the chronic effects of 2,4-dichlorophenol for either freshwater or marine organisms were not located in the available literature.

C. Plant Effects

Concentrations of 2,4-dichlorophenol that caused a 56 percent reduction in photosynthetic oxygen production or a complete destruction of

chlorophyll were 50,000 or 100,000 µg/l, respectively, in algal assays with Chlorella pyrenoidosa (Huang and Gloyna, 1968). An earlier study by Blackman, et al. (1955) reported a concentration of 2,4-dichlorophenol that caused a 50 percent reduction in chlorophyll to be 58,320 µg/l in the duckweed, Lemna minor. No marine plant species have been examined.

D. Residues

A bioconcentration factor of 130 has been estimated from the octanol-water partition coefficient of 2,4-dichlorophenol for aquatic organisms having a lipid content of eight percent. The estimated weighted average bioconcentration factor for the edible portion of aquatic organisms is 37.

E. Miscellaneous

Flavor impairment studies indicated that the highest concentration of 2,4-dichlorophenol in the exposure water which would not cause tainting of the edible portion of fish ranged from 0.4 µg/l for the largemouth bass (Micropterus salmoides), to 14 µg/l for the bluegill (Lepomis macrochirus). The value for the rainbow trout (Salmo gairdneri) was 1 µg/l (Shumway and Palensky, 1973).

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

Based upon the prevention of adverse organoleptic effects, the draft interim criterion for 2,4-dichlorophenol in water recommended by the U.S. EPA (1979) is 0.5 µg/l, although the recommended draft interim criterion could be 371 µg/l based on calculations by the U.S. EPA (1979) from subacute toxicity data in mice.

B. Aquatic

The draft criterion for protecting freshwater organisms is 0.4 µg/l as a 24-hour average concentration, not to exceed 110 µg/l. No criterion was derived for marine organisms (U.S. EPA, 1979).

2,4-DICHLOROPHENOL

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No. 76

2,6-Dichlorophenol

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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

2,6-DICHLOROPHENOL

Summary

There is no available information on the possible carcinogenic, teratogenic, or adverse reproductive effects of 2,6-dichlorophenol.

The compound did not show mutagenic activity in the Ames assay. A single report has indicated that 2,6-dichlorophenol produced chromosome aberrations in rat bone marrow cells; details of this study were not available for evaluation.

Prolonged administration of 2,6-dichlorophenol may produce hepatoxic effects. Pertinent data on the toxicity of 2,6-dichlorophenol to aquatic organisms were not found in the available literature. However, EPA/ECAO Hazard Profiles on related compounds may be consulted, including meta-chlorophenol, 2,4,5-trichlorophenol, and 2,3,4,6-tetrachlorophenol.

I. INTRODUCTION

2,6-Dichlorophenol, CAS registry number 87-65-0, exists as white needles and has a strong penetrating odor resembling o-chlorophenol. It has the following physical and chemical constants (Weast, 1972; Hawley, 1971):

Formula:	$C_6H_4Cl_2O$
Molecular Weight:	163
Melting Point:	68°C - 69°C
Boiling Point:	219°C - 220°C (740 torr)
Vapor Pressure:	1 torr @ 59.5°C
pH:	6.79
Production:	unknown

2,6-Dichlorophenol is produced as a by-product from the direct chlorination of phenol. It is used primarily as a starting material for the manufacture of trichlorophenols, tetrachlorophenols, and pentachlorophenols (Doldens, 1964).

II. EXPOSURE

A. Water

Phenols occur naturally in the environment and chlorophenols are associated with bad taste and odor in tap water (Bak, 1957). 2,6-Dichlorophenol has a taste and odor threshold of 0.002 mg/l and 0.003 mg/l, respectively (McKee and Wolf, 1963). Piet and DeGrunt (1975) found unspecified dichlorophenols in Dutch surface waters at 0.01 to 1.5 ug/l, and Burttschell, et al. (1959) demonstrated that chlorination of phenol-containing water produced, among other products, 2,6-dichlorophenol in a 25-percent yield after 18 hours of reaction.

B. Food

Pertinent data could not be located in the available literature.

C. Inhalation

Olie, et al. (1977) reported finding dichlorophenols in flue gas condensates from municipal incinerators. The levels were not quantified.

D. Dermal

Pertinent data could not be located in the available literature; however, it is known that dichlorophenols are less toxic by skin contact than mono-chlorophenols and less likely to be absorbed through the skin (Doldens, 1964).

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature. By comparison with other chlorophenols, it is expected that 2,6-dichlorophenol will be absorbed through the skin and from the gastrointestinal tract (U.S. EPA, 1979).

B. Distribution

Pertinent data could not be located in the available literature. The high lipid solubility of the compound would suggest that unexcreted compound distributes to adipose tissues.

C. Metabolism and Excretion

Pertinent data could not be located in the available literature. By comparison with other chlorophenols, it is expected that 2,6-dichlorophenol is rapidly eliminated from the body, primarily as urinary sulfate and glucuronide conjugates (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

2,6-Dichlorophenol did not show mutagenic activity in the Ames assay (Rasanen, et al. 1977). Chromosome aberrations in rat bone marrow cells have been observed following compound administration (route and dosage not indicated) (Chung, 1978).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Administration of 2,6-dichlorophenol to rats (route and dosage not specified) has been reported to produce hepatic degeneration (Chung, 1978).

E. Other Relevant Information

In vitro tests have indicated that 2,6-dichlorophenol will inhibit liver mitochondrial respiration (level not specified) (Chung, 1978).

V. AQUATIC TOXICITY

A. Acute

McLeese, et al. (1979) reported a 52-hour lethal threshold limit of 19,100 ug/l for marine shrimp (Crangon septemspinosa) exposed to 2,6-dichlorophenol.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Based on the organoleptic properties of 2,6-dichlorophenol, a water quality criterion of 3.0 ug/l has been recommended by the U.S. EPA (1979).

B. Aquatic

No existing criteria to protect fresh and saltwater organisms were found in the available literature.

No. 77

2,4-Dichlorophenoxyacetic Acid (2,4-D)

Health and Environmental Effects

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

APRIL 30, 1980

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2,4-DICHLOROPHENOXYACETIC ACID

Summary

Oral administration of 2,4-Dichlorophenoxyacetic acid (2,4-D) failed to produce carcinogenic effects in mice or dogs; however, feeding technical grade 2,4-D did produce tumors in a study with rats. Subcutaneous administration of the isooctyl ester of 2,4-D has been reported to produce reticulum cell sarcomas in mice.

A single study has indicated that 2,4-D produced mutagenic effects in Saccharomyces. Other investigations have failed to show mutagenic effects of the compound Salmonella, Drosophila, Saccharomyces, or the dominant lethal assay with mice.

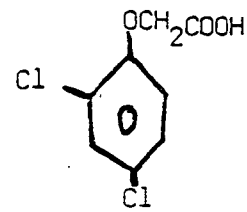
2,4-D and several of its esters failed to show teratogenic effects in mice; the propylene glycol butyl ether ester of the compound produced an increase in cleft palates in this study. Studies in hamsters orally administered 2,4-D and derivatives showed teratogenic effects. Oral administration of 2,4-D to rats failed to indicate teratogenicity in one study; another investigation using oral administration of 2,4-D to rats found teratogenic effects. A three-generation feeding study of 2,4-D to rats indicated fetotoxic effects at a dosage of 1,500 ppm.

Toxicity tests on a variety of aquatic organisms generally have demonstrated that various esters of 2,4-D are more toxic than the 2,4-D acid, dimethyl amine, or sodium salt. Freshwater trout and bluegill sunfish were adversely affected by the propylene glycol butylether (PGBE) ester at concentrations of 900 to 2,000 µg/l. Daphnids and freshwater seed shrimp were sensitive to the PGBE ester at concentrations of 100 to 300 µg/l. Chronic exposure of several species of fish to concentrations up to 310 µg/l has not demonstrated any toxic effect.

2,4-DICHLOROPHENOXYACETIC ACID

I. INTRODUCTION

2,4-Dichlorophenoxyacetic acid, CAS Registry number 94-75-7, commonly known as 2,4-D, is a white or slightly yellow crystalline compound which is odorless when pure. 2,4-D has the following physical and chemical properties (Herbicide Handbook, 1979):



Formula:	$C_8H_6Cl_2O_3$
Molecular Weight:	221.0
Melting Point:	135°C-138°C (technical); 140°C-141°C (pure)
Boiling Point:	160°C @ 0.4 torr
Density:	1.565^{30}
Vapor Pressure:	0.4 torr @ 160°C
Solubility:	Acetone, alcohol, dioxane ether, isopropyl alcohol; slightly soluble in benzene, solubility in water 0.09g/100g, H_2O
Production:	Unknown

2,4-D is used as an herbicide along with its various salts and esters, which vary its solubility properties. It is used mainly to control broad-leafed plants in pastures, and right-of-ways, and, and to keep lakes and ponds free of unwanted submersed and emersed weeds.

II. EXPOSURE

A. Water

No estimates of average daily uptake of 2,4-D from water, are available; however, after treatment for water milfoil in reservoirs in

Alabama and Tennessee, the Tennessee Valley Authority found the concentration at downstream monitoring stations to be 2 ppb. 2,4-D was not found in the harvested beans of red Mexican bean plants after irrigation with contaminated water (Gangst, 1979).

B. Food

The Food and Drug Administration, in monitoring milk and meat for residues of 2,4-D from 1963 to 1969, found no trace of the herbicide in 13,000 samples of milk and 12,000 samples of meat (Day, et al. 1978). Cattle and sheep which were fed 2,000 ppm of 2,4-D for 28 days had less than 0.05 ppm 2,4-D in the fat and muscle tissue and no detectable amount of 2,4-dichlorophenol. After seven days withdrawal from the 2,4-D diet, these tissue levels were drastically reduced (Clark, et al. 1975). Six species of fish were monitored for three weeks after the water in a pond was treated with a 2,4-D ester. The highest tissue concentration reached was 0.24 ppm eight days after application. Subsequently, the herbicide or its metabolite was eliminated rapidly. Clams and oysters accumulate more 2,4-D than do fish and crabs. Residue peaks occur from 1 to 9 days after application and then rapidly decline (Gangst, 1979).

C. Inhalation

Pertinent data were not found in the available literature; however, some 2,4-D esters which are much more volatile than the parent compound have been monitored in air up to 0.13 $\mu g/m^3$ (Farwell, et al. 1976; Stanley, et al. 1971).

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Human absorption of 2,4-D following oral intake is extensive; Kohli et al. (1974) have determined absorption of 75 to 90 percent of the total dietary intake of the compound. Animal studies have indicated that the gastrointestinal absorption of 2,4-D esters may be less efficient than that of the free acid or salt form of the compound (NRCC, 1978).

B. Distribution

The phenoxy herbicides are readily distributed throughout the body tissues of mammals. Tissue levels of herbicide may be higher in the kidney than in the blood; liver and muscle show levels lower than those determined in the blood (NRCC, 1978). Withdrawal of dietary compound produced almost complete tissue loss of residues in seven days (Clark, et al. 1975).

Small amounts of phenoxy herbicides are passed to the young through the mother's milk (Bjerke, et al. 1972). Transplacental transfer of 2,4-D has been reported in mice (Lindquist and Ullberg, 1971).

C. Metabolism

Sauerhoff, et al. (1976) determined that following oral administration of 2,4-D to human volunteers, the major amount excreted in the urine was free compound; a smaller amount was excreted as a conjugate. Tissue analysis of sheep and cattle fed 2 4-D have shown unchanged compound and 2,4-dichlorophenol to be present (Clark, et al. 1975).

D. Excretion

Elimination of orally administered 2,4-D by humans is primarily through the urine (95.1 percent of the initial dose); the half-life of the compound in the body has been estimated as 17.7 hours (Sauerhoff, et al. 1976). Clark, et al. (1964) have reported urinary elimination of 96 percent

of an oral dose of labelled 2,4-D within 72 hours by sheep; approximately 1.4 percent of the administered dose was eliminated in the feces.

The plasma half-life of 2,4-D has been estimated to be from 11.7 to 33 hours in humans (NRCC, 1978).

IV. EFFECTS

A. Carcinogenicity

Innes, et al. (1969) reported no significant increase in tumors following feeding of mice with 2,4-D for 18 months. A two-year feeding study in rats did indicate an increase in total tumors in females and malignant tumors in males following feeding of technical 2,4-D; a parallel study with dogs fed technical compound did not show carcinogenic effects (Hansen, et al. 1971).

Mice were administered maximum tolerated doses of 2,4-D and its butyl, isopropyl, and isooctyl esters in a long-term carcinogenicity study. Carcinogenic effects were seen after subcutaneous administration of the isooctyl ester (reticulum cell sarcomas) (NCI, 1968).

B. Mutagenicity

No mutagenic effects of 2,4-D in tests with Salmonella, Saccharomyces, or Drosophila were observed (Fahrig, 1974). Siebert and Lemperle (1974) have reported mutagenic effects following treatment of Saccharomyces cerevisiae strain D4 with aqueous 2,4-D solution (1,000 mg/l).

Gavage or intraperitoneal administration of 2,4-D to mice failed to show mutagenic effects in the dominant lethal assay (Epstein, et al. 1972).

C. Teratogenicity

Testing of 2,4-D and its n-butyl, isopropyl, and isooctyl esters in pregnant mice produced no significant teratogenic effects. There was a

significant increase in cleft palate deformities after administration of the propylene glycol butyl ether ester of 2,4-D (Courtney, 1974).

Subcutaneous injection of the two isopropyl esters and the isooctyl ester of 2,4-D in pregnant mice has been reported to produce teratogenic effects (Caujolle, et al. 1967), although the DMSO vehicle used is, itself, a teratogen. Bage, et al. (1973) have also reported teratogenic effects in mice following injection of 2,4-D.

Oral administration of 2,4-D to hamsters resulted in the production of some terata (Collins and Williams, 1971). Studies with rats reported that oral administration of the parent compound or its isooctyl and butyl esters, and butoxy ethanol and dimethylamine salts, produced teratogenic effects (Khera and McKinley, 1972). However, Schwetz, et al. (1971) were unable to show teratogenic effects in rats following the oral administration of 2,4-D or its isooctyl or propylene glycol butyl ether esters.

D. Other Reproductive Effects

Embryotoxic effects following subcutaneous administration of 2,4-D to pregnant mice have been reported (Caujolle, et al. 1967; Bage, et al. 1973).

Fetotoxic effects of the compound and its esters have been reported after oral administration of maximally tolerated doses (Schwetz, et al. 1971; Khera and McKinely, 1972).

Results of a three-generation study of rats fed 2,4-D indicate that at dietary levels up to 500 ppm, no reproductive effects are produced; at levels of 1,500 ppm, a decrease in survival and body weights of weanlings was observed (Hansen, et al. 1971). Bjorklund and Erne (1966) reported no adverse reproductive effects in rats fed 1,000 mg/l 2,4-D in drinking water.

E. Chronic Toxicity

Animal studies with prolonged oral administration of 2,4-D or its amine salt have indicated renal and hepatic effects (Bjorklund and Erne, 1971; Bjorn and Northen, 1948); the chemical purity of the material administered is not known. A feeding study in rats has reported histopathological liver changes at dietary levels of 2,4-D equivalent to 50 mg/kg (Dow Chemical, 1962).

V. AQUATIC TOXICITY

A. Acute Toxicity

The National Research Council of Canada (1978) has reviewed the toxic effects of 2,4-D to fish. For the bluegill sunfish (Lepomis macrochirus), 2,4-D acid and 2,4-D dimethyl amine produced toxic effects at concentrations greater than 100,000 µg/l. At 2,4-D concentrations of 50,000 µg/l or less, no increased mortalities were reported except in pink salmon. The isopropyl, butyl, ethyl, butoxy ethanol, and PGBE esters produced 48-hour LC_{50} values of 900, 1,300, 1,400, 2,100, and from 1,000 to 2,100 µg/l, respectively.

For other fish species, the results follow a similar trend in that the esters tend to be more toxic than other formulations. Meehan, et al. (1974) conducted tests of various formulations of 2,4-D on coho salmon fry and fingerlings (Oncorhycus Kitutch), chum salmon fry (O. keta), pink salmon fry (O. gorbuscha), sockeye salmon smolts (O. nerka), Dolly Varden (Salvelinus malma), and rainbow trout (Salmo gairdneri). The butyl ester was the most toxic ester tested, with concentrations of 1,000 µg/l or greater producing nearly 100 percent mortalities in all species tested. The PGBE ester was similar in toxicity to the butyl ester. Rainbow trout were reported to have shown a 48-hour LC_{50} value of 1,100 µg/l on exposure to

the PGBE ester of 2,4-D. Harlequin fish (Rasbora heteromorpha) showed a 48-hour LC_{50} value of 1,000 µg/l on exposure to the butoxyethyl ester of 2,4-D (National Research Council of Canada 1978). Rehwoldt, et al. (1977) have observed 96-hour LC_{50} values of 26,700; 40,000; 70,100; 70,700; 94,600; 96,500; and 300,600 µg/l for banded killifish (Fundulus diaphanus), white perch (Roccus americanus), stripped bass (Morone sazatilis), guppies (Libistes reticulatus), pumpkinseed sunfish (Lepomis gibbosus), carp (Cyprinus carpio), and American eel (Anguilla rostrata), respectively, exposed to commercial technical grade 2,4-D.

Sanders (1970) conducted a comparative study on the toxicities of various formulations of 2,4-D for six species of freshwater crustaceans. The PGBE ester was generally most toxic, while the dimethylamine salt was least toxic. The crayfish (Orconectes nails) was the most resistant species tested, with 48-hour static LC_{50} values greater than 100,000 µg/l for all formulations tested. The waterflea (Daphnia magna) and seed shrimp (Cypridopsis vidua) were most sensitive to the PGBE ester, with 48-hour LC_{50} values of 100 and 320 µg/l, respectively. Scuds (Gammarus fasciatus), sowbugs (Ascellus brevicaudus), and freshwater grass shrimp (Palaemonetes kadiakensis) were also moderately sensitive, with 48-hour LC_{50} values ranging from 2,200 to 2,700 µg/l. Sanders and Cope (1968) reported a 96-hour LC_{50} value of 1,600 µg/l for stonefly naiads (Pteronarcy californica) exposed to the butoxyethanol ester of 2,4-D. Technical grade 2,4-D produced a 96-hour LC_{50} value of 14,000 µg/l. Robertson and Bunting (1976) reported 96-hour LC_{50} values ranging from 5,320 to 11,570 µg/l for copepods (Cyclops vernalis) nauplli exposed to 2,4-D as free acid. The range of 96-hour LC_{50} values for nauplli exposed to 2,4-D alkonolamine salt was 120,000 to 167,000 µg/l.

Among marine invertebrates, those of commercial significance have been examined for toxic effects on exposure to 2,4-D formulations. Butler (1965) determined the 96-hour median effective concentration based on shell growth for oysters as 140 µg/l for the PGBE ester of 2,4-D. The 2,4-D acid had no detectable effect at exposures of 2,000 µg/l for 96-hours. Butler (1963) observed paralysis of brown shrimp (Penaeus aztecus) exposed to 2,4-D acid at a concentration of 2,000 µg/l for 48-hours. Sudak and Claff (1960) found a 96-hour LC_{50} value of 5,000,000 µg/l for fiddler crabs (Uca pugmax) exposed to 2,4-D.

McKee and Wolf (1963) have reviewed the toxic effects of 2,4-D to aquatic organisms. Toxic concentrations as low as 1,000 µg/l produced a 40 percent mortality for fingerling bluegills exposed to 2,4-D butyl ester. In general, esters of 2,4-D were reported to be more toxic than sodium salts of 2,4-D.

B. Chronic Toxicity

Rehwoldt, et al. (1970) exposed several species of fish to 100 µg/l 2,4-D for ten months and observed no overt effects to any tested species. The percent reduction of brain acetylcolinesterase ranged from 16 percent in white perch to 35 percent in American eels. In breeding experiments with guppies, a 100 µg/l concentration of 2,4-D had no significant effect on the reproductive process of the species under experimental conditions. Cope, et al. (1970) examined the chronic effects of PGBE ester of 2,4-D to bluegill sunfish. Fish were exposed to the herbicide in one-eighth acre ponds containing initial concentrations of up to 10,000 µg/l. Alterations in spawning activity, and the occurrence of pathological lesions of the liver, brain, and vascular system were reported for a period of up to 84

days. Mount and Stephan (1967) exposed 1-inch fathead minnows (Pimephales promelas) to a continuous series of concentrations of the butoxyethanol ester of 2,4-D ranging from 10 to 310 µg/l for a 10-month period. No deaths of deleterious effects, including abnormal spawning activity and reduced survival of eggs from exposed fish, were observed.

In static-renewal tests, Sigmon (1979) reported that the percent pupation and the percent emergence of Chironomus larvae were significantly reduced by exposure to 1,000 or 3,000 µg/l 1,4-D (acid equivalent in Weedone LV-4 formulation).

C. Plant Effects

The genera Microcystis, Scenedesmus, Chlorella, and Nitzschia showed no toxic response when exposed to 2,000 µg/l 2,4-D Lawrence (1962). Poorman (1973) treated cultures of Euglena gracilis with concentrations of 50,000 µg/l 2,4-D for 24 hours and observed depressed growth rates. Valentine and Bingham (1974) demonstrated that at 100,000 µg/l, 2,4-D reduced the cell numbers of Scenedesmus to one percent of control levels, Chlamydomonas to 48 percent of control levels, Chlorella to 66 percent of control levels, and Euglena to 90 percent of control levels within 4 to 12 days. The bluegreen algae (Nostoc muscorum) displayed a 68-percent reduction in growth when exposed to 100 µg/l 2,4-D (Cerci and Cavazzini, 1973). Singh (1974) exposed Cylindrospermum to 2,4-D sodium salt at concentrations ranging from 100,000 to 1,200,000 µg/l and reported that concentrations above 800,000 µg/l caused growth to cease completely. McKee and Wolf (1963) reviewed the effectiveness of 2,4-D in control of emergent aquatic plants and reported that concentrations ranging from 6,000 to 100,000 µg/l have been effective in controlling a number of species.

D. Residue

Cope, et al. (1970) examined residues of the PGBE ester of 2,4-D in the freshwater vascular plant, Potamogeten nodosus, in a one-eighth acre pond treated with single 100 to 10,000 µg/l applications of the chemical. A gradual depeletion of the herbicide to insignificant levels was demonstrated within three months.

Schultz and Gangstad (1976) reported that the flesh of fish exposed to 2,4-D dimethyl sodium salt in ponds treated with from 2.24 to 8.96 kg (as an acid equivalent) of the chemical did not attain the 100 µg/l level realized in the water two weeks after application.

The National Research Council of Canada (NRCC) (1978) has reviewed the bioconcentration data and associated residues of 2,4-D in a number of studies. NRCC indicated that a relatively short half-life of less than two days is found for fish and oyster. At water concentrations of 100 to 200 µg/l, the bioconcentration of 2,4-D various aquatic invertebrates was one to two orders of magnitude greater than in the water. Oysters (Crassostica virginica) were reported to have a bioconcentration factor of 180 when exposed to the butoxyethanol ester of 2,4-D. The freshwater bluegill and mosquito fish (Gambusia affinis) had bioconcentration factors ranging from 7 to 55, respective to water concentrations. Fish fed a diet containing 2,4-D bioconcentrated the 2,4-D acid by less than 0.2.

VI. EXISTING GUIDELINES

A. Human

The acceptable daily intake of 2,4-D for humans has been established at 0.3 mg/kg (FAO, 1969).

B. Aquatic

Pertinent data were not found in the available literature.

2,4-DICHLOROPHENOXYACETIC ACID

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No. 78

1,2-Dichloropropane

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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

1,2-DICHLOROPROPANE

Summary

The major environmental source of dichloropropane is from the use of a mixture of dichloropropanes and dichloropropenes as a soil fumigant. On chronic exposure of rats to dichloropropanes the only observed effect was a lack of normal weight gain. There is no evidence that dichloropropanes are carcinogens or teratogens. Dichloropropanes have produced mutations in bacteria and caused chromosomal aberrations in rats.

Aquatic toxicity tests of 1,2-dichloropropane are limited to four acute investigations. Two observed 96-hour LC_{50} values for the bluegill are 280,000 and 320,000 µg/l and the 48-hour LC_{50} value for Daphnia magna is 52,500 µg/l. A saltwater fish has a reported 96-hour LC_{50} value of 240,000 µg/l.

1,2-DICHLOROPROPANE

I. INTRODUCTION

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

1,2-Dichloropropane (1,2-PDC, molecular weight 112.99) is a liquid at environmental temperatures. This isomer of dichloropropane has a boiling point of 96.4°C, a density of 1.156 g/ml, a vapor pressure of 40 mm Hg at 19.4°C and a water solubility of 270 mg/100 at 20°C (U.S. EPA, 1979). Mixtures of 1,2-dichloropropane and cis-trans-1,3-dichloropropene are used as soil fumigants. For the purposes of discussion in this hazard profile document, dichloropropane refers to the 1,2-dichloropropane isomer. When heated to decomposition temperatures, 1,2-dichloropropane emits highly toxic fumes of phosgene (Sax, 1975).

II. EXPOSURE

A. Water

Dichloropropane can enter the aquatic environment as discharges from industrial and manufacturing processes, as run-off from agricultural land, and from municipal effluents. This compound was identified but not quantified in New Orleans drinking water (Dowty, et al. 1975).

B. Food

Information was not found concerning the concentration of dichloropropane in commerical foodstuffs; therefore, the amount of this compound ingested by humans through food is not known. The U.S. EPA (1979) has estimated the bioconcentration factor (BCF) of dichloropropane to be 20. This estimate is based on the octanol/water partition coefficients of dichloropropane. The weighted average BCF for edible portions of all aquatic organisms consumed by Americans is calculated to be 5.8.

C. Inhalation

Atmospheric levels of dichloropropane have not been positively determined. However, it is known that 5-10 percent of the dichloropropane which is applied to the soil as a fumigant is released to the air (Thomas and McKeury, 1973).

III. PHARMACOKINETICS

A. Absorption, Distribution and Metabolism

Pertinent data could not be located in available literature searches regarding the absorption of dichloropropane.

B. Excretion

Pertinent data could not be located in available literature searches regarding excretion of dichloropropane. In the rat, approximately 50 percent of an orally administered dose of dichlorocropane was eliminated in the urine in 24 hours (Hutson, et al. 1971).

IV. EFFECTS

A. Carcinogenicity

Only one study is reported on the carcinogenicity of dichloropropane. Heppel, et al. (1948) repeatedly exposed mice (37 exposure periods) to 1.76 mg dichloropropane per liter of air. Of the 80 mice, only three survived the exposure and subsequent observation period; however, the three survivors had multiple hepatomas at the termination of the experiment (13 months of age). Due to the high mortality, an evaluation based on this study cannot be made.

B. Mutagenicity

DeLorenzo, et al. (1977) and Bignami, et al. (1977) showed dichloropropane to be mutagenic in S. typhimurium strains TA 1535 and TA 100. Dichloropropane has also been shown to cause mutations in A. nidulans

(Bignami, et al. (1977), and to cause chromosomal aberrations in rat bone marrow (Dragusanu and Goldstein, 1975).

C. Teratogenicity

Pertinent information could not be located in available literature searches regarding teratogenicity.

D. Other Reproductive Effects

Pertinent information could not be located regarding other reproductive effects.

E. Chronic Toxicity

Pertinent information could not be located in available literature searches regarding chronic toxicity studies of dichloropropane exposure in humans. In one study by Heppel, et al. (1948) rats, guinea pigs, and dogs were exposed to 400 ppm of dichloropropane for 128 to 140 daily seven hour period (given five days per week). The only effect observed was a decreased weight in rats.

V. AQUATIC TOXICITY

A. Acute Toxicity

Two observed 96-hour LC_{50} values for the bluegill, Lepomis macrochirus, upon exposure to 1,2-dichloropropane were 280,000 and 320,000 µg/l (Dawson, et al. 1977; U.S. EPA, 1978). In the only freshwater invertebrate study reported, the 48-hour LC_{50} for Daphnia magna is 52,500 µg/l (U.S. EPA, 1979). Tidewater silverside, (Menidia bevyllina), has an observed 96- hour LC_{50} of 240,000 µg/l (Dawson, et al. 1977).

B. Chronic Toxicity

Chronic data are not available for any saltwater or freshwater species.

C. Plant Effects

The phytotoxicity of 1,2-dichloropropane has not been investigated.

D. Residues

No information available.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

The TLV for dichloropropane is 75 ppm (350 mg/m^3) (Am. Conf. Gov. Ind. Hyg., 1977). The draft water criteria for dichloropropane is 203 ug/l (U.S. EPA, 1979).

B. Aquatic

For 1,2-dichloropropane, the proposed draft criteria to protect freshwater aquatic life are 920 µg/l a 24-hour average and the concentration should not exceed 2,100 µg/l at any time. Criteria are not available for saltwater species (U.S. EPA, 1979).

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No. 79

Dichloropropane/Dichloropropenes

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.

DICHLOROPROPANES/DICHLOROPROPENES

SUMMARY

The major environmental source of dichloropropanes and dichloropropenes is from the use of these compounds as soil fumigants. Some mild kidney damage has been observed in rats chronically exposed to 1,3-dichlorpropene. Both dichloropropane and dichloropropene have been shown to be mutgenic in the Ames assay test. Data are not available to prove conclusively that these compounds are chemical carcinogens.

Aquatic toxicity studies suggest that the acute toxicity of the dichloropropanes decreases as the distance between the chlorine atoms increases. As an example, the reported 96-hour LC_{50} values for the bluegill, Lepomis macrochirus, for 1,1-, 1,2-, and 1,3-dichloropropane are 97,000, 280,000, and greater than 520,000 µg/l, respectively. For Daphnia magna, the corresponding reported 48-hour LC_{50} values are 23,000, 52,000, and 282,000 µg/l, respectively. Similar results have been obtained with marine organisms.

The dichloropropenes are considerably more toxic in acute exposure than the dichloropropanes. For 1,3-dichlorpropene, the 96-hour LC_{50} value for the bluegill is 6,060 µg/l compared to 520,000 µg/l for 1,3-dichloropropane. For Daphnia magna, the corresponding values are 6,150 and 282,000 µg/l, respectively. The EC_{50}, based on chlorophyll a for a freshwater alga, is 4,950 µg/l for 1,3-dichloropropene, and 48,000 for 1,3-dichloropropane. Data on measured residues could not be located in the available literature for any saltwater or freshwater species.

I. INTRODUCTION

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

Dichloropropanes (molecular weight 112.99) and dichloropropenes (molecular weight 110.97) are liquids at environmental temperatures. Their boiling points range from 76 to 120.4°C depending on the compound and the isomer. They are slightly denser than water, with densities ranging from 1.11 to 1.22. The principal uses of dichloropropanes and dichloropropenes are as soil fumigants for control of nematodes, in oil and fat solvents, and in dry cleaning and degreasing processes (Windholz, 1976). When heated to decomposition temperatures, 1,2-dichloropropane emits highly toxic fumes of phosgene, while 1,3-dichloropropene gives off toxic fumes of chlorides (Sax, 1975). Production of mixtures of dichloropropanes/dichloropropenes approached 60 million pounds per year prior to 1975 (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Dichloropropanes and dichloropropenes can enter the aquatic environment in discharges from industrial and manufacturing processes, as run-off from agricultural land, and from municipal effluents. These compounds have been identified but not quantified in New Orleans drinking water (Dowty, et al. 1975).

B. Food

Information was not found in the available literature concerning the concentrations of dichloropropanes and dichloropropenes in commercial food stuffs. Therefore, the amount of these compounds ingested by humans is not known. The U.S. EPA

(1979) has estimated the weighted average bioconcentration factors (BCFs) of dichloropropanes and dichloropropenes to range between 2.9 and 5.8 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficients of these compounds.

C. Inhalation

Atmospheric levels of dichloropropanes and dichloropropenes are not known. However, from information on loss of these compounds to the air after land application, it was estimated that, in California alone, about 72 tons (8 percent of the pesticide used) were released to the atmosphere in 1971 (Calif. State Dept. Agric. 1971).

III. PHARMACOKINETICS

A. Absorption, Distribution and Metabolism

Pertinent information regarding the absorption, distribution, and metabolism of the dichloropropanes and dichloropropenes could not be located in the available information.

B. Excretion

No human data are available on the excretion of dichloropropanes or dichloropropenes. In the rat, 80 to 90 percent of an orally administered dose of dichloropropane or dichloropropene was eliminated by all routes within 24 hours (Hutson, et al. 1971). Approximately 50 percent of the administered dose was eliminated in the urine within 24 hours.

IV. EFFECTS

A. Carcinogenicity

Information concerning the carcinogenicity of mixtures of dichloropropanes and dichloropropenes could not be located

in the available literature. However, cis-1,3-dichloropropane has produced local sarcomas at the site of repeated subcutaneous injections (Van Duuren, et al., in press). No remote treatment-related tumors were observed.

B. Mutagenicity

Mixtures of 1,2-dichloropropane and 1,3-dichloropropene are mutagenic to S. typhimurium strains TA 1535 and TA 100, as are the individual compounds. The mixture, but not the individual compounds, is also mutagenic to TA 1978 (in the presence of microsomal activation) indicating a frame-shift mutation not capable of being produced by the individual compounds.

C. Teratogenicity and Other Reproductive Effects

Pertinent information could not be located in the available literature.

D. Chronic Toxicity

Inhalation exposure of rats, guinea pigs, and dogs to 400 ppm of 1,2-dichloropropane for 128 to 140 daily 7-hour periods (5 days per week) decreased normal weight gain in rats (Heppel, et al., 1948). Inhalation exposures of rats to 3 ppm of 1,3-dichloropropene, 4 hours a day, for 125 to 130 days produced cloudy swelling in renal tubular epithelium which disappeared by 3 months after exposures ended (Torkelson and Oyen, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

Exposures of bluegill, Lepomis macrochirus, to 1,1-, 1,2-, and 1,3-dichloropropane under similar conditions yielded 96-hour LC_{50} values of 97,900, 280,000, and greater than 520,000

mg/l, respectively (U.S. EPA, 1978). These data suggest that toxicity decreases as the distance between the chlorine atoms increases. A reported 96-hour LC_{50} for 1,3-dichloropropene is 6,060 µg/l for the bluegill, approximately two orders of magnitude lower than for 1,3-dichloropropane (U.S. EPA, 1979). Under static test conditions, reported 48-hour LC_{50} values for 1,1-, 1,2-, and 1,3-dichloropropanes are 23,000, 52,500 and 282,000 µg/l, respectively, (U.S. EPA, 1978) for the only freshwater invertebrate species tested, Daphnia magna. The 48-hour LC_{50} value for 1,3-dichloropropene and Daphnia magna under static conditions is 6,150 µg/l (U.S. EPA, 1978).

The 96-hour LC_{50} values for the saltwater sheepshead minnow, Cyprinodon variegatus, exposed to 1,3-dichloropropane and 1,3-dichloropropene were 86,700 µg/l and 1,770 µg/l, respectively (U.S. EPA, 1978). Dawson, et al. (1977) obtained a 96-hour LC_{50} of 240,000 µg/l for the tidewater silverside, Menidia beryllina, for exposure to 1,2-dichloropropane.

For Mysidopsis bahia, the 96-hour LC_{50} for 1,3-dichloropropene was one-thirteenth that for 1,3-dichloropropane, i.e., 790 µg/l and 10,300 µg/l, respectively (U.S. EPA, 1978).

B. Chronic Toxicity

Chronic studies are limited to one freshwater study and one saltwater study. In an embryo-larval test, the chronic value for fathead minnows, Pimephales promelas, exposed to 1,3-dichloropropene was 122 µg/l (U.S. EPA, 1978). The chronic value for mysid shrimp, Mysidopsis bahia, was 3,040 µg/l for 1,3-dichloropropane in a life cycle study (U.S. EPA, 1978).

C. Plant Effects

For 1,3-dichloropropene, the 96-hour EC_{50} values, based on chlorophyll a concentrations and cell numbers of the freshwater alga, Selenastrum capricornutum, were 4,350 µg/l and 4,960 µg/l, respectively. The respective values obtained for 1,3-dichloropropane were 48,000 and 72,200 µg/l. Thus, the propene compound is much more toxic than the propane compound, as is true for the bluegill and Daphnia magna.

D. Residues

Measured steady-state bioconcentration factors (BCF) are not available for any dichloropropane or dichloropropene in any fresh or saltwater species. Based on octanol/water coefficients of dichloropropanes and dichloropropenes, the U.S. EPA (1979) has estimated the bioconcentration factors for these compounds to range between 10 and 35.

VI. Other Pertinent Information

In the non-aquatic environment, movement of 1,2-dichloropropane in the soil results from diffusion in the vapor phase, as these compounds tend to establish an equilibrium between the vapor phase, water and absorbing phases (Leistra, 1970). 1,2-dichloropropane appears to undergo minimal degradation in soil with the major route of dissipation appearing to be volatilization (Roberts and Staydin, 1976).

Following field application, movement of 1,3-dichloropropene in soil results in vapor-phase diffusion (Leistra, 1970). The distribution of 1,3-dichloropropene within soils depends on soil conditions. For example, cis-1,3-dichlorobenzene is chemically hydrolyzed in moist soils to the corresponding cis-

3-chloroalkyl alcohol, which can be microbially degraded to carbon dioxide and water by Pseudomonas sp. (Van Dijk, 1974).

VII. 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 may be changed.

A. Human

The TLV for dichloropropane is 75 ppm (350 mg/m^3) (Am. Conf. Gov. Ind. Hyg., 1977). The draft water criterion (U.S. EPA, 1979) for dichloropropane is 203 µg/l. The draft water criterion for dichloropropenes is 0.63 µg/l (U.S. EPA, 1979).

B. Aquatic

The draft criteria for the dichloropropanes and dichloropropenes to protect freshwater aquatic life are as follows (U.S. EPA, 1979):

Compound	24-Hour Average	Concentration not to be exceeded at any time
1,1-dichloropropane	410 µg/l	930 µg/l
1,2-dichloropropane	920 µg/l	2,100 µg/l
1,3-dichloropropane	4,800 µg/l	11,000 µg/l
1,3-dichloropropene	18 µg/l	250 µg/l

The draft criteria to protect saltwater species are as follows (U.S. EPA, 1979):

Compound	24-Hour Average	Concentration not to be exceeded at any time
1,1-dichloropropane	not derived	not derived
1,2-dichloropropane	400 µg/l	910 µg/l
1,3-dichloropropane	79 µg/l	180 µg/l
1,3-dichloropropene	5.5 µg/l	14 µg/l

DICHLOROPROPANES/DICHLOROPROPENES

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No. 80

Dichloropropanol

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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DICHLOROPROPANOL

Summary

There was no evidence found in the available literature to indicate that exposure to dichloropropanol produces carcinogenic effects. Conclusive evidence of mutagenic, teratogenic, or chronic effects of dichloropropanol was not found in the available literature. Acute exposure results in toxicity similar to that induced by carbon tetrachloride, including hepato- and nephrotoxicity. Data concerning the effects of dichloropropanol to aquatic organisms was not found in the available literature.

I. INTRODUCTION

This profile is based on computerized searches of Toxline, Biosis, and Chemical Abstracts, and review of other appropriate information sources as available. Dichloropropanol (molecular weight 128.9), a colorless, viscous liquid with a chloroform-like odor, refers to four isomers with the molecular formula $C_3H_6OCl_2$. The physical properties of each isomer are given below.

	Boiling Point	Density	Solubility (Weast, 1976)		
			Water	Alcohol	Ether
2,3-Dichloro-1-propanol	182°C	1.368	slight	miscible	miscible
1,3-Dichloro-2-propanol	174°C	1.367	very	very	miscible
3,3-Dichloro-1-propanol	82-83°C	1.316	not listed		
1,1-Dichloro-2-propanol	146-148°C	1.3334	slight	very	very

Additional physical data and synonyms of the above isomers are available in Heilbron (1965), Fairchild (1979), Sax (1979), Windholz (1976), and Verschueren (1977).

Dichloropropanol is prepared from glycerol, acetic acid, and hydrogen chloride. It is used as a solvent for hard resins and nitrocellulose, in the manufacture of photographic and Zapon lacquer, as a cement for celluloid, and as a binder for water colors (Windholz, 1976). The compound is considered to be a moderate fire hazard when exposed to heat, flame, or oxidizers, and a disaster hazard in that it may decompose at high temperatures to phosgene gas (Sax, 1979).

II. EXPOSURE

Dichloropropanol was detectable in the air of a glycerol manufacturing plant in the U.S.S.R. (Lipina and Belyakov, 1975). Unreacted dichloropropanol was also found in the wastewater effluent of a halohydrin manufacturing plant (Aoki and Katsube, 1975). No monitoring data are available to indicate ambient air or water levels of the compound.

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

Bioaccumulation data on dichloropropanol was not found in the available literature.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature on the metabolism, distribution, absorption, or excretion of dichloropropanol.

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

2,3-Dichloropropanol and 1,3-dichloropropanol were evaluated for mutagenicity by a modified Ames assay using S. typhimurium strains. Some evidence of mutagenic activity was seen, but the authors felt that further evidence and clarification of the metabolic activation pathway to mutagens via haloalkanols were necessary (Nakamura, et al. 1979).

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature.

D. Acute Toxicity

2,3-Dichloropropanol was found to have an oral LD_{50} in the rat of 90 mg/kg. The lowest published lethal concentration (LC_{LO}) in rats is 500 ppm by inhalation for 4 hours. A dose of 6,800 ug in the eye of the rabbit caused severe irritation (Fairchild, 1979). 1,3-Dichloropropanol was found to have an oral LD_{50} in the rat of 490 mg/kg and lowest published lethal concentration for inhalation exposure in rats of 125 ppm/4 hrs. Ten mg applied to the skin of the rabbit for 24 hours produced mild irritation, and 800 mg/kg was the LD_{50} for the same route and species (Fairchild, 1979).

Several references report the clinical indications of acute dichloropropanol intoxication as being similar to carbon tetrachloride poisoning, i.e., central nervous depression; hepatotoxicity, including hepatic cell necrosis and fatty infiltration; and renal toxicity, including fatty degeneration and necrosis of the renal tubular epithelium (Sax, 1979; Gosselin, et al. 1976).

V. AQUATIC TOXICITY

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

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The maximum allowable concentration of dichloropropanol in the working environment air in the U.S.S.R. is 5 mg/m^3 (Lipina and Belyakov, 1975).

The maximum allowable concentration in Class I waters for the production of drinking water is 1 mg/l (Verschueren, 1977).

B. Aquatic

The organoleptic limit in water set in the U.S.S.R. (1970) is 1.0 mg/l (Verschueren, 1977).

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No. 81

1,3-Dichloropropene

Health and Environmental Effects

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

APRIL 30, 1980

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1,3-DICHLOROPROPENE

SUMMARY

The major environmental source of dichloropropenes is from the use of a mixture of dichloropropenes and dichloropropanes as a soil fumigant. On chronic exposure of rats to dichloropropene mild kidney damage was observed. Dichloropropene has produced subcutaneous tumors at the site of injection, and has been shown to be mutagenic in bacteria. However, not enough information is available to classify this compound as a carcinogen.

The bluegill (Lepomis macrochirus) has a reported 96-hr LC_{50} value of 6060 µg/l; Daphnia magna has a reported 48-hr LC_{50} of 6130 µg/l. For the saltwater invertebrate, Mysidopsis bahia, a reported 96-hr LC_{50} value is 790 µg/l. In the only long-term study available, the value obtained for 1,3-dichloropropene toxicity to fathead minnows (Pimephales promelas) in an embryo-larval test is 122 µg/l. Based on chlorophyll a concentrations and cell numbers, the 96-hr EC_{50} values for the freshwater alga Selenastrum capricornutum are 4,950 and 4,960 µg/l, respectively; for the marine alga Skeletonema costatum, the respective values are 1,000 and 1,040 µg/l.

1,3-DICHLOROPROPENE

I. INTRODUCTION

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

1,3-dichloropropene (molecular weight 110.97) is a liquid at environmental temperatures. The isomers of 1,3-dichloropropene have boiling points of 104.3°C for the trans-isomer and 112°C for the cis-isomer, and the densities are 1.217 and 1.224 g/ml, respectively. The water solubility for the two isomers is approximately 0.275 percent. When heated to decomposition temperatures, 1,3-dichloropropene gives off toxic fumes of chlorides (Sax, 1975). Mixtures of cis- and trans- 1,3-dichloropropene and 1,2-dichloropropane are used as soil fumigants. In this document, dichloropropene will refer to either cis- or trans-1,3-dichloropropene. For more information regarding the dichloropropenes, the reader is referred to the EPA/ECAO Hazard Profile on Dichloropropanes/Dichloropropenes (U.S. EPA, 1979c).

II. EXPOSURE

A. Water

Dichloropropene can enter the aquatic environment in the discharges from industrial and manufacturing processes, in run-off from agricultural land, or from municipal effluents. This compound has been identified but not quantified in New Orleans drinking water (Dowty, et al. 1975).

B. Food

Information was found in the available literature concerning the concentration of dichloropropene in commercial foodstuffs. Thus, the amount of this compound ingested by humans is not known. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor (BCF) of dichloropropene to be 2.9 for the edible portions of fish and shellfish consumed by

Americans. This estimate is based on the octanol/water partition coefficient of dichloropropene.

C. Inhalation

Atmospheric levels of dichloropropene have not been measured. However, it is estimated that about 8 percent of the dichloropropene which is applied to the soil as a fumigant is released to the atmosphere (U.S. EPA, 1979a).

III. PHARMACOKINETICS

A. Absorption

Data on the absorption, distribution and metabolism of dichloropropene could not be located in the available literature.

Data on the excretion of dichloropropene by humans could not be located in the available literature. In the rat, however, approximately 80 percent of an orally administered dose of dichloropropene was eliminated in the urine within 24 hours (Hutson, et al. 1971).

IV. EFFECTS

A. Carcinogenicity

Van Duuren, et al. (1979) investigated the ability of dichloropropene to act as a tumor initiator or promoter in mouse skin, or to cause tumors after subcutaneous injection. Dichloropropene showed no initiation or promotion activity, and only local sarcomas developed in mice following subcutaneous administration. In none of the studies were treatment-related remote tumors observed.

B. Mutagenicity

DeLorenzo, et al. (1977) and Neudecker, et al. (1977) reported that dichloropropene was mutagenic in S. typhimurium strains TA1535 and TA100 but not in TA1978, TA1537, or TA98. Results did not differ with or without the

addition of liver microsomal fraction. Neudecker, et al. (1977) found the cis-isomer to be twice as reactive as the trans-isomer.

C. Teratogenicity and Other Reproductive Effects

No pertinent information regarding the teratogenicity and other reproductive effects could not be located in the available literature.

D. Chronic Toxicity

On exposure of rats to 3 ppm dichloropropene for period of 0.5, 1, 2 or 4 hours/day, 5 days a week for 6 months (Torkelson and Oyen, 1977), or rats, guinea pigs, and rabbits to 1 or 3 ppm of dichloropropene, 7 hours per day for 125-130 days over a 180-day period, only rats exposed 4 hours/day at 3.0 ppm showed an effect (U.S. EPA, 1979a). The only effect observed was a cloudy swelling of the renal tubular epithelium which disappeared by 3 months after exposures ended.

V. AQUATIC TOXICITY

A. Acute Toxicity

Tests on the bluegill, Lepomis macrochirus, yielded a 96-hr LC_{50} value of 6060 µg/l for 1,3-dichloropropene exposure. For Daphnia magna, the 48-hr LC_{50} value is 6,150 µg/l (U.S. EPA, 1978). The observed 96-hr LC_{50} for the saltwater myrid shrimp, Mysidopsis bahia, is 790 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

An embryo-larval test has been conducted with the fathead minnow (Pimephales promeles) and 1,3-dichloropropene. The observed chronic value was 122 µg/l (U.S. EPA, 1979a).

C. Plant Effects

Based on chlorophyll a concentrations and cell numbers, the 96-hr EC_{50} values for the freshwater alga, Selenestrum capricornutum, are 4,950

and 4,960 µg/l, respectively (U.S. EPA, 1978). The respective values for the saltwater alga Skeletonema costatum were 1,000 and 1,040 µg/l (U.S. EPA, 1978).

D. Residues

Measured steady-state bioconcentration factors (BCF) are not available for 1,3-dichloropropene. A BCF of 19 has been estimated based on the octonol/water coefficient for 1,3-dichloropropene (U.S. EPA, 1979a).

E. Other Relevant Information

Following field application, movement of 1,3-dichloropropene in soil results in vapor-phase diffusion (Leistra, 1970). The distribution of 1,3-dichloropropene within soils depends on soil conditions. For example, cis-1,3-dichloropropane is chemically hydrolyzed in moist soils to the corresponding cis-3-chloroalkyl alcohol, which can be microbially degraded to carbon dioxide and water by Pseudomonas sp. (Van Dijk 1974).

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 draft water criterion for 1,3-dichloropropene is 0.63 µg/l (U.S. EPA, 1979a).

B. Aquatic

The draft criterion to protect freshwater species is 18 µg/l as a 24-hr average not to exceed 250 µg/l at any time. For marine species, the value is 5.5 µg/l as a 24-hr average not to exceed 14 µg/l at any time (U.S. EPA, 1979).

1,3-DICHLOROPROPENE

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No. 82

Dieldrin

Health and Environmental Effects

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

APRIL 30, 1980

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SPECIAL NOTATION

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

DIELDRIN

SUMMARY

Dieldrin is a compound belonging to the group of cyclodiene insecticides. The chronic toxicity of low doses of dieldrin includes shortened life span, liver changes and teratogenic effects. The induction of hepatocellular carcinoma in mice by dieldrin leads to the conclusion that it is likely to be a human carcinogen. Dieldrin has been found to be non-mutagenic in several test systems. The WHO's acceptable daily intake for dieldrin is 0.0001 mg/kg/day.

The toxicity of dieldrin to aquatic organisms has been investigated in numerous studies. The 96-hour LC_{50} values for the common freshwater fish range from 1.1 to 360 µg/l. The acute toxicity is considerably more varied for freshwater invertebrates, with 96-hour LC_{50} values ranging from 0.5 µg/l for the stonefly to 740 µg/l for the crayfish. Acute LC_{50} values for eight saltwater fish species range from 0.66 to 24.0 µg/l in flow-through tests; LC_{50} values for estuarine invertebrates range from 0.70 to 240 µg/l. The only reported chronic values are 0.11 ug/l for steel head trout (Salmo guirdnes) in an embryolarval study and 0.4 µg/l for the guppy (Poecilia reticulata) in a life-cycle test. Both fresh and salt water algae are less sensitive to dieldrin toxicity than the corresponding fish and invertebrates. Bioconcentration factors were 128 for a fresnwater alga, 1395 for Daphnia magna, 2993 for the channel catfish, and 8000 for the edible tissues of the Eastern oyster.

DIELDRIN

I. INTRODUCTION

This profile is based on the draft Ambient Water Quality Criteria Document for Aldrin and Dieldrin (U.S. EPA, 1979). Dieldrin is a white crystalline substance with a melting point of 176-177°C and is soluble in organic solvents (U.S. EPA, 1979). The chemical name for dieldrin is 1,2,3,4,10,10-hexachlor-6,7-epoxy-1,4,4a,5,6,7,8,8a-octohydro-endo, exo-1,4:5,8-dimethanonaphthalene.

Dieldrin is extremely stable and persistant in the environment. Its persistance is due to its extremely low volatility (1.78×10^{-7} mm Hg at 20°C) and low solubility in water (186 µg/l at 25-29°C). The time required for 95 percent of the dieldrin to disappear from soil has been estimated to vary from 5 to 25 years depending on the microbial flora of the soil (Edwards, 1966). Patil, et al. (1972) reported that dieldrin was not degraded or metabolized in sea water or polluted water.

Dieldrin was primarily used as a broad spectrum insecticide until 1974, when the U.S. EPA restricted its use to termite control by direct soil injection, and non-food seed and plant treatment (U.S. EPA, 1979). From 1966 to 1970, the amount of dieldrin used in the United States decreased from 500 to approximately 335,000 tons (U.S. EPA, 1979). This decrease in use has been attributed primarily to increased insect resistance to dieldrin and to development of substitute materials. Although the production of dieldrin is restricted in the United States, formulated products containing dieldrin are imported from Europe (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Dieldrin has been applied to vast areas of agricultural land and aquatic areas in the United States, and in most parts of the world. As a result, this pesticide is found in most fresh and marine waters. Dieldrin has been measured in many freshwaters of the United States, with mean concentrations ranging from 5 to 395 ng/l in surface water and from 1 to 7 ng/l in drinking water (Epstein, 1976). Levels as high as 50 ng/l have been found in drinking water (Harris, et al. 1977). The half-life of dieldrin in water, 1 meter in depth, has been estimated to be 723 days (MacKay and Wolkoff, 1973).

B. Food

Dieldrin is one of the most stable and persistant organochlorine pesticides (Nash and Woolson, 1967), and because it is lipophilic, it accumulates in the food chain (Wurster, 1971). Its persistance in soil varies with the type of soil. (Matsumura and Boush, 1967).

The U.S. EPA (1971) estimated that 99.5 percent of all human beings have dieldrin residues in their tissue. These residues are primarily due to contamination of foods of animal origin. The overall concentration of dieldrin in the diet in the United States has been calculated to be approximately 43 ng/g of food consumed (Epstein, 1976). The U.S. EPA has estimated the weighted average bioconcentration factor for dieldrin to be 4,500 in the edible portion of fish and shellfish consumed by Americans (U.S. EPA, 1979). This estimate is based on measured

steady-state bioconcentration studies in several species of fish and shellfish.

C. Inhalation

Dieldrin enters the air through various mechanisms, such as spraying, wind action, water evaporation, and adhesion to particulates. The U.S. EPA detected dieldrin in more than 85 percent of the air samples tested between 1970-1972, with the mean levels ranging from 1 to 2.8 ng/m^3 (Epstein, 1976). From these levels, the average daily intake of dieldrin by respiration was calculated to be 0.035 to 0.098 µg.

Although dieldrin is no longer used in the United States, there is still the possibility of airborne contamination from other parts of the world.

D. Dermal

Dermal exposure to dieldrin is limited to those involved in its manufacture or application as a pesticide. Wolfe, et al. (1972) reported that exposure in workers was mainly through dermal absorption rather than inhalation. The ban on the manufacture of dieldrin in the United States has greatly reduced the risk of exposure.

III. PHARMACOKINETICS

A. Absorption

The absorption of dieldrin by the upper gastrointestinal tract begins almost immediately after oral administration in rats and has been found to vary with the amount of solvent used (Heath and Vandekar, 1964). These authors also demonstrated that absorption takes place via the portal vein, and that dieldrin

could be recovered from the stomach, small intestine, large intestine and feces one hour after oral administration.

B. Distribution

The distribution of dieldrin has been studied in numerous feeding experiments. Dieldrin has an affinity for fat, but high concentrations are also reported in the liver and kidney, with moderate concentrations in the brain one and two hours after administration in rats (Heath and Vandekar, 1964). Deichman, et al. (1968) fed dieldrin to rats for a period of 183 days. The mean concentration in the fat was 474 times that in the blood, while the concentration in the liver was approximately 29 times the blood concentration.

Additional animal studies on the distribution of dieldrin have shown that concentrations in tissues are dose related and may vary with the sex of the animal (Walker, et al. 1969). Matthews, et al. (1971) found that female rats administered oral doses of dieldrin had higher tissue levels of the compound than male rats. The females stored the compound predominatly as dieldrin. In males, other metabolites, identified as keto-dieldrin trans-hydro-aldrin and a polar metabolite, were detected.

The concentrations of dieldrin in human body fat were found to be 0.15 $\pm$ 0.02 µg/g for the general population and 0.36 µg/g in one individual exposed to aldrin (aldrin is metabolized to dieldrin) (Dale and Quinby, 1963). The mean concentrations of dieldrin in the fat, urine, and plasma of pesticide workers were 5.67, 0.242 and 0.0185 mg/g, respectively (Hayes and Curley, 1968). Correlations between the dose and length of exposure to dieldrin and the concentration of dieldrin in the blood and

other tissues have been reported (Hunter, et al. 1969). Dieldrin residues in the blood plasma of workers averaged approximately four times higher than that in the erythrocytes (Mick, et al. 1971).

C. Metabolism

The epoxidation of aldrin to dieldrin has been reported in many organisms, including man (U.S. EPA, 1979). The reaction is NADPH-dependent, and the enzymes have been found to be heat labile (Wong and Terriere, 1965).

The metabolism of dieldrin has been studied in several species, including mice, rats, rabbits, and sheep. Dieldrin metabolites have been identified in the urine and feces in the form of several compounds more polar than the parent compound (U.S. EPA, 1979). Bedford and Hutson (1976) summarized the four known metabolic products of dieldrin in rodents as 6,7-trans-dihydroxy-dihydro-aldrin (trans-diol) and tri-cyclic dicarborylic acid (both of which are products of the transformation of the epoxy group), the syn-12-hydroxy-dieldrin (a mono-hydro derivative), and the pentachloroketone. Male rats have been found to metabolize dieldrin more rapidly than females (U.S. EPA, 1979), and differences in the metabolism of dieldrin have been found between species (Baldwin, et al. 1972).

D. Excretion

Dieldrin is excreted mainly in the feces and, to some extent, in the urine in the form of several polar metabolites (U.S. EPA, 1979). However, rabbits fed ^{14}C-dieldrin over a 21 week period excreted 42 percent of the radioactivity by the end of 22 weeks, with 2 to 3 times as much excreted in the urine

as in the feces. Robinson, et al. (1969) found that 99 percent of the dieldrin fed to rats for 8 weeks was excreted during a subsequent 90-day observation period. The half-life of dieldrin in the liver and blood was 1.3 days for the period of rapid elimination and 10.2 days for a later, slower period. The half-life of dieldrin in adipose tissue and brain were 10.3 and 3.0 days, respectively.

The concentration of dieldrin in the urine of the general human population is 0.8 mg/l for man and 1.3 mg/l for women as compared to 5.3, 13.8, or 51.4 mg/l for men with low, medium, or high exposure (Ceuto and Biros, 1967). The half-life for dieldrin in the blood of humans ranges from 141-592 days with a mean of 369 days (Hunter, et al. 1969). Jager (1970) reported the half-life to be 266 days. Because there is a relationship between the concentration of dieldrin in the blood and that in adipose and other tissues, it seems likely that the half-life in the blood may reflect the over-all half-life in other tissues (U.S. EPA, 1979).

IV EFFECTS

A. Carcinogenicity

Dieldrin has produced liver tumors in several strains of mice according to six reports of chronic feeding studies (NCI, 1976 (43 FR 2450); Davis and Fitzhugh, 1962; Davis, 1965; Song and Harville, 1964; Walker, et al. 1972; Thorpe and Walker, 1973). In rats, dieldrin has failed to induce a statistically significant excess of tumors at any site in three strains during six chronic feeding studies (Treon and Cleveland, 1965; Cleveland, 1966;

Fitzhugh, et al. 1964; Deichman, et al. 1967; Walker, et al. 1969; Deichmann, et al. 1970).

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

B. Mutagenicity

Microbial assays concerning the mutagenicity of aldrin and dieldrin have yielded negative results even when some type of activation system was added (Fahrig, 1973; Bidwell, et al. 1975; Marshall, et al. 1976). A host-mediated assay and a dominant lethal test, also yielded negative results (Bidwell, et al. 1975). Majumdar, et al. (1977), however, found dieldrin to be mutagenic in S. typhiphimurium, although these positive results were questioned because several differences existed between their procedures and those recommended (U.S. EPA, 1977).

A decrease in the mitotic index was observed in vivo with mouse bone marrow cells and in vitro with human lung cells treated with 1 mg/kg and 1 µg/ml dieldrin, respectively (Majumdar, et al. 1976).

D. Teratogenicity

In 1967, Hathaway, et al. established that ^{14}C-dieldrin could cross the placenta in rabbits. Dieldrin caused significant increases in fetal death in hamsters, and increased fetal anomalies (i.e. open eye, webbed foot, cleft palate, and others)

in hamsters and mice when administered in single oral doses during gestation (hamsters 50, 30, 5 mg/kg and mice 25, 15, 2.5 mg/kg) (Ottolenghi, et al. 1974).

However, in subsequent studies no evidence has been found that dieldrin causes teratogenic effects in mice and rats (Chernoff, et al. 1975) or mice (Dix, et al. 1977).

D. Other Reproductive Effects

Deichmann (1972) reported that aldrin and dieldrin (25 mg/kg/diet) fed to mice for six generations affected fertility, gestation, viability, lactation, and survival of the young. However, no changes in weight or survival of fetuses were found in mice administered dieldrin for day 6 through 14 of gestation at doses already mentioned in this report (Ottolenghi, et al. 1974).

E. Chronic Toxicity

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

F. Other Relevant Information

Since aldrin and dieldrin are metabolized by way of the mixed function oxidase (MFO) system and dieldrin has been found to induce the production of these enzymes, any inducer or inhibitor of the MFO enzymes should affect the metabolism of dieldrin (U.S. EPA, 1979). Dieldrin fed in low doses prior to an acute dose of dieldrin alters its metabolism (Baldwin, et al. 1972). Dieldrin can effect the storage of DDT (U.S. EPA,

1979) and induce a greater number of tumors in mice when administered with DDT as compared to DDT alone (Walker, et al. 1972).

V. AQUATIC TOXICITY

A. Acute Toxicity

The acute toxicity of dieldrin has been investigated in numerous studies. Reported 96-hour LC_{50} values for freshwater fish are 1.1 to 9.9 µg/l for rainbow trout, Salmo gairdneri (Katz, 1961; Macek, et al. 1969); 16 to 36 µg/l for fathead minnows, Pimephales promelas (Henderson, et al. 1959; Tarzwell and Henderson, 1957); and 8 to 32 µg/l for the bluegill, Lepomis macrochirus (Henderson, et al. 1959; Macek, et al. 1969; Tarzwell and Henderson, 1957). Freshwater invertebrates appear to be more variable in their sensitivity to acute dieldrin toxicity. The 96-hour LC_{50} values range from 0.5 µg/l for the stone fly (Sanders and Cope, 1968) to 740 µg/l for the crayfish (Sanders, 1972).

The acute LC_{50} values for eight saltwater fish species range from 0.66 to 24.0 µg/l in flow-through tests (Butler, 1963; Earnest and Benville, 1972; Korn and Earnest, 1974; Parrish, et al. 1973; Schoettger, 1970; and Lowe, undated). LC_{50} values ranging from 0.7 to 240.0 µg/l have been reported for estuarian invertebrates species, with the most sensitive species tested being the commercially important pink shrimp, Penaeus duorarum (U.S. EPA, 1978).

B. Chronic Toxicity

Chronic toxicity has been studied in two species of freshwater fish. The chronic value for steelhead trout (Salmo gairdneri) from an embro-larval study is 0.11 µg/l (Chadwick

and Shumway, 1969). For the guppy, Poecilia reticulata, in a life-cycle test, the chronic value is 0.4 µg/l (Roelofs, 1971).

C. Plant Effects

Freshwater plants are less sensitive to dieldrin than freshwater fish or invertebrates. For example, a concentration of 100 µg/l caused a 22 percent reduction in the biomass of the alga Scenedlesmus quadricaudata (Stadnyk and Campbell, 1971), and 12,800 µg/l reduced growth by 50 percent in the diatom, Navicula seminulum after 5 days of exposure (Cairns, 1968). In a saltwater plant species growth rate was reduced at concentrations of approximately 950 µg/l (Batterton, et al. 1971).

D. Residues

Bioconcentration factors (BCF) have been determined for 9 freshwater species (U.S. EPA, 1978). Representative BCF values are 128 for the alga, Scendeasmus obliguus (Reinert, 1972, 1395 for Daphnia magna (Reinert, 1972), 2385-2993 for the channel catfish, Ictalurus punctatus (Shannon, 1977a; 1977b) and 68,268 for the yearling lake trout, Salvelinus namaycush (Reinert, et al. 1974). The edible tissue of the Eastern oyster, Crassostrea virginica, had a BCF value of 8000 after 392 days of exposure (Parrish, 1974). Spot, Leiostomus xanthurus, had a BCF of 2,300 after 35 days exposure to dieldrin (Parrish, et al. 1973).

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

The current exposure level for dieldrin set by OSHA is an air time-weighted average of 250 $\mu g/m^3$ for skin absorption (37 FR 22139). In 1969, the U.S. Public Health Service Advisory Committee recommended that the drinking water standard for dieldrin be 17 µg/l (Mrak, 1969). The U.N. Food and Agricultural Organization/World Health Organization's acceptable daily intake for dieldrin is 0.0001 mg/kg/day (Mrak, 1969).

The carcinogenicity data of Walker, et al. (1972) were used to calculate the draft ambient water quality criterion for dieldrin of 4.4×10^{-2} ng/l (U.S. EPA, 1979). This level keeps the lifetime cancer risk for humans below 10^{-5}.

B. Aquatic

The draft criterion to protect freshwater life is 0.0019 µg/l as a 24-hour average; the concentration should not exceed 1.2 µg at any time. To protect saltwater aquatic life, the draft criterion is 0.0069 µg/l as a 24-hour average; the concentration should not exceed 0.16 µg/l at any time.

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No. 83

o,o-Diethyl Dithiophosphoric Acid

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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

o,o-DIETHYL DITHIOPHOSPORIC ACID

Summary

There is no available information to indicate that o,o-diethyl dithiophosphoric acid produces carcinogenic, mutagenic, teratogenic, or adverse reproductive effects.

A possible metabolite of the compound, o,o-diethyl dithiophosphoric acid, did not show mutagenic activity in Drosophila, E. coli, or Saccharomyces.

The pesticide phorate, which may release o,o-diethyl dithiophosphoric acid as a metabolite, has shown some teratogenic effects in developing chick embryos and adverse reproductive effects in mice.

An acute value of 47.2 µg/l has been reported for rainbow trout exposed to a diethyl dithiophosphoric acid analogue, dioxathion. A synergistic toxic effect with the latter chemical and malathion is suggested.

I. INTRODUCTION

o,o-Diethyl hydrogen dithiophosphate, CAS registry number 298-06-6, also called o,o-diethyl phosphorodithioic acid or o,o-diethyl dithiophosphoric acid, is used primarily as an intermediate in the synthesis of several pesticides: azinphosmethyl, carbophenothion, dialifor, dioxathion, disulfoton, ethion, phorate, phosalone and terbufos. It is made from phosphorus pentasulfide (SRI, 1976).

II. EXPOSURE

A. Water

Pertinent data were not found in the available literature; however, if found in water, its presence would most likely be due to microbial action on phorate or disulfoton (Daughton, et al. 1979), or as a contaminant of any of the above pesticides for which it is a starting compound.

B. Food

Pertinent data were not found in the available literature; however, if present in food, the compound would probably originate from the same sources discussed above. Organophosphorus pesticide residues have been found in food (Vetterazzi, 1976).

C. Inhalation

Pertinent data were not found in the available literature; however, major exposure could come from fugitive emissions in manufacturing facilities.

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Information relating specifically to the absorption of o,o-diethyl dithophosphoic acid was not found in the available literature. Acute toxicity studies with the pesticides disulfoton and phorate indicate that these related organophosophorous compounds are absorbed following oral or dermal administration (Gaines, 1969).

B. Distribution

Pertinent data were not found in the available literature. Oral administration of labelled phorate, the S-(ethyl thio)methyl derivative of o,o-diethyl dithiophosphoric acid, to cows accumulated in liver, kidney, lung, alimentary tract, and glandular tissues; fat samples showed very low residues (Bowman and Casida, 1958).

C. Metabolism

Pertinent data were not found in the available literature. Metabolism studies with disulfoton (Bull, 1965) and phorate (Bowman and Casida, 1958) indicate that both compounds are converted to diethyl phosphorodithioate, diethyl phorphorothioate, and diethyl phosphate.

D. Excretion

Pertinent data were not found in the available literature. Based on animal studies with related organophosphorous compounds, the parent compound and its oxidative metabolites may be expected to eliminated primarily in the urine (Matsumura, 1975).

IV. EFFECTS

A. Carcinogenesis

The dioxane s-s diester with o,o-diethyl dithiophosphoric acid, dioxathion, has been tested for carcinogenicity in mice and rats by

long-term feeding. No carcinogenic effects were noted in either species (NCI, 1978).

B. Mutagenicity

Diethyl phosphorothioate, a possible metabolite of the parent compound, did not show mutagenic activity in Drosophila, E. coli, or Saccharomyces (Fahrig, 1974).

C. Teratogenicity

Pertinent data were not found in the available literature. Injection of phorate into developing chick embryos has been reported to produce malformations (Richert and Prahlad, 1972).

D. Other Reproductive Effects

Pertinent data were not found in the available literature. An oral feeding study conducted in mice with phorate (0.6 to 3.0 ppm) indicated that the highest level of compound did produce some adverse reproductive effects (American Cyanamid, 1966). Chronic feeding of mice with technical dioxathion at levels of 450 to 600 ppm produced some testicular atrophy (NCI, 1978).

E. Chronic Toxicity

Chronic feeding of technical dioxathion produced hyperplastic nodules in livers of male mice. o,o-Diethyl dithiophosphoric acid, like other organophosphates, is expected to produce cholinesterase inhibition (NAS, 1977).

V. AQUATIC TOXICITY

A. Acute

Marking (1977) reports on LC_{50} value of 47.2 µg/l for rainbow trout (Salmo gairdneri) exposed to the dithiodioxane analogue of bis(o,o-diethyl dithiophosphoric acid), dioxathion, and an LC_{50} value of

3.44 µg/l when this latter compound is applied in combination with malathion. The synergistic action with malathion suggests that the combination is more than eight times as toxic as either of the individual chemicals.

B. Chronic, Plant Effects, and Residues.

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES

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

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No. 84

O,O-Diethyl-S-methyl Phosphorodithioate

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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o,o-DIETHYL-S-METHYL PHOSPHORODITHIOATE

Summary

There is no available information on the possible carcinogenic, mutagenic, teratogenic or adverse reproductive effects of o,o-diethyl-S-methyl phosphorodithioate. Pesticides containing the o,o-diethyl phosphorodithioate moiety did not show carcinogenic effects in rodents (dioxathion) or teratogenic effects in chick embryos (phorate). The possible metabolite of this compound, o,o-diethyl phosphorothioate, did not show mutagenic activity in Drosophila, E. coli, or Saccharomyces. o,o-Diethyl-S-methyl phosphorodithioate, like other organophosphate compounds, is expected to produce cholinesterase inhibition in humans.

There is no available data on the aquatic toxicity of this compound.

o,o-DIETHYL-S-METHYL PHOSPHORODITHIOATE

I. INTRODUCTION

o,o-Diethyl-S-methyl phosphorodithioate (CAS registry number 3288-58-2) is described in German patents 1,768,141 (CA 77:151461s) and 1,233,390 (CA 66:115324p). The latter states the compound has "partly insecticidal, acaricidal and fungicidal activity" and is useful as an intermediate for organic synthesis. It has the following physical and chemical properties:

Formula:	C_5H_{13}
Molecular Weight:	200
Boiling Point: (CA 55:8335h)	100°C to 102°C (4 torr)
Density: (CA 55:8335h)	1.192420

Pertinent data were not found in the available literature with respect to production, consumption or the current use of this compound.

II. EXPOSURE

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Information relating specifically to the absorption of o,o-diethyl-S-methyl phosphorodithioate was not found in the available literature. Oral administration of the S-ethylthio derivative of this compound, the insecticide phorate, indicates that this derivative is absorbed from the gastrointestinal tract (Bowman and Casida, 1958).

B. Distribution

Pertinent data were not found in the available literature. Studies with ^{32}P radiolabelled phorate in the cow indicated that following oral administration, residues were found in the liver, kidney, lung,

alimentary tract, and glandular tissues; fat samples showed very low residues (Bowman and Casida, 1958).

C. Metabolism

Pertinent data were not found in the available literature. Based on metabolism studies with various organophosphates in mammals, o,o-diethyl-S-methyl phosphorodithioate may be expected to undergo hydrolysis to diethyl phosphorodithioic acid, diethyl phosphorothioic acid, and diethyl phosphoric acid (Matsumura, 1975).

D. Excretion

Pertinent data were not found in the available literature. Related metabolites (o,o-diethyl phosphorodithioic, phosphorothioic, and phosphoric acids) have been identified in the urine of rats fed phorate (Bowman and Casida, 1958).

IV. EFFECTS

A. Carcinogenicity

Pertinent data were not found in the available literature. The dioxane-S-S-diester with o,o-diethyl phosphorodithioate, dioxathion, has been tested for carcinogenicity in mice and rats by long-term feeding. No carcinogenic effects were noted in either species (NCI, 1978).

B. Mutagenicity

Pertinent data were not found in the available literature. Diethyl phosphorothioate, a possible metabolite of the parent compound, did not show mutagenic activity in Drosphila, E. coli, or Saccharomyces (Fahrig, 1974).

C. Teratogenicity

Pertinent data were not found in the available literature. Injection of phorate into developing chick embryos has been reported to produce malformations (Richert and Prahlad, 1972).

D. Other Reproductive Effects

Pertinent data were not found in the available literature. An oral feeding study conducted in mice with phorate (0.6 to 3.0 ppm) indicated that the highest level of compound did produce some adverse reproductive effects (American Cyanamid, 1966). Chronic feeding of rats with technical dioxathion at levels from 450 to 600 ppm produced some testicular atrophy (NCI, 1978).

E. Chronic Toxicity

Pertinent data were not found in the available literature. Chronic feeding of technical dioxathion produced hyperplastic nodules in the livers of male mice. O,O-Diethyl-S-methyl phosphorodithioate, like other organophosphates, is expected to produce cholinesterase inhibition (NAS, 1977).

V. AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

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

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No. 85

Diethyl Phthalate

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

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DIETHYL PHTHALATE

SUMMARY

Diethyl phthalate has been shown to produce mutagenic effects in the Ames Salmonella assay.

Teratogenic effects were reported following i.p. administration of diethyl phthalate to pregnant rats. This same study has also indicated fetal toxicity and increased resorptions after i.p. administration of DEP.

Evidence that diethyl phthalate produces carcinogenic effects has not been found.

A single clinical report indicates that the development of hepatitis in several hemodialysis patients may have been related to leaching of diethyl phthalate from the plastic tubings utilized.

Diethyl phthalate appears to be more toxic for marine species acutely tested, with a concentration of 7,590 µg/l being reported as the LC_{50} in marine invertebrates. The data base for the toxic effects of diethyl phthalates to aquatic organisms is insufficient to draft criterion for their protection.

DIETHYL PHTHALATE

I. INTRODUCTION

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

Diethyl phthalate (DEP) is a diester of the ortho form of benzene dicarboxylic acid. The compound has a molecular weight of 222.23, specific gravity of 1.123, boiling point of 296.1°C, and is insoluble in water (U.S. EPA, 1979a).

DEP is used as a plasticizer for cellulose ester plastics and as a carrier for perfumes.

The 1977 current production of diethyl phthalate was: 8.75×10^3 tons/year (U.S. EPA, 1979a).

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

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of the phthalates may occur through leaching of plasticizers from plastics, volatilization of phthalates from plastics, and the incineration of plastic items. Human exposure to phthalates includes contaminated foods and fish, dermal application in cosmetics, and parenteral administration by use of plastic blood bags, tubings, and infusion devices (mainly DEHP release) (U.S. EPA, 1979a).

Monitoring studies have indicated that most water phthalate concentrations are in the ppm range, or 1-2 µg/l (U.S. EPA, 1979a). Industrial air monitoring studies have measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1975). Information on levels of DEP in foods is not available. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for DEP to be 270 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

III. PHARMACOKINETICS

Specific information is not available on the absorption, metabolism, distribution, or excretion of DEP. The reader is referred to a general coverage of phthalate metabolism in the phthalate ester hazard profile (U.S. EPA, 1979b).

IV. EFFECTS

A. Carcinogenicity

Pertinent information could not be located in the available literature.

B. Mutagenicity

Diethyl phthalate has been shown to produce mutagenic effects in the Ames Salmonella assay (Rubin, et al. 1979).

C. Teratogenicity

Administration of DEP to pregnant rats by i.p. injection has been reported to produce teratogenic effects (Singh, et al. 1972).

D. Other Reproductive Effects

Fetal toxicity and increased resorptions were produced following i.p. injection of pregnant rats with DEP (Singh, et al. 1972).

E. Chronic Toxicity

A single clinical report has been cited by the U.S. EPA (1979a) which correlated leaching of DEP from hemodialysis tubing in several patients with hepatitis. Characterization of all compounds present in the hemodialysis fluids was not done.

V. AQUATIC TOXICITY

A. Acute Toxicity

Among aquatic organisms, the bluegill sunfish, Lepomis macrochirus, has been shown to be acutely sensitive to diethyl phthalate; a 96-hour static LC_{50} of 98,200 µg/l is reported (U.S. EPA, 1978). For the freshwater invertebrate, Daphnia magna, a 48-hour static LC_{50} of 51,100 µg/l was obtained. Marine organisms proved to be more sensitive, with the sheepshead minnow, Cyprinodon variegatus, showing a 96-hour static LC_{50} of 29,600 µg/l, while the mysid shrimp, Mysidopsis bahia, showed an 96-hour static LC_{50} of 7,590 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

Pertinent information could not be located in the available literature.

C. Plant Effects

Effective concentrations based on chlorophyl a content and cell number for the freshwater alga, Selena-

strum capricornutum, ranged from 85,600 to 90,300 µg/l, while the marine alga, Skeletonema costatum, was more sensitive, with effective concentrations ranging from 65,500 to 85,000 µg/l.

D. Residues

A bioconcentration of 117 was obtained for the freshwater invertebrate, Daphnia magna.

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

A. Human

Based on "no effect" levels observed in chronic feeding studies with rats or dogs, the U.S. EPA has calculated an acceptable daily intake (ADI) level of 438 mg/day for DEP.

The recommended water quality criterion level for protection of human health is 60 mg/l for DEP (U.S. EPA, 1979a).

B. Aquatic

Data are insufficient to draft criterion for the protection of either freshwater or marine organisms (U.S. EPA, 1979a).

DIETHYL PHTHALATES

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No. 86

Dimethylnitrosamine

Health and Environmental Effects

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APRIL 30, 1980

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DIMETHYLNITROSAMINE

SUMMARY

Dimethylnitrosamine produces liver and kidney tumors in rats. It is mutagenic in several assay systems. No information specifically dealing with the teratogenicity, chronic toxicity or other standard toxicity tests of dimethylnitrosamine was available for review.

Hepatocellular carcinoma has been induced in rainbow trout administered 200 to 800 µg dimethylnitrosamine in their diet.

DIMETHYLNITROSAMINE

I. INTRODUCTION

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

Specific information on the properties, production, and use of dimethylnitrosamine was not available. For general information on dimethylnitrosamine, refer to the ECAO/EPA Hazard Profile for Nitrosamines (U.S. EPA, 1979b).

Dimethylnitrosamine can exist for extended periods of time in the aquatic environment (Tate and Alexander, 1975; Fine, et al., 1977a).

II. EXPOSURE

A. Water

Dimethylnitrosamine has been detected at a concentration of 3 to 4 µg/l in wastewater samples from waste treatment plants adjacent to, or receiving effluent from, industries using nitrosamines or secondary amines in production operations (Fine, et al., 1977b).

B. Food

Dimethylnitrosamine was found to be present in a variety of foods (including smoked, dried or salted fish, cheese, salami, frankfurters, and cured meats) in the 1 to 10 µ/kg range and occasionally at levels up to 100 µg/kg (Montesano and Bartsch, 1976).

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for dimethylnitrosamine for the edible portions of fish and shellfish consumed by

Americans to be 0.06. This estimate is based on the n-octanol/water partition coefficient of dimethylnitrosamine.

C. Inhalation

Dimethylnitrosamine has been detected in ambient air samples collected near two chemical plants, one using the amine as a raw material and the other discharging it as an unwanted byproduct (Fine, et al., 1977a).

Tobacco smoke contains dimethylnitrosamine. The intake of dimethylnitrosamine from smoking 20 cigarettes per day has been estimated at approximately 2 µg/day (U.S. EPA, 1979a).

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature.

B. Distribution

Following intravenous injection into rats, dimethylnitrosamine is rapidly and rather uniformly distributed throughout the body (Magee, 1972).

C. Metabolism and Excretion

In vitro studies have demonstrated that the organs in the rat with the major capacity for metabolism of dimethylnitrosamine are the liver and kidney (Montesano and Magee, 1974). After administration of ^{14}C-labeled dimethylnitrosamine to rats or mice, about 60 percent of the isotope appears as $^{14}CO_2$ within 12 hours, while 4 percent is excreted

in the urine (Magee, et al., 1976). Dimethylnitrosamine is excreted in the milk of female rats (Schoental, et al., 1974).

IV. EFFECTS

A. Carcinogenicity

Chronic feeding of dimethylnitrosamine at doses of 50 mg/kg induces liver tumors in rats (Magee and Barnes, 1956; Rajewski, et al., 1966). Shorter, more acute exposures to dimethylnitrosamine ranging from 100 to 200 mg/kg produce kidney tumors in rats and liver tumors in hamsters (Magee and Barnes, 1959; Tomatis and Cafis, 1967). A single unspecified intraperitoneal dose given to newborn mice induced hepatocellular carcinomas (Toth, et al., 1964).

B. Mutagenicity

Dimethylnitrosamine and diethylnitrosamine have been reported to induce forward and reverse mutations in S. typhimurium, E. coli, Neurospora crassa and other organisms; gene recombination and conversion in Saccharomyces cerevisiae; "recessive lethal mutation" in Drosophila; and chromosome aberrations in mammalian cells (Montesano and Bartsch, 1976). Nitrosamines must be metabolically activated to be mutagenic in microbial assays (U.S. EPA, 1979a). Negative results were obtained in the mouse dominant lethal test (U.S. EPA, 1979a).

C. Teratogenicity and Other Reproductive Effects

Pertinent information could not be located in the available literature on the teratogenicity and other reproductive effects of dimethylnitrosamine.

D. Chronic Toxicity

Pertinent information could not be located in the available literature on the chronic activity of dimethylnitrosamines.

E. Other Relevant Information

Aminoacetonitrile, which inhibits the metabolism of dimethylnitrosamine, prevented the toxic and carcinogenic effects of dimethylnitrosamine in rat livers (Magee, et al., 1976).

Ferric oxide, cigarette smoke, volatile acids, aldehydes, methyl nitrite, and benzo(a)pyrene have been suggested to act in a cocarcinogenic manner with dimethylnitro-samine (Stenback, et al., 1973; Magee, et al., 1976).

V. AQUATIC TOXICITY

Pertinent information about acute and chronic aquatic toxicity was not found in the available literature. Additionally, no mention was made in any reports about plant effects or residues.

One study reported that Shasta strain rainbow trout (Salmo gairdneri), fed dimethylnitrosamine in their diet for 52 weeks, developed a dose-response incidence of hepatocellular carcinoma during a range of exposures from 200 to 800 mg dimethylnitrosamine per kg body weight 52 to 78 weeks after dosing (Grieco, 1978).

VI. EXISTING GUIDELINES AND STANDARDS

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

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

A. Human

The U.S. EPA (1979a) has estimated that the water concentrations of dimethylnitrosamine corresponding to lifetime cancer risks for humans of 10^{-5}, 10^{-6}, or 10^{-7} are 0.026 µg/l, 0.0026 µg/l, and 0.00026 µg/l, respectively.

B. Aquatic

Data are insufficient to draft freshwater marine criteria for dimethylnitrosamine.

DIMETHYLNITROSAMINE

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No. 87

2,4-Dimethylphenol

Health and Environmental Effects

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2,4-DIMETHYLPHENOL

Summary

2,4-Dimethylphenol (2,4-DMP) is an intermediate in a number of industrial and agricultural products. The main route of exposure for humans is dermal with 2,4-DMP being readily absorbed through the skin.

Little data is available on the mammalian effects of 2,4-DMP. Tests on mice conclude that the compound may be a promoting agent in carcinogenesis. 2,4-DMP inhibits vasoconstriction in isolated rat lungs; this ability may cause adverse health effects in chronically exposed humans.

A reported 96-hour LC_{50} value for fathead minnows is 16,750 µg/l; chronic value using embryo-larval stages of the same species is 1,100 µg/l. Daphnia magna has an observed 48-hour LC_{50} value of 2,120 µg/l. In limited testing, one aquatic alga and duckweed are over 100 times less sensitive than the Daphnia in acute exposures. The bioconcentration factor for 2,4- dimethylphenol is 150 for the bluegill. From half-life studies, residues of the chemical are not a potential hazard for aquatic species.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for 2,4-Dimethylphenol (U.S. EPA, 1979).

2,4-Dimethylphenol (2,4-DMP) is derived from coal and petroleum sources and occurs naturally in some plants. 2,4-DMP ($C_8H_{10}O$) is usually found with the five other dimethylphenol and three methylphenol isomers. It has a molecular weight of 122.17 and normally exists as a colorless crystalline solid. 2,4-DMP has a melting point of 27 to 28°C, a boiling point of 210°C (at 760 mm Hg), a vapor pressure of 1 mm Hg at 52.8°C, and a density of 0.0965 g/ml at 20°C (U.S. EPA, 1979).

2,4-DMP is a weak acid (pk_a-10.6) and is soluble in alkaline solutions. It readily dissolves in organic solvents and is slightly soluble in water (Weast, 1976).

2,4-DMP is a chemical intermediate in the manufacture of a number of industrial and agricultural products, including phenolic antioxidants, disinfectants, solvents, pharmaceuticals, insecticides, fungicides, plasticizers, rubber chemicals, polyphenylene oxide, wetting agents, and dyestuffs. It is also found in lubricants, gasolines, and cresylic acid (U.S. EPA, 1979).

Very little information exists on the environmental persistence of 2,4-DMP. Complete biodegradation of 2,4-DMP occurs in approximately two months (U.S. EPA, 1979); however, no environmental conditions were described.

II. EXPOSURE

A. Water

U.S. EPA (1979) reported that no specific data are available on the amounts of 2,4-DMP in drinking water. The concentrations of 2,4-DMP present in drinking water vary depending on the amounts present in untreated water

and on the efficiency of water treatment systems in removing phenolic compounds. In the U.S., the gross annual discharge of 2,4-DMP into waters was estimated to be 100 tons in 1975 (Versar, 1975). Manufacturing was the largest source of the discharge. Leachates from municipal and industrial wastes also contain the compound (U.S. EPA, 1979).

Hoak (1957) determined that, at 30°C, the odor threshold for 2,4-DMP was 55.5 µg/l.

B. Food

DMP's occur naturally in tea (Kaiser, 1967), tobacco (Baggett and Morie, 1973; Spears, 1963), marijuana (Hoffmann, et al. 1975), and a conifer (Gornostaeva, et al. 1977). There is no evidence to suggest that dimethylphenols occur in many plants used for food; however, it may be assumed that trace amounts are ingested (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for 2,4-DMP to be 340 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the measured steady-state bioconcentration studies in the bluegill.

C. Inhalation

2,4-Dimethylphenol has been found in commercial degreasing agents (NIOSH, 1978), cresol vapors (Corcos, 1939), cigarette smoke condensates (Baggett and Morie, 1973; Hoffmann and Wynder, 1963; Smith and Sullivan, 1964), marijuana cigarette smoke (Hoffmann, et al. 1975) and vapors from the combustion and pyrolysis of building materials (Tsuchiya and Sumi, 1975). Concentrations in smoke condensates from six different brands of American cigarettes ranged from 12.7 to 20.8 mg/cigarette without filters and 4.4 to 9.1 mg/cigarette with filters (Hoffman and Wynder, 1963).

There is no evidence in the available literature indicating that humans are exposed to 2,4-DMP other than as components of complex mixtures. Adverse health effects have been found in workers exposed to mixtures containing amounts of 2,4-DMP; however, the effects were not attributed to dimethylphenol exposure per se (NIOSH, 1978).

D. Dermal

Absorption through the skin is thought to be the primary route of human exposure to complex mixtures containing 2,4-DMP (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

2,4-DMP is readily absorbed through the skin (U.S. EPA, 1979). The dermal LD_{50} for molten 2,4-DMP is 1,040 mg/kg in the rat (Uzhdovini, et al. 1974).

B. Distribution

U.S. EPA (1979) found no pertinent data on the distribution of 2,4-DMP in humans or animals in the available literature. 2,6- or 3,4-DMP given orally to rats for eight months caused damage to the liver, spleen, kidneys, and heart (Maazik, 1968).

C. Metabolism

Urinary metabolites, resulting from oral administration of 850 mg of 2,4-DMP to rabbits, were primarily ether-soluble acid and ether glucuronide, with lesser amounts of ethereal sulfate, ester glucuronide and free non-acidic phenol (Bray, et al. 1950). Similar metabolism of the other dimethylphenol positional isomers was reported.

D. Excretion

A study done on rabbits by Bray, et al. (1950) indicates rapid metabolism and excretion of 2,4-DMP.

IV. EFFECTS

A. Carcinogenicity

Epidemiologic studies of workers exposed to 2,4-DMP were not located in the available literature.

In a carcinogenicity bioassay, 26 female Sutter mice were dermally exposed to 25 µl of 20 percent 2,4-DMP in benzene twice weeekly for 24 weeks. Twelve percent of the exposed mice developed carcinomas; however, benzene was not evaluated by itself in this study (Boutwell and Bosch, 1959). In a related study, Boutwell and Bosch (1959) applied 25 µl of 20 percent 2,4-DMP in benzene to the skin of female Sutter mice twice a week for 23 weeks following a single application of a subcarcinogenic dose (75 µg) of DMBA. Papillomas or carcinomas developed in 18 percent of the mice, indicating that 2,4-DMP may be a promoting agent for carcinogenesis.

Fractions of cigarette smoke condensate containing phenol, methylphenols and 2,4-DMP have been shown to promote carcinogenesis in mouse skin bioassays (Lazar, et al. 1966; Bock, et al. 1971; Roe, et al. 1959).

B. Mutagenicity, Teratogenicity and Other Reproductive Effects

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

C. Chronic Toxicity

Pertinent information concerning the chronic effects of 2,4- DMP was not located in the available literaturel(U.S. EPA, 1979); however, data was available on other positional isomers. Examination of rats treated orally with 6 mg/kg of 2,6-dimethylphenol or 14 mg/kg of 3,4-dimethylphenol for eight months revealed fatty dystrophy and atrophy of the hepatic cells,

hyaline-droplet dystrophy in the kidneys, proliferation of mycloid and reticular cells, atrophy of the lymphoid follicles of the spleen, and parenchymatous dystrophy of the heart cells (Maazik, 1968).

D. Other Relevant Information

Tests on isolated rat lungs indicate that 2,4-DMP may inhibit vasoconstriction, most likely due to its ability to block ATP (Lunde, et al. 1968). Because of 2,4-DMP's physiological activity, U.S. EPA (1979) reports that chronic exposure to the compound may cause adverse health effects in humans.

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature regarding any saltwater species.

A. Acute Toxicity

A reported 96-hour LC_{50} value for juvenile fathead minnows is 16,750 µg/l (U.S. EPA, 1979). For the freshwater invertebrate Daphnia magna, the observed 48-hour LC_{50} is 2,120 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

Based on an embryo-larval test with the fathead minnow, Pimephales promelas, the derived chronic value is 1,100 µg/l (U.S. EPA, 1978). No chronic values are available for invertebrate species.

C. Plant Effects

Based on chlorosis effects, the reported LC_{50} for duckweed, Lemna minor, is 292,800 µg/l for 2,4-dimethylphenol exposure (Blackman, et al. 1955).

D. Residues

A bioconcentration factor of 150 was obtained for the bluegill. The biological half-life in the bluegill is less than one day, indicating

that 2,4-dimethylphenol residues are probably not a potential hazard for aquatic organisms (U.S. EPA, 1978).

VI. EXISTING GUIDELINES AND STANDARDS

Standards have not been promulgated for 2,4-DMP for any sector of the environment or workplace.

A. Human

The draft criterion for 2,4-dimethylphenol in water recommended by the U.S. EPA (1979) is 15.5 µg/l based upon the prevention of adverse effects attributable to the organoleptic properties of 2,4-DMP.

B. Aquatic

For 2,4-dimethylphenol, the draft criterion to protect freshwater aquatic life is 38 µg/l as a 24-hour average; the concentration should not exceed 86 µg/l at any time. No criterion exists for saltwater species (U.S. EPA, 1979).

2,4-DIMETHYLPHENOL

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No. 88

Dimethyl Phthalate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

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DIMETHYL PHTHALATE

SUMMARY

Dimethyl phthalate has been shown to produce mutagenic effects in the Ames Salmonella assay.

Administration of dimethyl phthalate to pregnant rats by i.p. injection has been reported to produce teratogenic effects in a single study. Other reproductive effects produced by dimethyl phthalate included impaired implantation and parturition in rats following i.p. administration.

Chronic feeding studies in female rats have indicated an effect of dimethyl phthalate on the kidneys. There is no evidence to indicate that dimethyl phthalate has carcinogenic effects.

Among the four aquatic species examined, freshwater fish and invertebrates appeared to be more sensitive than their marine counterparts. Acute toxicity values at concentrations of 49,500 µg/l were obtained for freshwater fish. Criterion could not be drafted because of insufficient data concerning the toxic effects of dimethyl phthalates to aquatic organisms.

DIMETHYL PHTHALATE

I. INTRODUCTION

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

Dimethyl phthalate (DMP) is a diester of the ortho form of benzene dicarboxylic acid. The compound has a molecular weight of 194.18, specific gravity of 1.189, boiling point of 282°C, and a solubility of 0.5 gms in 100 ml of water (U.S. EPA, 1979a).

DMP is used as a plasticizer for cellulose ester plastics and as an insect repellant.

Current Production: 4.9×10^3 tons/year (in) 1977 (U.S. EPA, 1979a).

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

For additional information regarding the phthalate esters in general, the reader is referred to the EPA/ECAO Hazard Profile on Phthalate Esters (U.S. EPA, 1979b).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of phalates may occur through leaching of the compound from plastics, volatilization from plastics, or the incineration of plastic items. Sources of human exposure to phthalates include contaminated foods and fish, dermal application, and parenteral administration

by use of plastic blood bags, tubing, and infusion devices (mainly DEHP release). Relevant factors in the migration of phthalate esters from packaging materials to food and beverages are: temperature, surface area contact, lipoidial nature of the food, and length of contact (U.S. EPA, 1979a).

Monitoring studies have indicated that most water phthalate concentrations are in the ppm range, or 1-2 µg/liter (U.S. EPA, 1979a). Industrial air monitoring studies have measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1973). Information on levels of DMP in foods is not available.

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for BMP to be 130 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the measured steady-state bioconcentration studies in bluegills.

III. PHARMACOKINETICS

Specific information is not available on the absorption, distribution, metabolism, or excretion of DMP. The reader is referred to a general coverage of phthalate metabolism in the phthalate ester hazard profile (U.S. EPA, 1979b).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

Dimethyl phthalate has been shown to produce mutagenic effects in the Ames Salmonella assay (Rubin, et al. 1979).

C. Teratogenicity

Administration of DMP to pregnant rats by i.p. injection has been reported to produce teratogenic effects (Singh, et al. 1972). Intraperitoneal administration of DMP to pregnant rats in another study did not result in teratogenic effects (Peters and Cook, 1973).

D. D. Other Reproductive Effects

Adverse effects by DMP on implantation and parturition were reported by Peters and Cook (1973) following i.p. administration of the compound to rats.

E. Chronic Toxicity

Two-year feeding studies with dietary DMP have produced some kidney effects in female rats and minor growth effects (Draize, et al. 1948).

V. AQUATIC TOXICITY

A. Acute Toxicity

Two freshwater species were examined for acute toxicity from dimethyl phthalate exposure. The 48-hour static LC_{50} for the Cladoceran, Daphnia magna, was 33,000 µg/l (U.S. EPA, 1978). The 96-hour static LC_{50} value for the bluegill, Lepomis macrochirus, was 49,500 µg/l. For marine species, 96-hour static LC_{50} values for the sheepshead minnow, Cyprinodon variegatus, and mysid shrimp, Mysidopsis bahia, were 58,000 and 73,700 µg/l, respectively.

B. Chronic Toxicity

Pertinent information could not be located in the available literature.

C. Plant Effects

Effective concentrations based on chlorophyl a content and cell number for the freshwater algae Selenastrum capricornutum and the marine algae Skeletonema costatum ranged from 39,800 to 42,700 µg/l and 26,100 to 29,800 µg/l, respectively.

D. Residues

A bioconcentration factor of 57 was obtained for the freshwater bluegill, Lepomis macrochirus.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

Based on "no effect" levels observed in chronic feeding studies in rats and dogs, the U.S. EPA (1979a) has calculated an acceptable daily intake (ADI) level of 700 mg/day for DMP.

The recommended water quality criteria level for protection of human health is 160 mg/liter for DMP (U.S. EPA, 1979a).

B. Aquatic

The data base for toxicity of dimethyl phthalate was insufficient for drafting criterion for either freshwater or marine organisms (U.S. EPA, 1979a).

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No. 89

Dinitrobenzenes

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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DINITROBENZENES

Summary

Due to the lack of available information, no assessment of the potential of dinitrobenzenes to produce carcinogenic effects, mutagenic effects, teratogenic effects, or adverse reproductive effects can be made.

Dinitrobenzene is the most potent methemoglobin-forming agent of the nitroaromatics and rapidly produces cyanosis in exposed populations.

Fish have been acutely affected by exposure to non-specified isomers of dinitrobenzene at concentrations ranging from 2,000 to 12,000 ug/l.

DINITROBENZENE

I. INTRODUCTION

This profile is based on the Investigation of Selected Potential Environmental Contaminants: Nitroaromatics (U.S. EPA, 1976).

The dinitrobenzenes exist as the ortho, meta, or para isomers, depending on the position of the nitro group substitutents. Ortho-dinitrobenzene (1,2-dinitrobenzene, M.W. 168.1) is a white, crystalline solid with a boiling point of 319°C, a melting point of 118°C, and a specific gravity of 1.57. Meta-dinitrobenzene (1,3-dinitrobenzene) is a yellow, crystalline solid that melts at 89-90°C, boils at 300-303°C, and has a density of 1.55. Para-dinitrobenzene (1,4-dinitrobenzene) is a white, crystalline solid with a boiling point of 299°C, a melting point of 173-174°C, and a density of 1.63 (Windholz, 1976). The dinitrobenzenes have low aqueous solubility and are soluble in alcohol.

The dinitrobenzenes are used in organic synthesis, the production of dyes, and as a camphor substitute in celluloid production.

The domestic production volume of meta-dinitrobenzene in 1972 was approximately 6×10^3 tons (U.S. EPA, 1976).

Dinitrobenzenes are generally stable in neutral aqueous solutions; as the medium becomes more alkaline they may undergo hydrolysis (Murto, 1966). Para-dinitrobenzene will undergo photochemical reduction in isoproparol under nitrogen, but this reaction is quenched when the solvent is aerated (Hashimoto and Kano, 1972).

Biodegradation of dinitrobenzenes has been reported for acclimated microorganisms (Chambers, et al. 1963; Bringmann and Kuehn, 1959).

Based on the octanol/water partition coefficient, Neely et al. (1974) have estimated a low bioconcentration potential for the dinitrobenzenes.

II. EXPOSURE

Industrial dinitrobenzene poisoning reports have shown that workers will develop intense cyanosis with only slight exposure (U.S. EPA, 1976). Exposure to sunlight or ingestion of alcohol may exacerbate the toxic effects of dinitrobenzene exposure (U.S. EPA, 1976).

Monitoring data on levels of dinitrobenzenes in water, air, or food were not found in the available literature; human exposure from these sources cannot be evaluated.

III. PHARMACOKINETICS

A. Absorption

Methemoglobin formation in workers exposed to dinitrobenzene indicates that absorption of the compound by inhalation/dermal routes occurs. Animal studies demonstrate that dinitrobenzene is absorbed following oral administration.

B. Distribution

Pertinent information on distribution of dinitrobenzenes was not found in the available literature.

C. Metabolism

Dinitrobenzene undergoes both metabolic reduction and oxidation. Animal studies indicate that the major reduction productions following oral dinitrobenzene administration were nitroaniline and phenylene diamine (35% of the administered dose) (Parke, 1961). The major oxidative metabolites of meta-dinitrobenzene were 2,4-diaminophenol (31% of initial dose) and 2-amino-4-nitrophenol (14% of initial dose). The phenols are further conjugated as glucuronides or etheral sulfates (Parke, 1961).

D. Excretion

Oral administration of radiolabelled meta-dinitrobenzene to rabbits was followed by elimination of 65-93% of the dose within two days. Excretion was almost entirely via the urine; 1-5% of the administered label was determined in the feces (Parke, 1961).

IV. EFFECTS

A. Carcinogenicity

Information on the carcinogenicity of the dinitrobenzenes was not found in the available literature.

B. Mutagenicity

Information on the mutagenicity of the dinitrobenzenes was not found in the available literature. The possible dinitrobenzene metabolite, dinitrophenol (U.S. EPA, 1979), has been reported to induce chromatid breaks in bone marrow cells of injected mice (Micra and Manna, 1971).

C. Teratogenicity

Information on the teratogenicity of the dinitrobenzenes was not found in the available literature. The possible dinitrobenzene metabolite, dinitrophenol (U.S. EPA, 1979), has produced developmental abnormalities in the sea urchin (Hagstrom and Lonning, 1966). No effects were seen following injection or oral administration of dinitrophenol to mice (Gibson, 1973).

D. Other Reproductive Effects

Pertinent information was not found in the available literature.

E. Chronic Toxicity

Dinitrobenzene is the most potent methemoglobin-forming agent of the nitroaromatics. Poisoning symptoms in humans may be potentiated by exposure to sunlight or ingestion of alcohol (U.S. EPA. 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

McKee and Wolf (1963) have presented a brief synopsis of the toxic effects of dinitrobenzenes to aquatic life. A study by LeClerc (1960) reported lethal doses of non-specific isomers of dinitrobenzene for minnows (unspecified) at concentrations of 10,000 to 12,000 µg/l in distilled water or 8,000 to 10,000 µg/l in hard water. Meinck et al. (1956) reported lethal concentration of 2,000 µg/l for unspecified dinitrobenzenes for an unspecified fish species.

B. Chronic Toxicity

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

C. Plant Effects

Howard et al. (1976) report that the algae Chlorella sp. displayed inhibited photosynthetic activity upon exposure to m-dinitrobenzene at a concentration of 10^{-4} M.

VI. EXISTING GUIDELINES

The 8-hour time-weighted-average (TWA) occupational exposure limit for dinitrobenzenes is 0.15 ppm (ACGIH, 1974).

DINITROBENZENES

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No. 90

4,6-Dinitro-o-cresol

Health and Environmental Effects

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APRIL 30, 1980

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4,6-DINITRO-O-CRESOL

SUMMARY

There is no available evidence to indicate that 4,6-dinitro-ortho-cresol (DNOC) is carcinogenic.

This compound has produced some DNA damage in Proteus mirabilis but failed to show mutagenic effects in the Ames assay or in E. coli. Available information does not indicate that DNOC produces teratogenic or adverse reproductive effects.

Human exposure incidents have shown that DNOC produces an increase in cataract formation.

4,6-DINITRO-O-CRESOL

I. INTRODUCTION

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

Dinitrocresols are compounds closely related to the dinitrophenols; they bear an additional 2-position methyl group. The physical properties of 4,6-dinitro-ortho-cresol (DNOC, M.W. 198.13) include a melting point of 85.8°C and a solubility of 100 mg/l in water at 20°C (U.S. EPA, 1979a).

Dinitro-ortho-cresol is used primarily as a blossom thinning agent on fruit trees and as a fungicide, insecticide and miticide on the fruit trees during the dormant season. There is no record of current domestic manufacture of DNOC (U.S. EPA, 1979a). For additional information regarding the nitrophenols in general, the reader is referred to the Hazard Profile on Nitrophenols (U.S. EPA, 1979b).

II. EXPOSURE

The lack of monitoring data makes it difficult to assess exposure from water, inhalation, and foods. DNOC has been detected at 18 mg/l in effluents from chemical plants (U.S. EPA, 1979a).

Exposure to DNOC appears to be primarily through occupational contact (chemical manufacture, pesticide application). Contaminated water may result in isolated poisoning incidents.

The U.S. EPA (1979a) has estimated a weighted average bioconcentration factor for DNOC to be 7.5 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

III. PHARMACOKINETICS

A. Absorption

DNOC is readily absorbed through the skin, the respiratory tract, and the gastrointestinal tract (NIOSH, 1978).

B. Distribution

DNOC has been found in several body tissues; however, the compound may be bound to serum proteins, thus producing non-specific organ distribution (U.S. EPA, 1979a).

C. Metabolism

Animal studies on the metabolism of DNOC indicate that like the nitrophenols, both conjugation of the compound and reduction of the nitro groups to amino groups occurs. The metabolism of DNOC to 4-amino-4-nitro-o-cresol is a detoxification mechanism that is effective only when toxic doses of DNOC are administered (U.S. EPA, 1979a). The metabolism of DNOC is very slow in man as compared to that observed in animal studies (King and Harvey, 1953).

D. Excretion

The experiments of Parker and coworkers (1951) in several animal species indicates that DNOC is rapidly excreted following injection; however, Harvey, et al. (1951) have shown slow excretion of DNOC in volunteers given the compound orally. As in metabolism, there is a substantial difference in excretion patterns of humans vs. experimental animals.

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not located in the available literature.

B. Mutagenicity

Adler, et al. (1976) have reported that DNOC shows some evidence of producing DNA damage in Proteus mirabilis. Testing of this compound in the Ames Salmonella system (Anderson, et al., 1972) or in E. coli (Nagy, et al., 1975) failed to show any mutagenic effects.

C. Teratogenicity and Other Reproductive Effects

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

D. Chronic Toxicity

Human use of DNOC as a dieting aid has produced poisoning cases at accepted thereputic dose levels, as well as some cases of cataract development resulting from overdoses (NIOSH, 1978).

E. Other Relevant Information

DNOC is an uncoupler of oxidative phosphorylation, an effect which accounts for its high acute toxicity in mammals.

V. AQUATIC TOXICITY

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. An eight-hour TLV exposure limit of 0.2 mg/m^3 has been recommended for DNOC by the ACGIH (1971).

A preliminary draft water criterion for DNOC has been established at 12.8 µg/l by the U.S. EPA (1979a). This draft criterion has not gone through the process of public review; therefore, there is a possibility that the criterion may be changed.

B. Aquatic

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

VI. EXISTING GUIDELINES AND STANDARDS

A. An eight-hour TLV exposure limit of 0.2 mg/m^3 has been recommended for DNOC by the ACGIH (1971).

A preliminary draft water criterion for DNOC has been established at 12.8 µg/l by the U.S. EPA (1979a). This draft criterion has not gone through the process of public review; therefore, there is a possibility that the criterion may be changed.

B. Aquatic

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

No. 91

2,4-Dinitrophenol

Health and Environmental Effects

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

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2,4-DINITROPHENOL

Summary

There is no evidence to indicate that 2,4-dinitrophenol possesses carcinogenic activity.

Genetic toxicity testing has shown positive effects in mouse bone marrow cells and in E. coli. In vitro cell culture assays failed to show the potential for mutagenic activity of 2,4-dinitrophenol as measured by unscheduled DNA synthesis.

Teratogenic effects have been observed in the chick embryo following administration of 2,4-dinitrophenol. Studies in mammals failed to show that the compound produced any teratogenic effects. At the levels of compound used in these mammalian studies, embryotoxic effects were observed.

Human use of 2,4-dinitrophenol as a dieting aid has produced some cases of agranulocytosis, neuritis, functional heart damage, and cataract development.

For aquatic organisms LC_{50} values ranged from 620 µg/l for the bluegill to 16,700 µg/l for the fathead minnow.

2,4-DINITROPHENOL

I. INTRODUCTION

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

The dinitrophenols are a family of compounds composed of the isomers resulting from nitro-group substitution of phenol at various positions. 2,4-Dinitrophenol has a molecular weight of 184.11, a melting point of 114-115°C, a density of 1.683 g/ml and is soluble in water at 0.79 g/l (U.S. EPA, 1979a).

The dinitrophenols are used as chemical intermediates for sulfur dyes, azo dyes, photochemicals, pest control agents, wood preservatives, and explosives (U.S. EPA, 1979a). The 1968 production of 2,4-dinitrophenol was 4.3×10^2 tons/yr. (U.S. EPA, 1979a).

For additional information regarding the nitrophenols as a class, the reader is referred to the Hazard Profile on Nitrophenols (1979b).

II. EXPOSURE

The lack of monitoring data for the nitrophenols makes it difficult to assess exposure from water, innalation, and foods. Nitrophenols have been detected in effluents from chemical plants (U.S. EPA, 1979a). Dermal absorption of the dinitrophenols has been reported (U.S. EPA, 1979a).

Exposure to nitrophenols appears to be primarily through occupational contact (chemical plants, pesticide application). Contaminated water may contribute to isolated poisoning incidents. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for 2,4-dinitrophenol to be 2.4 for the edible

portions of fish and shellfish consumed by Americans. This estimate was based on the octanol/water partition coefficients of 2,4-dinitrophenol.

III. PHARMOCOKINETICS

A. Absorption

The dinitrophenols are readily absorbed following oral, inhalation, or dermal administration (U.S. EPA, 1979a).

B. Distribution

Dinitrophenol blood concentrations rise rapidly after absorption, with little subsequent distribution or storage at tissue sites (U.S. EPA, 1979a).

C. Metabolism

Metabolism of the nitrophenols occurs through conjugation and reduction of nitro-groups to amino-groups, or oxidation to dihydric-nitrophenols (U.S. EPA, 1979a).

D. Excretion

Experiments with several animal species indicate that urinary clearance of dinitrophenols is rapid (Harvey, 1959).

VI. EFFECTS

A. Carcinogenicity

2,4-Dinitrophenol has been found not to promote skin tumor formation in mice following DMBA initiation (Bautwell and Bosch, 1959).

B. Mutagenicity

Testing of 2,4-dinitrophenol has indicated mutagenic effects in E. coli (Demerec, et al. 1951). In vitro assays of unscheduled DNA synthesis (Friedman and Staub, 1976) and DNA

damage induced during cell culture (Swenberg, et al. 1976) failed to show the potential for mutagenic activity of this compound.

C. Teratogenicity

2,4-Dinitrophenol has been shown to produce developmental abnormalities in the chick embryo (Bowman, 1967; Miyatmoto, et al. 1975). No teratogenic effects were seen following intragastric administration to rats (Wulff, et al. 1935) or intraperitoneal administration to mice (Gibson, 1973).

D. Other Reproductive Effects

Feeding of 2,4-dinitrophenol to pregnant rats produced an increase mortality in offspring (Wulff, et al., 1935); similarly, intraperitoneal administration of the compound to mice induced embryotoxicity (Gibson, 1973). The influence of this compound on maternal health may have contributed to these effects.

E. Chronic Toxicity

Use of 2,4-dinitrophenol as a human dieting aid has produced some cases of agranulocytosis, neuritis, functional heart damage, and a large number of patients suffering from cataracts (Horner, 1942).

F. Other Relevant Information

2,4-Dinitrophenol is a classical uncoupler of oxidative phosphorylation, an effect which accounts for its high acute toxicity in mammals.

A synergistic action in producing teratogenic effects in the developing chick embryo has been reported with a combination of 2,4-dinitrophenol and insulin (Landauer and Clark, 1964).

V. AQUATIC TOXICITY

A. Acute

The bluegill (Lepomis macrochirus) was the most sensitive aquatic organism tested, with an LC_{50} of 620 µg/l in a static, 96-hour assay (U.S. EPA, 1978). Juvenile fathead minnows (Pimephales promelas) were more resistant in flow through tests, with an LC_{50} of 16,720 µg/l (Phipps, et al. manuscript). The freshwater cladoceran (Daphnia magna) displayed a range of observed LC_{50} values of 4,090 to 4,710 µg/l (U.S. EPA, 1979a). Acute values for the marine sheepshead minnow (Cyprinodon variegatus) are LC_{50} values ranging from 5,500 to 29,400 µg/l (Rosenthal and Stelzer, 1970). The marine mysid shrimp (Mysidopsis bahia) had an LC_{50} of 4,850 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

Pertinent data could not be located in the available literature.

C. Plant Effects

Effective concentrations for freshwater plants ranged from 1,472 µg/l for duckweed (Lemna minor) to 50,000 µg/l for the alga (Chlorella pyrenoidosa) (U.S. EPA, 1979a). The marine alga (Skeletonema costatum) was more resistant with a reported 96-hour EC_{50} value based on cell numbers of 98,700 µg/l.

D. Residues

Based on the octanol/water partition coefficient, a bioconcentration factor of 8.1 has been estimated for 2,4-dinitrophenol for aquatic organisms with a lipid content of 8 percent.

V. EXISTING GUIDELINES AND STANDARDS

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

A. Human

The draft water criterion for dinitrophenols, based on data describing adverse effects, has been estimated by the U.S. EPA (1979a) as 68.6 µg/l.

B. Aquatic

For protecting freshwater aquatic life, the draft criterion is 79 µg/l as a 24-hour average concentration not to exceed 180 µg/l. The marine criterion has been proposed as 37 µg/l as a 24-hour average not to exceed 84 µg/l at any time (U.S. EPA, 1979a).

To protect saltwater life, the draft criterion is 37 µg/l as a 24-hour average not to exceed 84 µg/l at any time (U.S. EPA, 1979a).

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No. 92

Dinitrotoluene

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.

DINITROTOLUENE

SUMMARY

Most of the information on the effects of dinitrotoluene deals with 2,4-dinitrotoluene. 2,4-Dinitrotoluene induces liver cancer and mammary tumors in mice and is mutagenic in some assay systems. Information on teratogenicity was not located in the available literature. Chronic exposure to 2,4-dinitrotoluene induces liver damage, jaundice, methemoglobinemia and anemia in humans and animals.

Acute studies in freshwater fish and invertebrates suggest that 2,3-dinitrotoluene is much more toxic than 2,4-dinitrotoluene.

DINITROTOLUENE

I. INTRODUCTION

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

There are six isomers of dinitrotoluene ($CH_3C_6H_3(NO_2)_2$; molecular weight 182.14), with the 2,4-isomer being the most important commercially. 2,4-Dinitrotoluene has a melting point of 71°C, a boiling point of 300°C with decomposition, and a solubility in water of 270 mg/l at 22°C. It is readily soluble in ether, ethanol, and carbon disulfide (U.S. EPA, 1979). 2,6-Dinitrotoluene has a melting point of 66°C and is soluble in alcohol. Production in 1975 was 273×10^3 tons per year for the 2,4- and 2,6- isomers combined (U.S. EPA, 1979).

Dinitrotoluene is an ingredient of explosives for commercial and military use, a chemical stabilizer in the manufacture of smokeless powder, an intermediate in the manufacture of toluene diisocyanates used in the production of urethane polymers, and a raw material for the manufacture of dyestuffs. Dinitrotoluenes are relatively stable at ambient temperatures (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Data on concentration levels for dinitrotoluene were not available. Dinitrotoluene waste products are dumped into surface water or sewage by industries that manufacture dyes, isocyanates, polyurethanes and munitions (U.S. EPA, 1979).

B. Food

According to the U.S. EPA (1979), the likelihood of dinitrotoluene existing in food is minimal since it is not used as a pesticide or herbicide.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for 2,4-dinitrotoluene to be 5.5 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

C. Inhalation

Exposure to dinitrotoluene by inhalation is most likely to occur occupationally (U.S. EPA, 1979). However, pertinent data could not be located in the available literature on atmospheric concentrations of dinitrotoluene and, thus, possible human exposure cannot be estimated.

III. PHARMACOKINETICS

A. Absorption

The absorption of ^{14}C-labeled isomers of dinitrotoluene after oral administration to rats was essentially complete within 24 hours, with 60 to 90 percent of the dose being absorbed. The 2,4- and 3,4-isomers were absorbed to a greater extent than the 3,5- and 2,5- isomers, which in turn were absorbed to a greater extent than the 2,3- and 2,6-isomers (Hodgson, et al. 1977). 2,4-Dinitrotoluene is known to be absorbed through the respiratory tract and skin (U.S. EPA, 1979).

B. Distribution

Tissue/plasma ratios of radioactivity after administration of ^{14}C-labeled dinitrotoluene to rats indicated retention of ^{14}C DNT in both the liver and kidneys but not in other tissues (Hodgson, et al., 1977). A similar experiment with tritium-labeled 2,4-dinitrotoluene (^{3}H-2,4-DNT) in the rat showed relatively high amounts of radioactivity remaining in adipose tissue, skin, and liver seven days after administration (Mori, et al., 1977).

C. Metabolism

No studies characterizing the metabolism of dinitrotoluene in mammals are available. However, on the basis of a comparison of the metabolism of 2,4-dinitrotoluene and 2,4,6-trinitrotoluene in microbial systems, and the known metabolism of 2,4,6-trinitrotoluene in mammals, the U.S. EPA (1979) speculated that the metabolites of 2,4-dinitrotoluene in mammals would be either toxic and/or carcinogenic.

D. Excretion

In studies involving oral administration of ^{14}C-dinitrotoluene or ^{3}H-2,4-dinitrotoluene to rats (Hodgson, et al., 1977; Mori, et al., 1977), elimination of radioactivity occurred mainly in urine and feces. No radioactivity was recovered in the expired air. About 46 percent of the administered dose in the latter study was excreted in the feces and urine during the seven days following administration.

IV. EFFECTS

A. Carcinogenicity

2,4-Dinitrotoluene fed to rats and mice for two years produced dose-related increases in fibromas of the skin in male rats and fibroadenomas of the mammary gland in female rats. All of these were benign tumors. No statistically significant increase in tumor incidence was noted in mice (Natl. Cancer Inst., 1978).

In a second bioassay of rats and mice fed 2,4-dinitrotoluene for two years, the findings in rats included a significant increase of hepatocellular carcinomas and neoplastic nodules in the livers of females, a significant increase of mammary gland tumors in females, and a suspicious increase of hepatocellular carcinomas of the liver in males. Male mice had a highly significant increase of kidney tumors (Lee, et al., 1978).

B. Mutagenicity

2,4-Dinitrotoluene was mutagenic in the dominant lethal assay and in Salmonella typhimurium strain TA1535 (Hodgson, et al. 1976). Cultures of lymphocytes and kidney cells derived from rats fed 2,4-dinitrotoluene had significant increases in the frequency of chromatid gaps but not in translocations or chromatid breaks (Hodgson, et al., 1976).

The mutagenic effects of products from ozonation or chlorination of 2,4-dinitrotoluene and other dinitrotoluenes

were negative in one study (Simmon, et al., 1977), and, for products of ozonation alone, were ambiguous in another study (Cotruvo, et al., 1977).

C. Teratogenicity and other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Chronic exposure to 2,4-dinitrotoluene may produce liver damage, jaundice, methemoglobinemia and reversible anemia with reticulocytosis in humans and animals (Linch, 1974; Key, et al. 1977; Proctor and Hughes, 1978; Kovalenko, 1973).

E. Other Relevant Information

Animals were more resistant to the toxic effects of 2,4-dinitrotoluene administered in the diet when given diets high in fat or protein (Clayton and Baumann, 1944, 1948; Shils and Goldwater, 1953) or protein (Shils and Goldwater, 1953).

Alcohol has a synergistic effect on the toxicity of 2,4-dinitrotoluene (Friedlander, 1900; McGee, et al., 1942).

In subacute studies (13 weeks), 2,4- and 2,6-dinitrotoluene caused methemoglobinemia, anemia with reticulocytosis, gliosis and demyelination in the brain, and atrophy with aspermatogenesis of the testes in several species (Ellis, et al., 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

Static assays with the freshwater bluegill (Lepomis macrochirus) produced a 96-hour LC_{50} value of 330 µg/l for 2,3-dinitrotoluene (U.S. EPA, 1978), while the same assay with the fathead minnow (Pimephales promelas) produced a 96-hour LC_{50} value of 31,000 µg/l for 2,4-dinitrotoluene (U.S. Army, 1976). The greater toxicity of 2,3-dinitrotoluene when compared to that of 2,4-dinitrotoluene, was demonstrated in 48-hour static assays with the freshwater cladoceran, Daphnia magna, with LC_{50} values of 660 µg/l(U.S. EPA, 1978) and 35,000 µg/l (U.S. Army, 1976) being reported. A single marine fish, sheepshead minnow (Cyprinodon variegatus), has been tested for adverse acute effects of 2,3-dinitrotoluene. A 96-hour static assay LC_{50} value of 2,280 µg/l was reported (U.S. EPA, 1978). For marine invertebrates a 96-hour static LC_{50} value of 590 µg/l was obtained for the mysid shrimp (Mysidopsis bahia) with 2,3-dinitrotoluene.

B. Chronic Toxicity

The sole chronic study examining the effects of 2,3-dinitrotoluene in an embryo-larval assay on the fathead minnow produced a chronic value of 116 µg/l based on reduced survival of these stages. No marine chronic data were presented (U.S. EPA, 1979).

C. Plant Effects

Concentrations of 2,3-dinitrotoluene that caused 50 percent adverse effects in cell numbers or chlorophyll

a in the freshwater algae, Selenastrum capricornutum, were 1,370 or 1,620 µg/l, respectively. These same effects measured in the marine algae, Skeletonema costatum, showed it to be more sensitive. EC_{50} values were 370 or 400 µg/l, respectively.

D. Residues

A bioconcentration factor of 19 was obtained for aquatic organisms having a lipid content of 8 percent (U.S. EPA, 1979).

VI. EXISTING STANDARDS AND GUIDELINES

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

A. Human

Based on the induction of fibroadenomas of the mammary gland in female rats (Lee, et al., 1978), and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of 2,4-dinitrotoluene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteri			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.		7.4 ng/l	74.0 mg/l	740 ng/l
Consumption of fish and shellfish only.		.156 µg/l	1.56 µg/l	15.6 µg/l

The American Conference of Governmental Industrial Hygienists (1978) recommends a TLV-time weighted average for 2,4-dinitrotoluene of 1.5 mg/m^3 with a short term exposure limit of 5 mg/m^3.

B. Aquatic

A criterion to protect freshwater life has been drafted as 620 µg/l for a 24-hour average not to exceed 1,400 µg/l for 2.4-dinitrotoluene and 12 µg/l not to exceed 27 µg/l for 2,3-dinitrotoluene. For marine environments a criterion has been drafted for 2,3-dinitrotoluene as a 4.4 µg/l as a 24-hour average not to exceed 10 µg/l. Data was insufficient to draft a criterion for 2,4-dinitrotoluene for marine environments.

DINITROTOLUENE

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No. 93

2,4-Dinitrotoluene

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 2,4-dinitrotoluene and has found sufficient evidence to indicate that this compound is carcinogenic.

2,4-DINITROTOLUENE

Summary

2,4-Dinitrotoluene induces liver cancer and mammary tumors in mice and is mutagenic in some assay systems. Information on teratogenicity was not located in the available literature. Chronic exposure to 2,4-dinitrotoluene induces liver damage, jaundice, methemoglobinemia and anemia in humans and animals.

Two acute studies, one on freshwater fish and the other on freshwater invertebrates, provide the only data of 2,4-dinitrotoluene's adverse effects on aquatic organisms. Acute LC_{50} values were reported as 17,000 and 30,000 µg/l. No marine data are available.

2,4-DINITROTOLUENE

I. INTRODUCTION

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

2,4-Dinitrotoluene (2,4-DNT) has a melting point of 71°C, a boiling point of 300°C with decomposition, and a solubility in water of 270 mg/l at 22°C. It is readily soluble in ether, ethanol, and carbon disulfide (U.S. EPA, 1979a).

Production in 1975 was 273 x 10^3 tons/year for the 2,4- and 2,6-isomers combined (U.S. EPA, 1979a). 2,4-Dinitrotoluene is an ingredient in explosives for commercial and military use, a chemical stabilizer in the manufacture of smokeless powder, an intermediate in the manufacture of toluene diisocyanates used in the production of urethane polymers, and a raw material for the manufacture of dye-stuffs. Dinitrotoluenes are relatively stable at ambient temperatures (U.S. EPA, 1979a). For additional information regarding the dinitrotoluenes in general, the reader is referred to the EPA/ECAO Hazard Profile on Dinitrotoluenes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

Data on concentration levels of 2,4-DNT in water were not available. Dinitrotoluene waste products are dumped into surface water or sewage by industries that manufacture dyes, isocyanates, polyurethanes and munitions (U.S. EPA, 1979a).

B. Food

According to the U.S. EPA (1979a), the likelihood of 2,4-dinitrotoluene existing in food is minimal since it is not used as a pesticide or herbicide.

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for 2,4-dinitrotoluene to be 5.5 for edible portions of fish and shellfish consumed by Americans. This estimate was based on the octanol/water partition coefficient.

C. Inhalation

Exposure to dinitrotoluene by inhalation is most likely to occur occupationally (U.S. EPA, 1979a). However, pertinent data could not be located in the available literature on atmospheric concentrations of dinitrotoluene; thus, possible human exposure cannot be estimated.

III. PHARMACOKINETICS

A. Absorption

The absorption of ^{14}C-labeled isomers of dinitrotoluene after oral administration to rats was essentially complete within 24 hours, with 60 to 90 percent of the dose being absorbed. The 2,4-and 3,4-isomers were absorbed to a greater extent than the 3,5- and 2,5-isomers, which in turn were absorbed to a greater extent than the 2,3- and 2,6-isomers (Hodgson, et al. 1977). From toxicity studies, 2,4-Dinitrotoluene is known to be absorbed through the respiratory tract and skin (U.S. EPA, 1979a).

B. Distribution

Tissue/plasma ratios of radioactivity after administration of ^{14}C-labeled dinitrotoluene (DNT) to rats indicated retention of ^{14}C 2,4-DNT in both liver and kidneys but not in other tissues (Hodgson, et al. 1977). A similar experiment with tritium-labeled 2,4-dinitrotoluene (^{3}H-2,4-DNT) in the rat showed relatively high amounts of radioactivity remaining in adipose tissue, skin, and liver seven days after administration (Mori, et al. 1977).

C. Metabolism

No studies characterizing the metabolism of 2,4-dinitrotoluene in mammals are available. However, on the basis of a comparison of the metabolism of 2,4-dinitrotoluene and 2,4,6-trinitrotoluene in microbial systems, and the metabolism of 2,4,6-trinitrotoluene in mammals, the U.S. EPA (1979a) speculated that the metabolites of 2,4-dinitrotoluene in mammals would be either toxic and/or carcinogenic.

D. Excretion

In studies involving oral administration of ^{14}C-dinitrotoluene or ^{3}H-2,4-dinitrotoluene to rats (Hodgson, et al. 1977; Mori, et al, 1977), elimination of radioactivity occurred mainly in urine and feces. No radioactivity was recovered in the expired air. About 46 percent of the administered dose in the latter study was excreted in the feces and urine during the seven days following administration.

IV. EFFECTS

A. Carcinogenicity

2,4-Dinitrotoluene fed to rats and mice for two years produced dose-related increases in fibromas of the skin in male rats and fibroadenomas of the mammary gland in female rats. These tumors were benign. No statistically significant reponse was noted in mice (Natl. Cancer Inst., 1978).

In a second bioassay of rats and mice fed 2,4-dinitrotoluene for two years, the findings in rats included a significant increase of hepatocellular carcinomas and neoplastic nodules in the livers of females, a significant increase of mammary gland tumors in females, and a suspicious increase of hepatocellular carcinomas of the liver in males. Mice had a highly significant increase of kidney tumors in males (Lee, et al. 1978).

B. Mutagenicity

2,4-Dinitrotoluene was mutagenic in the dominant lethal assay and in Salmonella typhimurium strain TA 1535 (Hodgson, et al. 1976). Cultures of lymphocytes and kidney cells derived from rats fed 2,4-dinitrotoluene had significant increases in the frequency of chromatid gaps but not in translocations or chromatid breaks (Hodgson, et al. 1976).

The mutagenic effects of products from ozonation or chlorination of 2,4-dinitrotoluene and other dinitrotoluenes were negative in one study (Simmon, et al. 1977) and, of products from ozonation alone, were ambiguous in another study (Cotruvo, et al. 1977).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Chronic exposure to 2,4-dinitrotoluene may produce liver damage, jaundice, methemoglobinemia and reversible anemia with reticulocytosis in humans and animals (Linch, 1974; Key, et al. 1977; Proctor and Hughes, 1978; Kovalenko, 1973).

E. Other Relevant Information

Animals were more resistant to the toxic effects of 2,4-dinitrotoluene administered in the diet when given diets high in fat (Clayton and Baumann, 1944, 1948; Shils and Goldwater, 1953) or protein (Shils and Goldwater, 1953).

Alcohol has a synergistic effect on the toxicity of 2,4-dinitrotoluene (Friedlander, 1900; McGee, et al. 1942).

In subacute studies (13 weeks) of several species, 1,2,4-dinitrotoluene caused methemoglobinemia, anemia with reliculocytasis, gliosis, and demyelination in the brain, and atrophy with aspermatogenesis of the testes (Ellis et al., 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

The only toxicity data available for the effects of 2,4-dinitrotoluene in aquatic animals are from a single freshwater fish and invertebrate species (U.S. Army, 1976). A 96-hour static LC_{50} value for the fathead minnow (Pimephales promelas) was reported as 31,000 µg/l and a 48-hour static LC_{50} value for the cladoceran, Daphnia magna, was reported as 35,000 µg/l.

B. Chronic Toxicity and Plant Effects

Pertinent data could not be located in the available literature.

C. Residues

A bioconcentration factor of 19 was obtained for 2,4-dinitrotoluene.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

Based on the induction of fibroadenomas of the mammary gland in female rats (Lee, et al. 1978), and using the "one-hit" model, the U.S. EPA (1979a) has estimated levels of 2,4-dinitrotoluene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
Consumption of 2 liters of drinking water and 18.7 grams fish and shellfish.		7.4 ng/l	74.0 ng/l	740 ng/l
Consumption of fish and shellfish only.		.156 µg/l	1.56 µg/l	15.6 µg/l

The American Conference of Governmental Industrial Hygienists (1978) recommends a TLV-time-weighted average for 2,4-dinitrotoluene of 1.5 mg/m^3 with a short term exposure limit of 5 mg/m^3.

B. Aquatic

A criterion has been drafted for protecting freshwater life from the toxic effects of 2,4-dinitrotoluene. A 24-hour average concentration of 620 µg/l, not to exceed 1,400 µg/l, has been proposed. Data are insufficient for drafting a marine criterion.

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No. 94

2,6-Dinitrotoluene

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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2,6-Dinitrotoluene

SUMMARY

2,6-Dinitrotoluene is known to cause methemoglobinemia in cats, dogs, rats, and mice. When administered orally to these animals for a maximum of thirteen weeks, the major effects seen in addition to the blood effects were depressed spermatogenesis, degeneration of the liver, bile duct hyperplasia, incoordination and rigid paralysis of the hind legs, and kidney degeneration.

Positive results were obtained with mutagenicity testing in a number of Salmonella typhimurium strains.

2,6-DNT has been found in tap water in the United States. The nitro groups on the aromatic ring retard degeneration so there is a potential for it to accumulate in the aquatic environment.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dinitrotoluene (U.S. EPA, 1979b) and a U.S. EPA report entitled "Investigation of Selected Potential Environmental Contaminants: Nitroaromatics" (1976).

2,6-Dinitrotoluene (2,6-DNT; $C_7H_6N_2O_4$; molecular weight 182.14) is a solid at room temperature. It is in the shape of rhombic needles and is soluble in ethanol. Its melting point is 66°C and its density is 1.28 at 111°C (Weast, 1975).

A review of the production range (includes importation) statistics for 2,6-dinitrotoluene (CAS. No. 606-20-2) which is

listed in the initial TSCA Inventory (1979a) has shown that between 50,000,000 and 100,000,000 pounds of this chemical were produced/imported in 1977.*/

Mixtures of the dinitrotoluene isomers are intermediates in the manufacture of toluene diisocyanates, toluene diamines and trinitrotoluene (Wiseman, 1972). Dinitrotoluene (both 2,4- and 2,6-) is an ingredient in explosives for commercial and military use and is also used as a chemical stabilizer in the manufacture of smokeless powder (U.S. EPA, 1979b).

II. EXPOSURE

A. Environmental Fate

Based on the photodecomposition of trinitrotoluene (TNT) described by Burlinson et al. (1973), 2,6-dinitrotoluene would be expected to react photochemically. Decomposition of 65% of the TNT had occurred when the decomposition products were examined.

2,6-Dinitrotoluene would be expected to biodegrade to a limited extent. The nitro groups retard biodegradation and studies with soil microflora have shown that mono- and di-substituted nitrobenzenes persist for more than 64 days (Alexander and Lustigmann, 1966). McCormick et al. (1976) and Bringmann and Kuehn (1971) reported microbial degradation of 2,6-DNT by anaerobic and aerobic bacteria, respectively.

*/ 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

B. Bioconcentration

In general nitroaromatic compounds do not have high bioconcentration potential based on calculations using their octanol-water partition coefficients. They are not expected to biomagnify based on their water solubility (U.S. EPA, 1976).

C. Environmental Occurrence

2,6-Dinitrotoluene has been identified in tap water in the United States (Kopfler and Melton, 1975). Its environmental contamination would come almost exclusively from the chemical plants where it is produced. It was detected in the water effluent from a TNT plant in Radford, Virginia at concentrations of 3.39 to 56.3 ppm. It was also found in the raw waste of a DNT plant at 150 ppm. The raw effluent contained 0.68 ppm and the pond effluent 0.02 ppm (U.S. EPA, 1976).

III. PHARMACOKINETICS

2,6-Dinitrotoluene can enter the body through inhalation of vapors or dust particles, ingestion of contaminated food, and absorption through the skin (EPA, 1979b). Hodgson et al. (1977) traced the pathway of ^{14}C labeled di- and tri-substituted nitrotoluenes after oral administration of the compounds to rats. All of the compounds were well absorbed with 60 to 90% absorption after 24 hours. The radiolabel was found in the liver, kidneys and blood but not in other organs; none was found in the expired air indicating that the aromatic ring was not broken down through metabolism of the compounds. Most of the labeled compounds were

Regulations (40 CFR 710).

eliminated in the urine as metabolites; biliary excretion was also an important elimination pathway.

IV. HEALTH EFFECTS

A. Carcinogenicity

No carcinogenicity testing of 2,6-DNT has been reported in the literature. The National Cancer Institute conducted a bioassay to determine the carcinogenicity of 2,4-DNT by administering it to rats and mice in their diet. 2,4-DNT induced benign tumors in male and female rats, however, the benign tumors were not considered a sufficient basis for establishing carcinogenicity. The assay produced no evidence of carcinogenicity of the compound in mice (NCI, 1978).

B. Mutagenicity

Simmon et al. (1977) tested 2,6-dinitrotoluene for mutagenicity in Salmonella typhimurium. Positive results were obtained with strains TA1537, TA1538, TA98, and TA100, but not TA1535. These results were obtained without metabolic activation.

C. Other Toxicity

1. Chronic

The subchronic toxicity of 2,6-dinitrotoluene was determined by oral administration to dogs, rats, and mice for about 13 weeks. The primary effects were on red blood cells, the nervous system, and the testes. Both dogs and rats had decreased muscular coordination primarily in the hind legs, rigidity in extension of the hind legs, decreased appetite, and weight loss. The

mice experienced only the decreased appetite and weight loss. All of the animals had methemoglobinemia, and anemia with reticulocytosis. The tissue lesions seen were extramedullary hematopoeisis in the spleen and liver, gliosis and demyelination in the brain, and atrophy with aspermatogenesis in the testes (Ellis et al., 1976). Methemoglobinemia was also found in cats administered 2,6-DNT (U.S. EPA, 1979b).

2. Acute

Oral LD50's have been reported for rats and mice. They are 180 mg/kg and 1,000 mg/kg respectively (Vernot et al., 1977). A mixture of 2,4-DNT and 2,6-DNT was applied to the skin of rabbits in a series of 10 doses over a two week period and no cumulative toxicity was found (U.S. EPA, 1976).

VI. EXISTING GUIDELINES

The OSHA standard for 2,6-DNT in air is a time-weighted average of 1.5 mg/m^3 (39 FR 23540).

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No. 95

Di-n-octyl Phthalate

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

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DI-n-OCTYL PHTHALATE

Summary

Di-n-octyl phthalate has produced teratogenic effects following i.p. injection of pregnant rats. This same study has also indicated some increased resorptions and fetal toxicity.

Evidence is not available indicating mutagenic or carcinogenic effects of di-n-octyl phthalate.

Data pertaining to the aquatic toxicity of di-n-octyl phthalate is not available.

DI-n-OCTYL PHTHALATE

I. INTRODUCTION

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

Di-n-octyl phthalate (DOP) is a diester of the ortho form of benzene dicarboxylic acid. The compound has a molecular weight of 391.0, specific gravity of 0.978, boiling point of 220°C at 5 mm Hg, and is insoluble in water.

DOP is used as a plasticizer in the production of certain plastics.

Current Production: 5.8×10^3 tons/year in 1977 (U.S. EPA, 1979a).

Phthalates have been detected in soil, air, and water samples; in animal and human tissues, and in certain vegetation. Evidence from *in vitro* studies indicates that certain bacterial flora may be capable of metabolizing DOP to the monoester form (Engelhardt, et al. 1975). For additional information regarding the phthalate esters in general, the reader is referred to the EPA/ECAO Hazard Profile on Phthalate Esters (U.S. EPA 1979b).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of phthalates may occur through leaching of the compound from plastics, volatilization from plastics, or the incineration of plastic items. Sources of human exposure to phthalates include contaminated foods and fish, dermal application, and parenteral administration by use of plastic blood bags, tubings, and infusion devices (mainly DEHP release). Relevant factors in the migration of phthalate esters from packaging materials to food and beverages are: temperature, surface area contact, lipoidal nature of the food, and length of contact (U.S. EPA, 1979a).

Monitoring studies have indicated that most water phthalate concentrations are in the ppm range, or 1-2 μg/liter (U.S. EPA, 1979a). Industrial air monitoring studies have measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1973).

Information on levels of DOP in foods is not available. Bioconcentration factor is not available for DOP.

III. PHARMACOKINETICS

Specific information could not be located on the absorption, distribution, metabolism, or excretion of DOP. The reader is referred to a general coverage of phthalate metabolism (U.S. EPA, 1979b).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

Pertinent data could not be located in the available literature.

C. Teratogenicity

Administration of DOP to pregnant rats by i.p. injection has been reported to produce some teratogenic effects, although less so than several other phthalates tested (Singh, et al. 1972).

D. Other Reproductive Effects

An increased incidence of resorption and fetal toxicity was produced following i.p. injection of pregnant rats with DOP (Singh, et al. 1972).

E. Chronic Toxicity

Pertinent data could not be located in the available literature.

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

Pertinent data concerning the acceptable daily intake (ADI) level in humans of DOP could not be located in the available literature.

Recommended water quality eriterion level for protection of human health is not available for DOP.

B. Aquatic

Pertinent data is not available pertaining to the aquatic toxicity of di-n-octyl phthalate; therefore, no criterion could be drafted.

DI-N-OCTYL PHTHALATE

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No. 96

1,2-Diphenylhydrazine

Health and Environmental Effects

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

APRIL 30, 1980

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 1,2-diphenylhydrazine and has found sufficient evidence to indicate that this compound is carcinogenic.

1,2-DIPHENYLHYDRAZINE

Summary

The adverse effects of exposure to 1,2-diphenylhydrazine include damage to both the kidney and liver. Acute LD_{50} values have ranged from 300 to 960 mg/kg in experimentally dosed rats. No data concerning the absorption, distribution, or excretion of the 1,2-diphenylhydrazine have been generated. Benzidine has been identified as a metabolite in urine of rats exposed to the chemical. Diphenylhydrazine is carcinogenic in both sexes of rats and in female mice.

The only aquatic toxicity data for diphenylhydrazine are for freshwater organisms. Acute toxicity levels of 270 and 4,100 µg/l were reported for bluegill and Daphnia magna, respectively, and a single chronic value of 251 µg/l was reported for Daphnia magna.

1,2-DIPHENYLHYDRAZINE

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Diphenylhydrazine.

Diphenylhydrazine (DPH) has a molecular weight of 184.24, a melting point of 131°C and a boiling point of 220°C. DPH is slightly soluble in water and is very soluble in benzene, ether and alcohol.

The symmetrical isomer of diphenylhydrazine, 1,2-diphenylhydrazine is used in the synthesis of benzidine for use in dyes, and in the synthesis of phenylbutazone, an anti-arthritic drug.

The reported commercial production of more than 1000 pounds annually, as of 1977, is most likely an underestimation of the total amount of diphenylhydrazine available. Diphenylhydrazine is produced in several synthetic processes as an intermediate and a contaminant, but there is no way of estimating these substantial quantities.

II. EXPOSURE

A. Water

The highest reported concentration of 1,2-diphenylhydrazine in drinking water is one µg/l (U.S. EPA, 1975).

B. Food

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for diphenylhydrazine to be 29 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of diphenylhydrazine.

C. Inhalation

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

Pertinent information could not be located in the available literature regarding absorption, distribution and excretion.

A. Metabolism

Various metabolites, including the known carcinogen benzidine, have been identified in the urine of rats. 1,2-Diphenylhydrazine was administered orally (200,400 mg/kg), intraperitoneally (200 mg/kg), intratracheally (5,10 mg/kg) and intravenously (4,8 mg/kg). The metabolites detected were not dependent upon the base or route of administration (Williams, 1959).

IV. EFFECTS

A. Carcinogenicity

Diphenylhydrazine has been identified as producing significant increases in hepatocellular carcinoma at 5 µg/kg/day and 18.8 µg/kg/day in both sexes of rats; Zymbal's gland squamous-cell tumors in male rats at 18.8 µg/kg/day; neoplastic liver nodules in female rates at 7.5 µg/kg/day; and hepatocellular carcinomas in female mice at 3.75 µg/kg/day (NCI, 1978). Diphenylhydrazine was not carcinogenic in male mice.

B. Mutagenicity

No microbial mutagenetic assays with or without metabolic activation have been conducted on diphenylhydrazine. An intraperitoneal dose of 100 mg/kg had an inhibitory effect on the incorporation of (^{3}H)-thymidine into testicular DNA of experimental mice (Sieler, 1977).

C. Teratogenicity

Pertinent information could not be located in the available literature.

D. Toxicity

One study reported an LD_{50} of 959 mg/kg for male rats administered DPH as a five percent solution. In the Registry of Toxic Effects of Chemical Substances, the oral LD_{50} is listed as 301 mg/kg. Neoplasms resulted in rats after 52 weeks with a total dose of 16 g/kg DPH administered subcutaneously. In 2 mice studies, neoplasms resulted after 25 weeks with topical application of 5280 mg/kg and after 38 weeks with subcutaneous injection of 8400 mg/kg DPH. Liver and kidney damage have been implicated in the adverse effects of diphenylhydrazine chronically administered to rats. No experimental or epidemiological studies have been conducted on the effects of diphenylhydrazine in humans.

V. AQUATIC TOXICITY

A. Acute

Ninety-six-hour LC_{50} values for freshwater organisms have been reported as 270 µg/l for the bluegill, Lepomis macrochirus, and the 48-hour LC_{50} for the cladoceran, Daphnia magna, is 4,100 µg/l (U.S. EPA, 1978). No toxicity data for marine animals could be located in the available literature.

B. Chronic

A chronic value of 251 µg/l has been obtained for the freshwater cladoceran, Daphnia Magna (U.S. EPA, 1978). No chronic tests of diphenylhydrazine are available for marine organisms.

C. Plants

Pertinent data could not be located in the available literature.

D. Residues

Based on the octanol/water partition coefficient of 870 for 1,2-diphenylhydrazine, a bioconcentration factor of 100 has been estimated for aquatic organisms with a lipid content of 8 percent.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Humans

No standards were found for humans exposed to diphenylhydrazine in occupational or ambient settings.

Recommended draft criteria for the protection of human health are as follows:

Exposure Assumptions	Risk Levels and Corresponding Criteria							
	0	10^{-7}		10^{-6}		10^{-5}	
2 liters of drinking water and consumption of 18.7 grams fish and shellfish (2)	0	4	ng/l	40	ng/l	400	ng/l
Consumption of fish and shellfish only.	0	.019	µg/l	0.19	µg	1.9	µg/l

B. Aquatic

Criterion to protect freshwater aquatic life from toxic effects of diphenylhydrazine have been drafted as a 24-hour average concentration of 17 µg/l and not to exceed 38 µg/l at any time.

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No. 97

Disulfoton

Health and Environmental Effects

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

APRIL 30, 1980

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DISULFOTON

Summary

Disulfoton is a highly toxic organophosphorous insecticide used on many agricultural crops. The human oral LD_{Lo} is estimated at 5 mg/kg body weight. Exposure results in central nervous system toxicity. The LD_{50} for several animal species ranges from 3.2 to 6 mg/kg. Carcinogenic, mutagenic, and teratogenic studies were not found in the available literature. The occupational threshold limit value for disulfoton is 10 $\mu g/m^3$. Allowable residue tolerances for agricultural commodities range from 0.3 to 11.0 ppm.

Although disulfoton is considered toxic to aquatic organisms, specific studies on aquatic toxicity were not located in the available literature.

I. INTRODUCTION

Disulfoton is a highly toxic organophosphorous insecticide used in agriculture to control mainly sucking insects such as aphids and plantfeeding mites. Small amounts are used on home plants and gardens in the form of dry granules with low content of active ingredient (U.S. EPA, 1974). Disulfoton was introduced in 1956 by Bayer Leverkusen (Martin and Worthing, 1974), and today it is produced by only one U.S. manufacturer, Mobay Chemical Corporation, at its Chemogro Agricultural Division in Kansas City, Missouri (Stanford Research Institute (SRI), 1977). An estimated 4500 tonnes were produced in 1974 (SRI, 1977). Disulfoton is made by interaction of O,O-diethyl hydrogen phosphorodithioate and 2-(2-ethylthio)ethylchloride (Martin and Worthing, 1974). Disulfoton is slightly soluble in water and readily soluble in most organics. Its overall degradation constant is 0.02/day. Disulfoton has a bioconcentration factor of 1.91 and an octanol/water partition coefficient of 1.0 (see Table 1).

II. EXPOSURE

A. Water

Disulfoton concentrations are highest during the production process. Concentrated liquid wastes are barged to sea (150-200 mi; 240-320 km), and sludge wastes are disposed in landfills.

Agricultural application rates normally range from 0.25 to 1.0 lb/acre (0.28-1.1 kg/ha); to a maximum of 5.0 lb/acre (5.5 kg/ha) for some uses. Target crops include small grains, sorgum, corn, cotton, other field crops; some vegetable, fruit and nut crops; ornamentals (Fairchild, 1977).

Disulfoton is considered stable in groundwater. Less than 10 percent is estimated to decompose in five days (equivalent to 50-250 mi; 80-400

TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF DISULFOTON

Synonyms: O,O-Diethyl S-(2-(ethylthio)ethyl) phosphorodithioate; O,O-Diethyl S-(2-(ethylthio)ethyl) dithiophosphate; Thiodemeton; Frumin; Glebofos; Ethylthiometon B; VUAgT 1964; Di-Syston G; Disipton; ENT-23437; Ethyl thiometon; VUAgT 1-4; Bay 19639; M 74 [pesticide]; Ekatin TD; CAS Reg. No. 298-04-4; M 74 (VAN); Bayer 19639; Di-Syston; Dithiodemeton; Dithiosystox; Solvirex; Frumin AL; Frumin G

Structural Formula: $(C_2H_5O)_2(P{=}S)SCH_2CH_2SC_2H_5$

Molecular Weight: 274.4

Description: Colorless oil; technical product is a dark yellowish oil; readily soluble in most organics

Specific Gravity and/or Density: $d_4^{20} = 1.144$

Melting and/or Boiling Points: bp 62°C at 0.01 mm Hg

Stability: Relatively stable to hydrolysis at pH below 8
Overall degradation rate constant (0.02/day)

Solubility (water): 25 ppm at room temp.

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

Vapor Pressure: 1.8×10^{-4} mm Hg at 20°C

Bioconcentration Factor (BCF) and/or
Octanol/water partition coefficient (K_{ow}): $K_{ow} = 1.91$
BCF = 1.0

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

km) in a river environment. Decomposition in a lake environment is estimated to be near 90 percent in one year (U.S. EPA 1980).

B. Food

In a study by Van Dyk and Krause (1978), disulfoton was applied as a granular formulation at 2 g/m length in rows during cabbage planting (5 percent active ingredients, rows one meter apart, plants 0.5 meters apart). The disulfoton sulphone concentration reached a maximum in 18 to 32 days and decreased to between 0.3 and 6.4 mg/kg 52 days after application. The cabbage residue of disulfoton at harvest time was below the maximum limit of 0.5 mg/kg.

Disulfoton applied at about 1.5 kg/10 cm-ha (hectare slice) persisted for the first week, and residue levels declined slowly the following week. After one month, only 20 percent of the amount applied was found. Disulfoton was not found to translocate into edible parts of lettuce, onions, and carrots (less than 5 ppb), but was present at about 20 ppb in the root system of lettuce (Belanger and Hamilton, 1979).

C. Inhalation and Dermal

Data are not available indicating the number of people subject to inhalation or dermal exposure to disulfoton. The primary human exposure would appear to occur during production and application. The U.S. EPA (1976) listed the frequency of illness, by occupational groups caused by exposure to organophosphorous 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), trac-

tor drivers and irrigators (23), workers exposed to pesticide drift (22), pilots (crop dusters) (17), and flaggers for aerial application (6). Most illnesses were a result of 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 to increase pesticide levels and dust on the crops.

III. PHARMACOKINETICS

A. Absorption, Distribution, and Excretion

Pertinent data could not be located in the available literature.

B. Metabolism

Disulfoton is metabolized in plants to sulfoxide and sulfone and the corresponding derivatives of the phosphorothioate and demeton-S. This is also the probable route in animals (Martin and Worthing, 1974; Menzie 1974; Fairchild, 1977).

IV. EFFECTS

A. Carcinogenicity, Mutagenicity and Teratogenicity

Pertinent data could not be located in the available literature.

B. Chronic Toxicity and Other Relevant Information

Disulfoton is highly toxic to all terrestrial and aquatic fauna. Human oral LD_{Lo} is estimated to be 5 mg disulfoton per kilogram body weight (5 mg/kg). The symptoms produced by sublethal doses are typical of central and peripheral nervous-system toxicity (Gleason, et al. 1969). The reported LD_{50} concentrations for other species are summarized below (Fairchild, 1977).

Species	Exposure Route	LD_{50} (mg/kg)
rat	oral	5
rat	dermal	6
rat	intraperitoneal	5.4
rat	intravenous	5.5
mouse	oral	5.5
mouse	intraperitoneal	7
bird	oral	3.2

Rats survived for 60 days at 0.5 mg/kg/day (Martin and Worthing 1974). The no-effect level in the diet was 2 ppm for rats and 1 ppm for dogs (Fairchild, 1977).

In rats, single injections of 1.2 mg disulfoton per kg body weight caused 14 percent reductions of hippocampal norepinephrine within 3 hours of exposure. Norepinephrine returned to control levels within 5 days (Holt and Hawkins, 1978). In female chicks administered with disulfoton intraperitoneally (single dose 8.6 mg/kg), the total lipid content of the sciatic nerve, kidney and skeletal muscles increased whereas that of the brain and spinal cord remained the same or decreased. When female chicks were orally administered with disulfoton (0.29 mg/kg daily for 71 days), the total lipid content in all the organs except the liver and sciatic nerves decreased. Although degenerative changes were indicated in both exposure studies, no adverse effect on the growth of chicks was noted (Gopel and Ahuja, 1979).

Disulfoton applied at 1 to 1.5 kg/ha very markedly decreased the populations of soil bacteria (Tiwari, et al. 1977).

V. AQUATIC TOXICITY

The 96-hour TL_m (equivalent to a 96-hour LC_{50}) for fathead minnows was found to be 2.6 mg/l in hard water and 3.7 mg/l in soft water.

Both tests were conducted at 25°C. The corresponding value for bluegills is estimated to be 0.07 mg/l (McKee and Wolf, 1963).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The occupational threshold limit value for air has been established as 100 $\mu g/m^3$. Established residue tolerance for crops range from 0.3 to 12.0 ppm; 0.75 ppm for most (Fairchild, 1977).

B. Aquatic

Pertinent data could not be located in the available literature.

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No. 98

Endosulfan

Health and Environmental Effects

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

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DISCLAIMER

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

ENDOSULFAN

Summary

Endosulfan is an insecticide and is a member of the organochlorocyclodiene insecticides. Endosulfan does not appear to be carcinogenic, mutagenic or teratogenic. In humans, chronic toxic effects have not been observed when endosulfan has been properly handled occupationally. Chronic feeding of endosulfan to rats and mice produced kidney damage, parathyroid hyperplasia, testicular atrophy, hydropic change of the liver, and lowered survival. Oral administration of endosulfan to pregnant rats increased fetal mortality and resorptions. Sterility can be induced in embryos in sprayed bird eggs. At very high levels of acute exposure, endosulfan is toxic to the central nervous system. The U.S. EPA has calculated an ADI of 0.28 mg based on a NOAEL of 0.4 mg/kg for mice in a chronic feeding study. The ADI established by the Food and Agricultural Organization (1975) and World Health Organization is 0.0075 mg/kg.

Ninety-six hour LC_{50} values ranged from 0.3 to 11.0 µg/l for five freshwater fish; from 0.09 to 0.6 µg/l for five saltwater fish in 48- or 96-hour tests; from 0.04 to 380 µg/l (EC_{50} and LC_{50}) for seven saltwater invertebrate species; and from 62 to 166 µg/l for Daphnia magna (48-hour LC_{50}). In the only chronic aquatic study involving endosulfan, no adverse effects on fathead minnows were observed at 0.20 µg/l.

I. INTRODUCTION

Endosulfan (6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide; $C_9Cl_6H_6O_3S$; molecular weight 406.95) is a light to dark brown crystalline solid with a terpene-like odor. Endosulfan is a broad spectrum insecticide of the group of polycyclic chlorinated hydrocarbons called cyclodiene insecticides. It also has uses as an acaricite. It has a vapor pressure of 9×10^{-3} mm Hg at 80 degrees centigrade. It exhibits a solubility in water of 60 to 150 µg/l and is readily soluble in organic solvents (U.S. EPA, 1979). The trade names of endosulfan include Beosit, Chlorithiepin, Cyclodan, Insectophene, Kop-Thiodan, Malix, Thifor, Thisnuml, Thioden, and Thionex (Berg, 1976).

Technical grade endosulfan has a purity of 95 percent and is composed of a mixture of two stereoisomers referred to as alpha-endosulfan and beta-endosulfan or I and II. These isomers are present in a ratio of 70 parts alpha-endosulfan to 30 parts beta-endosulfan. Impurities consist mainly of the degradation products and may not exceed 2 percent endosulfandiol and 1 percent endosulfan ether (U.S. EPA, 1979).

Production: three million pounds in 1974 (U.S. EPA, 1979).

Endosulfan is presently on the Environmental Protection Agency's restricted list. However, significant commercial use for insect control on vegetables, fruits, and tobacco continues (U.S. EPA, 1979).

Endosulfan is stable to sunlight but is susceptible to oxidation and the formation of endosulfan sulfate in the presence of growing vegetation (Cassil and Drummond, 1965). Endosulfan is readily adsorbed and absorbed by sediments (U.S. EPA, 1979). It is metabolically converted by microorganisms, plants, and animals to endosulfan sulfate, endosulfandiol, endosulfan ether, endosulfan hydroxyether and endosulfan lactone (Martens, 1976; Chopra

and Manfouz, 1977; Gorbach, et al. 1968; Miles and Moy, 1979). The end-product, endosulfan lactone, disappears quickly once formed. Accumulation of endosulfan sulfate may be favored in acidic soils (Miles and Moy, 1979).

II. EXPOSURE

A. Water

Endosulfan has been detected in water samples from some of the streams, rivers, and lakes in the United States and Canada and in Ontario municipal water supplies. The maximum concentration of endosulfan monitored in municipal water was 0.083 µg/l, which was found in Ontario municipal water samples but 68 µg/l has been measured in irrigation run-off (U.S. EPA, 1979). Endosulfan contamination of water results from agricultural runoff, industrial effluents, and spills. One serious accidental industrial discharge in Germany in 1969 caused a massive fishkill in the Rhine River. Most of the river water samples contained less than 500 ng/l endosulfan. Residues in run-off water from sprayed fields can be as high as 220 µg/l (U.S. EPA, 1979).

B. Food

An average daily intake (ADI) less than or equal to 0.001 mg of endosulfan and endosulfan sulfate was estimated for 1965-1970 from the market basket study of the FDA (Duggan and Corneliussen, 1972). The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for endosulfan to be 28 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies with mussels. The processing of leafy vegetables causes endosulfan residues to decline from 11 µg/kg to 6 µg/kg (Corneliussen, 1970).

C. Inhalation

In 1970, air samples from 16 states showed an average level of 13.0 ng/m^3 alpha-endosulfan and 0.2 ng/m^3 beta-endosulfan. None of the air samples collected in 1971 or 1972 contained detectable levels of either isomer (Lee, 1976). Endosulfan residues (endosulfan and endosulfan sulfate) have been detected in most types of U.S. tobacco products in recent years (U.S. EPA, 1979). Average residue levels range from 0.12 mg/kg to 0.83 mg/kg for 1971-1973 (Domanski, et al. 1973,1974; Dorough and Gibson, 1972). The extent to which endosulfan residues in tobacco products contribute to human exposure is not known. Spray operators can be exposed up to 50 µg/hour of endosulfan from a usual application of a 0.08 percent spray (Wolfe, et al. 1972). Non-target deposition on untreated plants after spraying may lead to residues of up to 679 µg/kg (Keil, 1972).

D. Dermal

Wolfe, et al. (1972) estimated that sprayers applying a 0.08 percent aqueous solution are exposed dermally to 0.6 to 98.3 mg/hour. Endosulfan can persist on the hands for 1 to 112 days after exposure (Kazen, et al. 1974).

III. PHARMACOKINETICS

A. Absorption

Undiluted endosulfan is slowly and incompletely absorbed from the mammalian gastointestinal tract, whereas endosulfan dissolved in cottonseed oil is readily though not completely absorbed (Boyd and Dobos, 1969; Maier-Bode, 1968). The beta-isomer is more readily absorbed than the alphaisomer. Alcohols, oils, and emulsifiers accelerate the absorption of endosulfan by the skin (Maier-Bode, 1968). Inhalation is not considered to be an important route of absorption for endosulfan except in spray operators (U.S. EPA, 1979).

B. Distribution

After ingestion by experimental animals, endosulfan is first distributed to the liver and then to the other organs of the body and the remainder of the gastrointestinal tract (Boyd and Dobos, 1969; Maier-Bode, 1968). In cats, endosulfan levels peaked in brain, liver, spinal cord and plasma, with the brain and liver retaining the highest concentrations after administration of a 3 mg/kg dose (Khanna, et al. 1979).

In mice, 24 hours after oral administration of ^{14}C-endosulfan, residues were detected in fat, liver, kidney, brain, and blood (Deema, et al. 1966).

Data from autopsies of three suicides show levels of endosulfan in brain which were much lower than those in liver and kidney, which in turn, were lower than levels in blood (Coutselinis, et al. 1978). Data from another suicide indicate higher levels of endosulfan in liver and kidneys than in blood (Demeter, et al. 1977).

C. Metabolism

Endosulfan sulfate is the metabolite most commonly present in tissues, feces, and milk of mammals after administration of endosulfan (Whitacre, 1970; Demma, et al. 1966; FMC, 1963). The largest amounts of endosulfan sulfate are found in small intestine and visceral fat with only traces in skeletal muscle and kidney (Deema, et al. 1966). Endosulfan sulfate has been detected in the brains of two humans who committed suicide by ingesting endosulfan (Demeter and Heyndrickx, 1978), but not in the brains of mice given nonfatal doses of endosulfan. However, it has been detected in liver, visceral fat and small intestines of mice (Deema, et al. 1966). Other metabolites of endosulfan are endosulfan lactone, endosulfandiol, endosulfan hydroxyether, and endosulfan ether (Knowles, 1974; Menzie, 1974). These metabolites have also been found in microorganisms and plants (U.S. EPA, 1979).

D. Excretion

The principal route of excretion for endosulfan and endosulfan sulfate is in the feces (U.S. EPA, 1979). Other metabolites are also excreted in the feces and to a small extent in the urine, the metabolites in the latter being mainly in the form of endosulfan alcohol (U.S. EPA, 1979). In studies with sheep receiving a single oral dose of radiolabeled endosulfan, 92 percent of the dose was eliminated in 22 days. The organ with the highest concentration of radiolabeled endosulfan after 40 days was the liver. Major metabolites did not persist in the fat or in the organs (Gorbach, et al. 1968). After a single oral dose, the half-life of radiolabeled endosulfan in the feces and urine of sheep was approximately two days (Kloss, et al. 1966). Following 14 days of dietary exposure of female rats, the half-life of endosulfan residues was approximately seven days (Dorough, et al. 1978).

IV. EFFECTS

A. Carcinogenicity

In bioassays on both mice and rats, orally administered endosulfan was not carcinogenic even though doses were high enough to produce symptoms of toxicity (Kotin, et al. 1968; Innes, et al. 1969; Weisburger, et al. 1978).

B. Mutagenicity

Data from assays with Salmonella typhimurium (with and without microsomal activation) (Dorough, et al. 1978), Saccharomyces cerevisiae, Escherichia coli, and Serratia marcescens (Fahrig, 1974) indicate that endosulfan is not mutagenic.

C. Teratogenicity

Endosulfan did not produce teratogenic effects in rats (Gupta, 1978).

D. Other Reproductive Effects

In rats, endosulfan produced dose-related increases in maternal toxicity and caused increases in fetal mortality and resorptions (Gupta, 1978). Doses of 100 mg/kg reduce hatchability of fertile white leghorn chicken eggs by 54 percent, but this was dependent on carrier (Dunachie and Fletcher, 1969). Alterations in the gonads of the embryos within sprayed hens' eggs were noted and the progeny of hens and quails, Coturnix Coturnix japonica, were sterile (U.S. EPA, 1979).

E. Chronic Toxicity

In the NCI bioassays (Kotin, et al. 1968; Weisberger, et al. 1978) endosulfan was toxic to the kidneys of rats of both sexes, and to the kidneys of male mice. Other signs of toxicity were parathyroid hyperplasia, testicular atrophy in male rats, and high early death rates in male mice.

In a two-year feeding study with rats (Hazelton Laboratories, 1959), endosulfan at 10 mg/kg diet reduced testis weight in males and lowered survival in females; at 100 mg/kg diet, renal tubular damage and some hydropic changes in the liver were induced.

In humans, there has been an absence of toxic effects with proper handling of endosulfan in the occupational setting (Hoechst, 1966).

F. Other Relevant Information

The acute toxicity of endosulfan sulfate is about the same as that of endosulfan. The LD_{50} for technical endosulfan in rats is $\sim$ 22 to 46 mg/kg and 6.9 to 7.5 mg/kg in mice (Gupta, 1976). Reagent grade a- and β-endosulfan are less toxic to rats (76 and 240 mg/kg, respectively; Hoechst,

1967). The inhalation 4-hour LC_{50} values for rats have been reported as 350 and 80 µg/l for males and females, respectively (Ely, et al. 1967). Acute toxicities of other metabolites (endosulfan lactone, endosulfandiol, endosulfan hydroxyether and endosulfan ether) are less than that of the parent compound (Dorough, et al. 1978).

At very high levels of acute exposure, endosulfan is toxic to the central nervous system (U.S. EPA, 1979). Endosulfan is a convulsant and causes fainting, tremors, mental confusion, irritability, difficulty in urination, loss of memory and impairment of visual-motor coordination. Acute intoxification can be relieved by diazepam but chronic effects are manifested in central nervous system disorders (Aleksandrowicz, 1979).

There appear to be sex differences (see previous Chronic Toxicity section) and species differences in sensitivity to endosulfan. Of the species tested with endosulfan, cattle are the most sensitive to the neurotoxic effects of endosulfan and appear to be closer in sensitivity to humans. Dermal toxicity of endosulfan-sprayed cattle is also high. Typical symptoms are listlessness, blind staggers, restlessness, hyperexcitability, muscular spasms, goose-stepping and convulsions (U.S. EPA, 1979).

Endosulfan is a nonspecific inducer of drug metabolizing enzymes (Agarwal, et al. 1978). Protein deficient rats are somewhat more susceptible to the toxic effects of endosulfan than controls (Boyd and Dobos, 1969; Boyd, et al. 1970).

V. AQUATIC TOXICITY

A. Acute Toxicity

Ninety-six hour LC_{50} values, using technical grade endosulfan, for five species of freshwater fish range from 0.3 µg/l for the rainbow trout, Salmo gairdneri, (Macek, et al. 1969) to 11.0 µg/l for carp finger-

lings, Cyprinus carpio (Macek, et al. 1969; Schoettger, 1970; Ludemann and Neumann, 1960; Pickering and Henderson, 1966). Among freshwater invertebrates, Daphnia magna is reported to have 48-hour LC_{50} values ranging from 62 to 166 µg/l (Macek, et al. 1976; Schoettger, 1970), with three other invertebrates yielding 96-hour LC_{50} values of 2.3 (Sanders and Cope, 1968) to 107 µg/l (Sanders, 1969; Schoettger, 1970). Levels of 400 and 800 ng/l of technical endosulfan damaged the kidney, liver, stomach and intestine of Gymonocorymbus ternetzi. The 96-hour LC_{50} value was 1.6 µg/l (Amminikutty and Rege, 1977,1978).

Of the five saltwater fish species tested, the reported 48- or 96-hour LC_{50} values ranged from 0.09 (Schimmel, et al. 1977) to 0.6 µg/l (Butler, 1963,1964; Korn and Earnest, 1974; Schimmel, et al. 1977). The most sensitive species was the spot (Leiostomus xanthurus).

The seven saltwater invertebrate species tested showed a wide range of sensitivity to endosulfan. The range of EC_{50} and LC_{50} values is from 0.04 (Schimmel, et al. 1977) to 380 µg/l with the most sensitive species being the pink shrimp (Penaeus duorarum).

B. Chronic Toxicity

Macek, et al. (1976) provided the only aquatic chronic study involving endosulfan. No adverse effects on fathead minnow, Pimephales promelas, parents or offspring were observed at 0.20 µg/l. Gymonocorymbus ternetzi chronically exposed to 400 and 530 ng/l for 16 weeks evinced necrosis of intestinal mucosa cells, ruptured hepatic cells and destruction of pancreatic islet cells (Amminikutty and Rege, 1977,1978).

C. Plant Effects

Little data is available concerning the effects of endosulfan on aquatic micro/macrophytes. Growth of Chlorella vulgaris was inhibited > 2000 µg/l (Knauf and Schulze, 1973).

D. Residues

Schimmel, et al. (1977) studied the uptake, depuration, and metabolism of endosulfan by the striped mullet, Mugil cephalus. When the concentrations of endosulfans I and II and endosulfan sulfate were combined to determine the bioconcentration factor (BCF), an average whole-body BCF of 1,597 was obtained. Nearly all the endosulfan was in the form of the sulfate. Even though the duration of the study was 28 days, this investigator questioned whether a steady-state condition was reached. Complete depuration occurred in just two days in an endosulfan-free environment. Residues in pond sediments may be as high as 50 µg/kg B-endosulfan and 70 µg/kg of endosulfan sulfate 280 days after insecticidal endosulfan application (FMC, 1971).

Dislodgable residues on cotton foliage in Arizona declined to 10 percent and one-third for the low-melting and high-melting isomers, respectively, 24 hours after application of 1.1 kg/ha endosulfan. However, though residues had declined to 4 percent and 11 percent respectively, 4 days after application endosulfan sulfate residues on the leaves increased markedly to 0.14 $\mu g/cm^2$ (Estesen, 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

The U.S. EPA (1979) has recommended a draft criterion for endosulfan in ambient water of 0.1 mg/l based on an ADI of 0.28 mg/day. This ADI was calculated from a NOAEL of 0.4 mg/kg obtained for mice in a chronic feeding study (Weisburger, et al. 1978) and an uncertainty factor of 100.

The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) TLV time weighted average for endosulfan is 0.1 mg/m^3. The tentative value for the TLV short-term exposure limit (15 minutes) is 0.3 mg/m^3.

The ADI for endosulfan established by the Food and Agricultural Organization and the World Health Organization is 7.5 µg/kg (FAO, 1975).

8. Aquatic

For endosulfan, the draft criterion to protect freshwater aquatic life is 0.042 µg/l in a 24-hour average and not to exceed 0.49 µg/l at any time. Saltwater criteria cannot be developed because of insufficient data (U.S. EPA, 1979).

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No. 99

Endrin

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.

ENDRIN

SUMMARY

Endrin does not appear to be carcinogenic. Endrin is teratogenic and embroytoxic in high doses and produces gross chromosomal abnormalities when administered intratesticularly. Chronic administration of endrin causes damage to the liver, lung, kidney, and heart of experimental animals. No information about chronic effects in humans is available. The ADI established by the Food and Agricultural Organization and World Health Organization is 0.002 mg/kg.

Endrin has proven to be extremely toxic to aquatic organisms. In general, marine fish are more sensitive to endrin with an arithmetic mean LC_{50} value of 0.73 µg/l, than freshwater fish with an arithmetic mean LC_{50} value of 4.42 µg/l. Invertebrate species tend to be more resistant than fish with arithmetic mean LC_{50} values of 3.80 and 58.91 µg/l for marine and freshwater invertebrates, respectively.

ENDRIN

I. INTRODUCTION

Endrin (molecular weight 374) is a broad spectrum insecticide of the group of polycyclic chlorinated cyclodiene hydrocarbons of which the insecticides aldrin and dieldrin are also members. Endrin is isomeric with dieldrin and is used as a rodenticide and ovicide. The endrin sold in the U.S. is a technical grade product containing not less than 95 percent active ingredient. The solubility of endrin in water at 25°C is about 200 µg/l (U.S. EPA, 1979). Its vapor pressure is 2 x 10^{-7} mm Hg at 25°C (Martin, 1971).

Endrin is used primarily as an insecticide and also as a rodenticide and avicide. Over the past several years, endrin utilization has been increasingly restricted (U.S. EPA, 1979. Endrin production in 1978 was approximately 400,000 pounds (U.S. EPA, 1978). Endrin persists in the soil (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Occasionally, groundwater may contain more than 0.1 µg/l. Levels as high as 3 µg/l have been correlated with precipitation and run off following endrin applications (U.S. EPA, 1978).

Concentrations of endrin in finished drinking water have been decreasing. In a study of ten municipal water treatment plants on the Mississippi or Missouri Rivers, the number of finished water samples containing concentrations of endrin exceeding 0.1 µg/l decreased from ten percent in 1964-

1965 to zero in 1966-1967 (Schafer, et al., 1969). The highest concentration of endrin in drinking water in New Orleans, Louisiana measured by the U.S. EPA in 1974 was 4 ng/l (U.S. EPA, 1974).

B. Food

The general population is rarely exposed to endrin through the diet. In the market basket study by the FDA, the total average daily intake from food ranged from approximately 0.009 µg/kg body weight in 1965 to 0.0005 µg/kg body weight in 1970 (Duggan and Lipscomb, 1969; Duggan and Corneliussen, 1972).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of endrin at 1,900 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in six species (both freshwater and saltwater).

C. Inhalation

Exposure of the general population to endrin via the air decreased from a maximum level of 25.6 $\mu g/m^3$ in 1971 to a maximum level of 0.5 $\mu g/m^3$ in 1975 (U.S. EPA, 1979).

Tobacco products are contaminated with endrin residues. Average endrin residues for various types of tobacco products have been reported in the range of 0.05 µg/g to 0.2 µg/g (Bowery, et al., 1959; Domanski and Guthrie, 1974).

Inhalation exposure of users and manufacturers of endrin sprays may be around 10 µg/hour (Wolfe, et al. 1967) but use of dusts can produce levels as high as 0.41 mg/hour (Wolfe, et al. 1963).

D. Dermal

Dermal exposure of spray operators can range up to 3 mg/body/hour even for operators wearing standard protective clothing (Wolfe, et al. 1963, 1967). The spraying of dusts can lead to exposures of up to 19 mg/hour (Wolfe, et al. 1963).

III. PHARMACOKINETICS

A. Absorption

Endrin is known to be absorbed through the skin, lungs, and gut, but data on the rates of absorption are not available (U.S. EPA, 1979).

B. Distribution

Endrin is not stored in human tissues in significant quantities. Residues were not detected in plasma, adipose tissue, or urine of workers exposed to endrin (Hayes and Curley, 1968). Measurable levels of endrin have not been detected in human subcutaneous fat or blood, even in persons living in areas where endrin is used extensively (U.S. EPA, 1979). Endrin residues have been detected in the body tissues of humans only immediately after an acute exposure (U.S. EPA, 1979; Coble, et al. 1967).

In a 128 day study, dogs were fed 0.1 mg/endrin/kg body weight/day. Concentrations of endrin in the tissues at the end of the experiment were as follows: adipose tissue, 0.3 to 0.8 µg/g; heart, pancreas, and muscle, 0.3 µg/l; liver, kidney and lungs, 0.077 to 0.085 µg/g; blood, 0.002 to 0.008 µg/g (Richardson, et al., 1967). In a six month feeding study with dogs at endrin levels of 4 to 8 ppm in the

diet, concentrations of endrin were 1 µg/g in fat, 1 µg/g in liver, and 0.5 µg/g in kidney (Treon, et al., 1955).

C. Metabolism

In rats, endrin is readily metabolized in the liver and excreted as hydrophilic metabolites including hydroxyendrins, and 12-ketoendrin (also known as 9-ketoendrin). Hydroxyendrins and especially 12-ketoendrin have been reported to be more acutely toxic to mammals than the parent compound (Bedford, et al., 1975; Hutson, et al., 1975). The 12-ketoendrin is also more persistent in tissues. Female rats metabolize endrin more slowly than males (Jager, 1970).

D. Excretion

Endrin is one of the least persistent chlorinated hydrocarbon pesticides (U.S. EPA, 1979). Body content of endrin declines fairly rapidly after a single dose or when a continuous feeding experiment is terminated (Brooks, 1969). In rats, endrin and its metabolites are primarily excreted with the feces (Cole, et al., 1968; Jager, 1970). The major metabolite in rats is anti-12-hydroxyendrin which is excreted in bile as the glucuronide. 12-Ketoendrin was observed as a urinary metabolite in male rats; the major urinary metabolite in female rats is anti-12-hydroxyendrin-O-sulfate (Hutson, et al., 1975).

In rabbits, excretion is primarily urinary. In females, endrin excretion also occurs through the milk. Although endrin is rapidly eliminated from the body, some of its metabolites may persist for longer periods of time (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

In lifetime feeding studies with Osborne-Mendel rats, endrin was neither tumorigenic nor carcinogenic (Deichmann, et al., 1970; Deichmann and MacDonald, 1971; Deichmann, 1972). A recent NCI bioassay concluded that endrin was not carcinogenic for Osborne-Mendel rats or for B6C3F1 mice (DHEW, 1979). However, a different conclusion has been reached by Reuber (1979) based only on one study (National Cancer Institute, 1977), compared with eight other inconclusive or unsatisfactory studies.

B. Mutagenicity

Endrin (1 mg/kg) administered intratesticularly caused chromosomal aberrations in germinal tissues of rats, including stickiness, bizarre configurations, and abnormal disjunction (Dikshith and Datta, 1972, 1973).

C. Teratogenicity

An increased incidence of club foot was found in fetuses of mice that had been treated with endrin (0.58 mg/kg) before becoming pregnant (Nodu, et al., 1972).

Treatment of pregnant hamsters with endrin (5 mg/kg) produced the following congenital abnormalities: open eye, webbed foot, cleft palate, fused ribs, and meningoencephalocele (Ottolenghi, et al., 1974; Chernoff, et al., 1979). Treatment of pregnant mice with endrin (2-5 mg/kg) produced open eye and cleft palate in the offspring (Ottolenghi, et al., 1974). Single doses which produced terato-

genic effects in hamsters and mice were one-half the LD_{50} in each species (Ottolenghi, et al., 1974).

D. Other Reproductive Effects

Endrin given to hamsters during gestation produced behavioral effects in both dams and offspring (Gray, et al., 1979). In another study endrin produced a high incidence of fetal death and growth retardation (Ottolenghi, et al., 1974).

E. Chronic Toxicity

Mammals appeared to be sensitive to the toxic effects of endrin at low levels in their diet. Significant mortality occurred in deer mice fed endrin at 2 mg/kg/day in the diet (Morris, 19[illegible]). The mice exhibited symptoms of CNS toxicity including convulsions. Lifetime feeding of endrin to rats at 12 mg/kg/day in the diet decreased viability and produced moderate increases in congestion and focal hemorrhages of the lung; slight enlargment, congestion and mottling of the liver, and slight enlargement, discoloration or congestion of the kidneys (Deichmann, et al., 1970). After 19 months on diets containing 3 mg/kg/day endrin, dogs had significantly enlarged kidneys and hearts (Treon, et al., 1955).

Chronic administration of relatively small doses of endrin to monkeys produced a characteristic change in the electroencephalogram (EEG); at higher doses, electrographic seizures developed. EEG and behavior were still abnormal three weeks after termination of endrin administration; sei-

zures recurred under stress conditions months after termination of endrin administration (Revin, 1968).

F. Other Relevant Information

Endrin is more toxic, in both acute and chronic studies, than other cyclodiene insecticides (U.S. EPA, 1979).

Female rats metabolize and eliminate endrin more slowly than males (Jager, 1970) and are more sensitive to endrin toxicity (U.S. EPA, 1979). Dogs and monkeys are more susceptible to endrin toxicity than other species (U.S. EPA, 1979).

Endrin, given in equitoxic doses with delnav, DDT, or parathion gave lower than expected LD_{50} values, suggestive of antagonism. Endrin given in equitoxic doses with aldrin (a closely related compound) or chlordane gave higher than expected LD_{50} values suggestive of synergism (Keplinger and Deichmann, 1967). Humans poisoned acutely exhibit convulsions, vomiting, abdominal pain, nausea, dizziness, mental confusion, muscle twitching and headache. Such symptoms have been elicited by doses as low as 0.2 mg/kg body weight. Any deaths have usually occurred through respiratory failure (Brooks, 1974).

V. AQUATIC TOXICITY

A. Acute

The toxic effects of endrin have been extensively studied in freshwater fish. LC_{50} values for static bioassays ranged from 0.046 µg/l for carp fry (Cyprinus carpio) fry to 140.00 µg/l for adult carp (Iyatomi, et al.,

1958). Excluding the results of age factor differences for this species, adjusted static LC_{50} values ranged from 0.27 µg/l for large mouth bass (Microptecus salmoides) (Fabacler, 1976) to 8.25 µg/l for the bluegill (Lepomis macrochirus) (Katz and Chadwick, 1961). The LC_{50} values for flow-through assays were 0.27 µg/l for the bluntnose minnow (Pimeplales notatus) to 2.00 µg/l for the bluegill (U.S. EPA, 1979). Twenty-five LC_{50} values for 17 species of freshwater invertebrates were reported, and ranged from 0.25 µg/l for stoneflies (Pteronarcys californica) to 500.0 µg/l for the snail, (Physa gyrina) (U.S. EPA, 1979).

For marine fish, LC_{50} values ranged from 0.005 µg/l for the Atlantic silversides (Menidia menidia) (Eisler, 1970) to 3.1 µg/l for the northern puffer (Sphaeroides maculatus). A total of 17 species were tested in 33 bioassays. The most sensitive marine invertebrate tested was the pink shrimp, (Penaeus duordrum) with an LC_{50} value of 0.037 µg/l, while the blue crab (Callinectes sapidus) was the most resistant, with an LC_{50} of 25 µg/l.

B. Chronic

Freshwater fish chronic values of 0.187 µg/l and 0.257 µg/l were reported for fathead minnows (Pimephales promelas) (Jarvinen and Tyo, 1978) and flagfish (Jordanella floridae) Hermanutz, 1978), respectively, in life cycle toxicity tests. No freshwater invertebrate species have been chronically examined. The marine fish, the sheepshead minnow (Cyprinodon variegatus) has provided a chronic value of 0.19 µg/l from embryolarval tests (Hansen, et al., 1977). The

grass shrimp (Palaemonetes pugio) must be exposed to less than a chronic concentration of 0.038 µg/l for reproductive success of this marine invertebrate species (TylerShroeder, in press).

C. Plants

Toxic effects were elicited at concentrations for freshwater algae ranging from 475 µg/l for Anacystis nidularas (Batterton, 1971) to >20,000 µg/l for Scenedesmus quadricauda and Oedogonium sp. Marine algae appeared more sensitive with effective concentration ranging from 0.2 µg/l for the algae, Agmenellum quadruplicatum (Batterton, 1978), to 1,000 µg/l for the algae Dunaliella tertiotecta (U.S. EPA, 1979).

D. Residues

Bioconcentration factors ranged from 140 to 222 in four species of freshwater algae. Bioconcentration factors ranging from 1,640 for the channel catfish Ictalurus punctatus (Argyle, et al. 1973) to 13,000 for the flagfish Jordanella floridae (Hermanutz, 1978) have been obtained. Among four marine species, bioconcentration factors ranging from 1,000 to 2,780 were observed for invertebrates and from 1,450 to 6,400 for marine fish. Residues as high as 0.5 ppm have been found in the mosquito fish, Gambusia affinis (Finley, et al. 1970) and fish frequently have contained levels above 0.3 ppm (Jackson, 1976).

VI. EXISTING GUIDELINES AND STANDARDS

Both the human health and aquatic criteria derived by U.S. EPA (1979), 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

The U.S. EPA (1979) has calculated an ADI for endrin of 70 µg from a NOAEL of 0.1 mg/kg for dogs in a 128 day feeding study and an uncertainity factor of 100. The U.S. EPA (1979) draft criterion of 1 µg/l for endrin in ambient water is based on the 1 µg/l maximum allowable concentration for endrin in drinking water proposed by the Public Health Service in 1965 (Schafer, et al., 1969) and on the calculations by EPA. Human exposure is assumed to come from drinking water and fish products only.

A maximum acceptable level of 0.002 mg/kg body weight/day (ADI) was established by the Food and Agricultural Organization (1973) and the World Health Organization.

A time weighted average TLV for endrin of 100 $\mu g/m^3$ has been established by OSHA (U.S. Code of Federal Regulations, 1972) and ACGIH (Yobs, et al., 1972).

The U.S. EPA (40 CFR Part 129.102) has promulgated a toxic pollutant effluent standard for endrin of 1.5 µg/l per average working day calculated over a period of one month, not to exceed 7.5 µg/l in any sample representing one working-day's effluent. In addition, discharge is not to exceed 0.0006 kg per 1,000 kg of production.

B. Aquatic

The draft criterion for the protection of freshwater aquatic life is 0.0020 µg/l as a 24 hour average concentration not to exceed 0.10 µg/l. For marine organisms, the draft criterion is 0.0047 µg/l as a 24 hour average not to exceed 0.031 µg/l.

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No. 100

Epichlorohydrin (1-chloro-2,3-epoxypropane)

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 ( ) 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 epichlorohydrin and has found sufficient evidence to indicate that this compound is carcinogenic.

1-CHLORO-2,3-EPOXYPROPANE

(Epichlorohydrin)

Summary

The adverse health effects associated with exposure to epichlorohydrin are extreme irritation to the eyes, skin, and respiratory tract. Inhalation of vapor and percutaneous absorption of the liquid are the normal human routes of entry. Exposure to epichlorohydrin usually results from occupational contact with the chemical, especially in glycerol and epoxy resin operations. Pulmonary effects have been well documented. Recent studies have demonstrated epichlorohydrin to be a potent carcinogen to nasal tissue in experimental animals. Cytogenic studies both *in vitro* and *in vivo* in humans and experimental animals have indicated epichlorohydrin to be an active clastogenic agent. No data on the concentration of epichlorohydrin in drinking water or foods have been reported. Studies on the effects of epichlorohydrin to aquatic organisms could not be located in the available literature.

I. INTRODUCTION

This profile is based primarily on a comprehensive review compiled by Santodonato, et al. (1979). The health hazards of epichlorohydrin have also been reviewed by the National Institute for Occupational Safety and Health (NIOSH, 1976) and the Syracuse Research Corporation (SRC, 1979).

Epichlorohydrin (CH_2OCHCH_2Cl; molecular weight 92.53) is a colorless liquid at room temperature with a distinctive chloroform-type odor. The boiling point of epichlorohydrin is 116.4°C, and its vapor pressure is 20 mm Hg at 29°C. These factors contribute to the rapid evaporation of the chemical upon release into the environment.

Epichlorohydrin is a reactive molecule forming covalent bonds with biological macromolecules. It tends to react more readily with polarized groups, such as sulfhydryl groups.

The total U.S. production for epichlorohydrin was estimated at 345 million pounds in 1973 (Oesterhof, 1975), with 160 million pounds used as feedstock for the manufacture of glycerine and 180 million pounds used in the production of epoxy resins. Production levels for the year 1977 have been estimated at 400 million pounds.

II. EXPOSURE

A. Water

No ambient monitoring data on epichlorohydrin are available from which reliable conclusions on the potential exposure from drinking water may be made. However, if a major release of epichlorohydrin were realized, the chemical is stable enough to be transported significant distances. The rate of evaporative loss would give an estimated half-life of about two days for epichlorohydrin in surface waters (to a depth of 1m). The only reported contamination of a public water supply resulted from a tank car derailment

and subsequent spillage of 20,000 gallons (197,000 pounds) of epichlorohydrin at Point Pleasant, West Virginia on January 23, 1978. Wells at the depth of 25 feet were heavily contaminated. More specific information is not yet available.

B. Food

Epichlorohydrin is used as a cross-link in molecular sieve resins, which are, in turn, used in the treatment of foods (21 CFR 173.40). Food starch may be etherified with epichlorohydrin, not to exceed 0 alone or in combination with propylene oxide, acetic anhyd cc anhydride (21 CFR 172.892). No data concerning concentrations of epichlorohydrin in foodstuffs has been generated.

C. Inhalation

Numerous environmental sources of epichlorohydrin have been identified (SRC, 1979). Epichlorohydrin is released into the atmosphere through waste ventilation processes from a number of industrial operations which result in volatilization of the chemical. No quantitative monitoring information is available on ambient epichlorohydrin concentrations. High concentrations have been observed in the immediate vicinity of a factory discharging epichlorohydrin into the atmosphere, but these were quickly despersed, with no detection of the chemical at distances greater than 600 M (Fomin, 1966).

III. PHARMACOKINETICS

A. Absorption

Absorption of epichlorohydrin in man and animals occurs via the respiratory and gastointestinal tracts, and by percutaneous absorption (U.S. EPA, 1979). Blood samples obtained from rats after 6 hours exposure to (^{14}C)epichlorohydrin at doses of 1 and 100 ppm in air revealed 0.46±0.19 and 27.8±4.7 μg epichlorohydrin per ml of plasma, respectively. The rates

epichlorohydrin per ml of plasma, respectively. The rates of uptake at these exposure levels were determined as 15.48 and 1394 ug per hour, and the dose received was 0.37 and 33.0 mg/kg (Smith, et al. 1979).

B. Distribution

The distribution of radioactivity in various tissues of rats fed (^{14}C)-epichlorohydrin has been examined (Weigel, et al. 1978). The chemical was rapidly absorbed with tissue saturation occurring within two hours in males and four hours in females. The kidney and liver accumulated the greatest amounts of radioactivity. Major routes of excretion were in the urine (38 to 40 percent), expired air (18 to 20 percent), and the feces (4 percent). The appearance of large amounts of $^{14}CO_2$ in expired air suggests a rapid and extensive metabolism of (^{14}C)-epichlorohydrin in rats.

C. Metabolism

Limited data concerning mammalian metabolism of epichlorohydrin suggest in vivo hydrolysis of the compound, yielding alpha-chlorohydrin (Jones, et al. 1969). Upon exposure to radioactively-labeled epichlorohydrin a small percentage of the radioactivity was expired as intact epichlorohydrin, while a large percentage of the radioactivity was excreted as $^{14}CO_2$, indicating a rapid and extensive metabolism of the (^{14}C)epichlorohydrin. Metabolites in the urine have been obtained by these researchers, but the final analysis as to the identity of the compounds is not yet complete. Van Duuren (1977) has suggested a metabolite pathway of epichlorohydrin to include glycidol, glycidaldehyde and epoxy-propionic acid.

D. Excretion

The percentages of total radioactivity recovered in the urine and expired air as $^{14}CO_2$ were 46 percent and 33 percent in the 1 ppm group, and 54 percent and 25 percent in the 100 ppm group, respectively. Rats

orally treated with 100 mg/kg excreted 51 percent of the administered epichlorohydrin in the urine and 38 percent in expired air, while 7 to 10 percent remained in the body 72 hours after exposure. Tissue accumulation of radioactivity was highest in kidneys and liver.

IV. EFFECTS

A. Carcinogenicity

Epichlorohydrin appears to have low carcinogenic activity following dermal application. In two studies, epichlorohydrin applied topically to shaved backs of rats or mice did not induce any significant occurrence of skin tumors (Weil, 1964; Van Duuren, et al. 1974). However, subcutaneous injection of epichlorohydrin at levels as low as 0.5 mg have resulted in the induction of tumors at the injection site.

Extensive inhalation studies have recently identified epichlorohydrin as a potent nasal carcinogen in rats. At concentrations of 100 ppm, significant increases in the occurrence of squamous cell carcinomas of the nasal turbinates have been observed. Such tumors have been reported in lifetime exposure studies at 30 ppm but not at 10 ppm (Nelson, 1977, 1978).

Several recent epidemiological studies have suggested the risk of cancer as a result of occupational epichlorohydrin exposure. Both respiratory cancers and leukemia are in excess among some exposed worker populations, but this increase was not shown to be statistically significant (Enterline and Henderson, 1978; Enterline, 1979). The data suggest a latency period of roughly 15 years before the onset of carcinogenic symptoms. A second survey has failed to substantiate these findings (Shellenberger, et al. 1979). However, this survey used a younger study population with less exposure to epichlorohydrin.

B. Mutagenicity

Epichlorohydrin has been shown to cause reverse mutations in several organisms (SRC, 1979).

Cytogenetic studies with experimental animals have revealed increased aberrations in animals treated with epichlorohydrin. Both mice and rats have displayed dose-dependent increases in abnormal chromosome morphology at exposure levels ranging from 1 to 50 mg/kg (Santodonato, et al. 1979).

In humans, the clastogenic properties of epichlorohydrin have been reported in workers occupationally exposed to the chemical and in cultured "normal" lymphocytes exposed to epichlorohydrin (SRC, 1979). Cytogenetic evaluation of exposed workers has shown an increase of somatic cell chromosome aberrations associated with concentrations ranging from 0.5 to 5.0 ppm (2.0 to 20 mg/m^3) (SRC, 1979). Such chromosomal damage appears to be reversible once exposure to the chemical ceases.

C. Teratogenicity

Pregnant rats and rabbits exposed to 2.5 to 25 ppm epichlorohydrin during days 6 to 15 or days 6 to 18 of gestation showed a mild teratogenic response (John, et al. 1979). However examinations of all fetal tissue have not been completed. The incidence of resorbed fetuses was not altered by exposure to epichlorohydrin at the doses employed.

D. Other Reproductive Effects

The antifertility properties of epichlorohydrin have been examined by several investigators. Administration of 15 mg/kg/day of epichlorohydrin for 12 days resulted in reduced fertility of male rats (Halen, 1970). Five repeated doses of 20 mg/kg were more effective in rendering male rats infertile than was one 100 mg/kg dose or five 50 mg/kg doses (Cooper, et al.

1974). The suggested mode of action of epichlorohydrin is via the *in vivo* hydrolysis of the compound which produces alpha-chlorohydrin. Altered reproductive function has been reported for workers occupationally exposed to epichlorohydrin at concentrations less than 5 ppm.

E. Chronic Effects

Two species of rats and one specie of mice (both sexes) were exposed to 5 to 50 ppm epichlorohydrin for six hours per day, five days per week for a total of 65 exposures. All species and sexes displayed inflammatory and degenerative changes in nasal tissue, moderate to severe tubular nephrosis, and gross liver pathology at 50 ppm exposure (Quast, et al. 1979a). The same research group has also examined the effect of 100 ppm exposure for 12 consecutive days. The toxicity to nasal tissues was similar (Quast, et al. 1979b).

Altered blood parameters (e.g. increased neutrophilic megamyelocytes, decreased hemoglobin, hematocrit, and erythrocytes) have been observed in rats exposed to 0.00955 to 0.04774 ml epichlorohydrin per kg body weight administered intraperitoneally (Lawrence, et al. 1972). Lesions of the lungs and reduced weight gains were also observed.

Toxicity studies with various animal species have established that epichlorohydrin is moderately toxic by systemic absorption (Lawrence, et al. 1972). Acute oral LD_{50} values in experimental animals have ranged from 155 to 238 mg/kg for the mouse and from 90 to 260 mg/kg in the rat. Inhalation LC_{50} values range from 360 to 635 ppm in rats, to 800 ppm in mice (SRC, 1979). Single subcutaneous injections of epichlorohydrin in rats at doses of 150 or 180 mg/kg have resulted in severe injury to the kidney (Rotara and Pallade, 1966).

Accidental human exposures have been reviewed (NIOSH, 1976; Santodonato, et al. 1979). Direct exposure to epichlorohydrin vapor results in severe irritation of the eyes and respiratory membranes, followed by nausea, vomiting, headache, dyspnea, and altered liver function. A significant decrease was reported in pulmonary function among workers exposed to epichlorohydrin in an epoxy-resin manufacturing process. Workers were simultaneously exposed to dimethyl amino propylamine.

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Existing occupational standards for exposure to epichlorohydrin are reviewed in the NIOSH (1976) criteria document. The NIOSH recommended environmental exposure limit is a 2 mg/m^3 10-hour time-weighted average and a 19 mg/m^3 15-minute ceiling concentration. The current Occupational Safety and Health Administration standard is an 8-hour time-weighted average concentration of 5 ppm (20 mg/m^3).

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No. 101

Ethyl Methacrylate

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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ETHYL METHACRYLATE

Summary

Information on the carcinogenic and mutagenic effects of ethyl methacrylate was not found in the available literature. Ethyl methacrylate has, however, been shown to cause teratogenic effects in rats.

Chronic occupational exposure to ethyl methacrylate has not been reported in the available literature.

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

ETHYL METHACRYLATE

I. INTRODUCTION

Ethyl methacrylate (molecular weight 114.15) is the ethyl ester of methacrylic acid. It is a crystalline solid that melts at less than 75°C, has a boiling point of 117°C, a density of 0.9135, and an index of refraction of 1.4147. It is insoluble in water at 25°C and is infinitely soluble in alcohol and ether (Weast, 1975). It possesses a characteristic unpleasant odor (Austian, 1975).

Widely known as "Plexiglass" (in the polymer form), ethyl methacrylate is used to make polymers, which in turn are used for building, automotive, aerospace, and furniture industries. It is also used by dentists as dental plates, artificial teeth, and orthopedic cement (Austian, 1975).

II. EXPOSURE

Ethyl methacrylate is used in large quantities and therefore has potential for industrial release and environmental contamination. Ethyl methacrylate in the polymerized form is not toxic; however, chemicals used to produce ethyl methacrylate are extremely toxic. No monitoring data are available to indicate ambient air or water levels of the compound.

Human exposure to ethyl methacrylate from foods cannot be assessed due to a lack of monitoring data.

Bioaccumulation data on ethyl methacrylate were not found in the available literature.

III. PHARMACOKINETICS

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

No evidence has been found of the presence of ethyl methacrylate in the human urine. Therefore, it is hypothesized that it is rapidly metabolized and undergoes complete oxidation (Austian, 1975).

IV. EFFECTS

A. Carcinogenicity and Mutagenicity

Information on the carcinogenic and mutagenic effects of ethyl methacrylate was not found in the available literature.

B. Teratogenicity

Ethyl methacrylate is teratogenic in rats. Female rats were given intraperitoneal injections of 0.12 mg/kg, 0.24 mg/kg, and 0.41 mg/kg, on days 5, 10, and 15 of gestation. These doses were 10, 20, and 33 percent, respectively, of the acute intraperitoneal LD_{50} dose. Animals were sacrificed one day before parturition (day 20).

Deleterious effects were observed in the developing embryo and fetus. Effects were compound and generally dose-related. A 0.1223 ml/kg injected dose resulted in unspecified gross abnormalities and skeletal abnormalities in 6.3 percent and 5.0 percent of the test animals, respectively, when compared to the untreated controls. A dose of 0.476 ml/kg resulted in gross abnormalities in 15.7 percent of the treated animals and skeletal abnormalities in 11.7 percent of the treated animals (Singh, et al. 1972).

C. Other Reproductive Effects and Chronic Toxicity

Information on other reproductive effects and chronic toxicity of ethyl methacrylate was not found in the available literature.

D. Acute Toxicity

Lower molecular weight acrylic monomers such as ethyl methacrylate cause systemic toxic effects. Its administration results in an immediate

increase in respiration rate, followed by a decrease after 15-40 minutes. A prompt fall in blood pressure also occurs, followed by recovery in 4-5 minutes. As the animal approaches death, respiration becomes labored and irregular, lacrimation may occur, defecation and urination increase, and finally reflex activity ceases, and the animal lapses into a coma and dies (Austian, 1975).

Acrylic monomers are irritants to the skin and mucous membranes. When placed in the eyes of animals, they elicit a very severe response and, if not washed out, can cause permanent damage (Austian, 1975).

As early as 1941, Deichmann demonstrated that injection of 0.03 cc/kg body weight ethyl methacrylate caused a prompt and sudden fall in blood pessure, while respiration was stimulated immediately and remained at this level for 30 minutes. The final lethal dose (0.90-.12 cc/kg) brought about respiratory failure, although the hearts of these animals were still beating (Deichmann, 1941).

Work by Mir, et al. (1974) demonstrated that respiratory system effects alone may not kill the animal, but that cardiac effects may also contribute to the cause of death (Austian, 1975). Twelve methacrylate esters and methacrylic acid were tested on isolated perfused rabbit heart. Concentrations as low as 1 part in 100,000 (v/v) produced significant effects. The effects were divided into three groups according to the reversibility of the heart response. Ethyl methacrylate was placed in "Group 1", in which the heart response is irreversible at all concentrations (1:100,000; 1:10,000; 1:1,000). Five percent (v/v) caused a 41.2 percent decrease in the heart rate of isolated rabbit heart. The same concentration reduced heart contraction by 64 percent and coronary flow by 61.5 percent (Austian, 1975).

The findings of Deichmann (1941) that ethyl methacrylate affects blood pressure and respiration is substantiated by studies of Austian (1975). Response following administration of ethyl methacrylate was characterized by a biphenic response, an abrupt fall in blood pressure followed by a more sustained rise. Austian (1975) also found that the respiration rate is increased, the duration of effect being approximately 20 minutes, after which time the respiration rate returned to normal.

In the available literature LD_{50} values were found for only rabbit and rat; these were established by Deichmann in 1941. The oral value for the rat is 15,000 mg/kg, as opposed to 3,654-5,481 mg/kg for the rabbit. Inhalation values for the rat have been reported to be 3,300 ppm for 8 hours (Patty, 1962). Deichmann also established a skin toxicity LD_{50} for rabbit which was greater than 10 ml/kg. This was substantiated by another test which showed that moderate skin irritation (in rabbits) does result from ethyl methacrylate exposure (Patty, 1962).

VI. EXISTING GUIDELINES AND STANDARDS

Information on existing guidelines and standards was not found in the available literature.

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No. 102

Ferric Cyanide

Health and Environmental Effects

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

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FERRIC CYANIDE

I. INTRODUCTION

Ferric cyanide is a misnomer and is not listed as a specific compound in the comprehensive compendia of inorganic compounds (Weast, 1978). There are, however, a class of compounds known as "iron cyanide blues" consisting of various salts where the anions are the ferricyanide, $[Fe(CN)_6]^{3-}$, or the ferrocyanide, $[Fe(CN)_6]^{4-}$, and the cations are either Fe(III) or Fe(II) and sometimes mixtures of Fe(II) and potassium (Kirk and Othmer, 1967). The empirical formula of the misnamed ferric cyanide, $Fe(CN)_3$, corresponds actually to one of the ferricyanide compounds, the ferric ferricyanide with the actual formula $Fe[Fe(CN)_6]$, also known as Berlin green. The acid from which these salts are derived is called ferricyanic acid, $H_3[Fe(CN)_6]$ (also known as hexacyanoferric acid), molecular weight 214.98, exists as green-blue deliquescent needles, decomposes upon heating, and is soluble in water and alcohol. In this EPA/ECAO Hazard Profile only ferric ferricyanide, $Fe[Fe(CN)_6]$, and ferric ferrocyanide, $Fe_4[Fe(CN)_6]_3$, are considered; other ferrocyanide compounds are reported in a separate EPA/ECAO Hazard Profile (U.S. EPA, 1980).

These compounds are colored pigments, insoluble in water or weak acids, although they can form colloidal dispersions in aqueous media. These pigments are generally used in paint, printing inks, carbon paper inks, crayons, linoleum, paper pulp, writing inks and laundry blues. These compounds are sensitive to alkaline decomposition (Kirk and Othmer, 1967).

II. EXPOSURE

Exposure to these compounds may occur occupationally or through ingestion of processed food or contaminated water. However, the extent of food or water contamination from these compounds has not been described in the

available literature. Prussian blue, potassium ferric hexacyanoferrate (II), has been reported as an antidote against thallium toxicity. When administered at a dose of 10 g twice daily by duodenal intubation, it prevents the intestinal reabsorption of thallium (Dreisbach, 1977).

III. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data could not be located in the available literature.

B. Metabolism

There is no apparent metabolic alteration of these compounds. As for the other ferrocyanide and ferricyanide salts, these compounds are not cyanogenic (Gosselin, et al. 1976).

C. Excretion

No information is available for ferric hexacyanoferrates (II) or (III), but information is available for other related ferrocyanide and ferricyanide salts (U.S. EPA, 1980; Gosselin, et al. 1976) which seems to be rapidly excreted in urine apparently without metabolic alteration.

IV. EFFECTS

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

Pertinent data could not be located in the available literature.

B. Acute Toxicity

No adequate toxicity data are available. All ferrocyanide and ferricyanide salts are reported as possibly moderately toxic (from 0.5 to 5.0 mg/kg as a probable lethal dose in humans) (Gosselin, et al. 1976).

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature regarding the aquatic toxicity of ferric cyanide.

VI. EXISTING GUIDELINES AND STANDARDS

Pertinent data could not be located in the available literature.

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No. 103

Fluoranthene

Health and Environmental Effects

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FLUORANTHENE

SUMMARY

No direct carcinogenic effects have been produced by fluoranthene after administration to mice. The compound has also failed to show activity as a tumor initiator or promoter. However, it has shown cocarcinogenic effects on the skin of mice when combined with benzo(a)pyrene, increasing tumor incidence and decreasing tumor latency.

Fluoranthene has not shown mutagenic, teratogenic or adverse reproductive effects.

Daphnia magna appears to have low sensitivity to fluoranthene with a reported 48-hour EC_{50} of 325,000 µg/l. The bluegill, however, is considerably more sensitive with an observed 96-hour LC_{50} value of 3,980. The 96-hour LC_{50} for mysid shrimp is 16 µg/l, and a reported chronic value is 16 µg/l. Observed 96-hour EC_{50} values based on cell numbers for fresh and saltwater algae are over 45,000 µg/l.

FLUORANTHENE

I. INTRODUCTION

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

Fluoranthene (1,2-benzacenapthene, M.W. 202) is a polynuclear aromatic hydrocarbon of molecular formula $C_{16}H_{10}$. Its physical properties include: melting point, 111°C; boiling point, 375°C; water solubility, 265 µg/l (U.S. EPA, 1978).

Fluoranthene is chemically stable, but may be removed from water by biodegradation processes (U.S. EPA, 1979). The compound is relatively insoluble in aqueous systems. Fluoranthene may be adsorbed and concentrated on a variety of particulate matter. Micelle formation through the action of organic solvents or detergents may occur. (U.S. EPA, 1979).

Flouranthene is produced from the pyrolytic processing of coal and petroleum and may result from natural biosynthesis (U.S. EPA, 1979).

II. EXPOSURE

Fluoranthene is ubiquitous in the environment; it has been monitored in food, water, air, and in cigarette smoke (U.S. EPA, 1979). Sources of contamination include industrial effluents and emissions, sewage, soil infiltration, and road runoff (U.S. EPA, 1979). Monitoring of drinking water has shown an average fluoranthene concentration of 27.5 ng/l in positive samples (Basu, et al. 1978). Food

levels of the compound are in the ppb range, and will increase in smoked or cooked foods (pyrolysis of fats) (U.S. EPA, 1979). Borneff (1977) has estimated that dietary intake of fluoranthene occurs mainly from fruits, vegetables, and bread.

An estimated daily exposure to fluoranthene has been prepared by EPA (1979):

Source	Estimated Exposure
Water	0.017 µg/day
Food	1.6 - 16 µg/day
Air	0.040 - 0.080 µg/day

Based on the octanol/water partition coefficient, the U.S. EPA (1979) has estimated weighted average bioconcentration factor of 890 for fluoranthene for the edible portion of fish and shellfish consumed by Americans.

III. PHARMACOKINETICS

A. Absorption

Based on animal toxicity data (Smythe, et al. 1962), fluoranthene seems well absorbed following oral or dermal administration. The related polynuclear aromatic hydrocarbon (PAH), benzo(a)pyrene, is readily absorbed across the lungs (Vainio, et al. 1976).

B. Distribution

Pertinent information could not be located in the available literature. Experiments with benzo(a)pyrene indicate localization in a wide variety of body tissues, primarily in body fats (U.S. EPA, 1979).

C. Metabolism

Pertinent information could not be located in the available literature. By analogy with other PAH compounds, fluoranthene may be expected to undergo metabolism by the mixed function oxidase enzyme complex. Transformation products produced by this action include ring hydroxylated products (following epoxide intermediate formation) and conjugated forms of these hydroxylated products (U.S. EPA, 1979).

D. Excretion

Pertinent information could not be located in the available literature. Experiments with PAH compounds indicate excretion through the hepatobiliary system and the feces; urinary excretion varies with the degree of formation of conjugated metabolites (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

Testing of fluoranthene in a marine carcinogenesis bioassay failed to show tumor production following dermal or subcutaneous administration of fluoranthene (Barry, et al., 1935).

Skin testing of fluoranthene as a tumor promoter or initiator in mice has also failed to show activity of the compound (Hoffman, et al., 1972; Van Duuren and Goldschmidt, 1976).

Fluoranthene has been demonstrated to have carcinogenic activity (Hoffmann and Wynder, 1963; Van Duuren