1,1-Dichlorethylene

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.

1,1-DICHLOROETHYLENE

Summary

Ambient levels of 1,1-dichloroethylene have not been determined. The primary effect of acute and chronic occupational exposure to 1,1-dichloroethylene is depression of the central nervous system. In experimental animals, both liver and kidney damage have been noted after exposure, regardless of the route of administration. 1,1-Dichloroethylene has been shown to be a mutagen in bacterial systems and a carcinogen in mice. Both kidney adenocarcinomas and mammary adenocarcinomas were produced after exposure to 1,1-dichloroethylene by inhalation. No teratogenic effects have been observed.

For freshwater fish, the reported 96-hour LC_{50} values range from 73,900 to 108,000 μg/l 1,1-dichloroethylene. Reported 48-hour EC_{50} values for Daphnia magna range from 11,600 to 79,000 μg/l. 96-Hour LC_{50} values of over 224,000 μg/l have been observed for saltwater fish and invertebrates. An embryo-level test with freshwater fish resulted in an adverse effect occurring at 2,800 μg/l. Algae, both fresh and saltwater, apparently are not affected by concentrations of 1,1-dichloroethylene as high as 716,000 μg/l.

1,1-DICHLOROETHYLENE

I. INTRODUCTION

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

1,1-Dichloroethylene ($C_2H_2Cl_2$; molecular weight 96.95) is a clear colorless liquid used as a chemical intermediate in the synthesis of methyl-chloroform and in the production of polyvinylidene chloride copolymers (PVCDs). Prior to 1976, annual production of 1,1-dichloroethylene was approximately 120,000 metric tons (Arthur D. Little, Inc., 1976). 1,1-Di-chloroethylene has the following physical/chemical properties: water solubility of 2,500 μg/ml, vapor pressure 591 mm Hg, and a melting point of -122.1°C. For more general information regarding the dichloroethylenes, the reader is referred to the EPA/ECAO Hazard Profile on Dichloroethylenes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

The National Organic Monitoring Survey (U.S. EPA, 1978a) reported detecting 1,1-dichloroethylene in finished drinking waters; however, neither the amount nor the occurrence was quantified.

B. Food

Pertinent data could not be located in the available literature on the ingestion of 1,1-dichloroethylene in foods. The U.S. EPA (1979a) has estimated the weighted bioconcentration factor for 1,1-dichloroethylene to be 6.9 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on the octanol/water partition coefficient of 1,1-dichloroethylene.

C. Inhalation

The population at risk due to vinylidene chloride exposure is composed primarily of workers in industrial or commercial operations manufacturing or using it. Airborne emissions of vinylidene chloride are not likely to pose a significant risk to the general population. Emissions during production, storage, and transport can be controlled by methods similar to those planned for control of vinyl chloride (Hushon and Kornreich, 1978).

III. PHARMACOKINETICS

A. Absorption

Specific data on the absorption of dichloroethylenes are unavailable. However, a recent study by McKenna, et al. (1978b) suggests that in rats most, if not all, of the orally administered dose is absorbed at two dose levels: 1 and 50 mg/kg.

B. Distribution

Distribution of 1,1-dichloroethylene was studied in rats following inhalation (Jaeger, et al. 1977). The largest concentrations were found in kidney, followed by liver, spleen, heart, and brain, and fasting made no difference in the distribution pattern. At the subcellular level 1,1-dichloroethylene or its metabolites appear to bind to macromolecules of the microsomes and mitochondria (Jaeger, et al. 1977). There is also some association with the lipid fraction.

C. Metabolism

In the intact animal, a large portion of the systemically absorbed 1,1-dichloroethylene is metabolically converted, with 36 percent appearing in the urine of rats within 26 hours (Jaeger, et al. 1977). The essential

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feature of 1,1-dichloroethylene metabolism is the presence of epoxide inter-
mediates, which are reactive and may form covalent bonds with tissue macro-
molecules (Henschler, 1977). In rats and mice, covalently bound metabolites
are found in the kidney and liver (McKenna, et al. 1978b). Interaction of
1,1- dichloroethylene with the microsomal mixed function oxidase system is
not clear, since both inhibitors (dithiocarbamate) and inducers (phenobarbi-
tal) decreased the toxic effects of the compound (Anderson and Jenkins,
1977; Reynolds, et al. 1975; Jenkins, et al. 1972). However, Carlson and
Fuller (1972) reported increased mortality from 1,1-dichloroethylene in rats
following phenobarbital pretreatment. There is evidence that the 1,1-di-
chloroethylene metabolites are conjugated with glutathione, which presumably
represents a detoxification step (McKenna, et al. 1978a).

D. Excretion

It is speculated that 1,1-dichloroethylene has a rapid rate of
elimination, since a substantial fraction of the total absorbed dose may be
recovered in the urine within 26 to 72 hours (Jaeger, et al. 1977; McKenna,
et al. 1978a). Also, disappearance of covalently bonded metabolites of 1,1-
dichloroethylene (measured as TCA-insoluble fractions) appears to be fairly
rapid, with a reported half-life of 2 to 3 hours (Jaeger, et al. 1977).

IV. EFFECTS

A. Carcinogenicity

1,1-Dichloroethylene has been shown to produce kidney adenocarci-
nomas in male mice and mammary adenocarcinomas in female mice upon inhala-
tion of 100 mg/m^3 (Maltoni, 1977; Maltoni, et al. 1977). In similar ex-
periments with Sprague-Dawley rats exposed up to 800 mg/m^3, no significant
increase in tumor incidence was noted. Also, hamsters exposed to the same

conditions as the mice failed to exhibit an increased tumor incidence (Maltoni, et al. 1977). In rats exposed to 1,1-dichloroethylene in their drinking water (200 mg/l), there was no evidence of increased tumors (Rampy, et al. 1977). There was an increased incidence of mammary tumors in rats receiving 20 mg of 1,1-dichloroethylene by gavage 4 to 5 days a week for 52 weeks. The incidence was 42 percent in the treated animals and 34 percent in the controls; however, the data was not analyzed statistically (Maltoni, et al. 1977).

B. Mutagenicity

1,1-Dichloroethylene has been shown to be mutagenic in $\underline{S.\ typhimurium}$ (Bartsch, et al. 1975) and $\underline{E.\ coli}$ K12 (Greim, et al. 1975). In both systems, mutagenic activity required microsomal activation. In mammalian systems, 1,1-dichloroethylene was negative in the dominant lethal assay (Short, et al. 1977b; Anderson, et al. 1977).

C. Teratogenicity

A study by Murrary, et al. (1979) failed to show teratogenic effects in rats or rabbits inhaling concentrations of up to 160 ppm 1,1-dichloroethylene for 7 hours per day or in rats given drinking water containing 200 ppm 1,1-dichloroethylene.

D. Other Reproductive Effects

Pertinent data could not be located in the available literaure.

E. Chronic Toxicity

In animal studies, liver damage is associated with exposure, either in the air or water, to 1,1-dichloroethylene (6 $\mu g/m^3$ or 0.79 $\mu g/l$) with transitory damage appearing as vacuolization in liver cells. In both guinea pigs and monkeys, continuous exposure to 1,1-dichloroethylene produced increased mortality, while intermittent exposure to the same concentration in

air produced no increase in mortality (U.S. EPA, 1979a). Less attention has been paid to the renal toxicity of 1,1-dichloroethylene despite the occurrence of histologically demonstrated damage at exposures equal to or less than those required for hepatotoxicity (Predergast, et al. 1967; Short, et al. 1977a).

F. Other Relevant Information

Alterations in tissue glutathione concentrations affect the hepatotoxicity of 1,1-dichloroethylene, with decreased tissue glutathione associated with greater toxicity and elevated glutathione associated with decreased toxicity (Jaeger, et al. 1973,1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

Dill, et al. calculated, for the fathead minnow, Pimephales promelas, 96-hour LC_{50} values of 169,000 µg/l using static techniques and 108,000 µg/l using flow-through tests with measured concentrations. The reported 96-hour LC_{50} value for the bluegill, Lepomis macrochirus, is 73,900 µg/l in a static test (U.S. EPA, 1978b). Two 48-hour tests with Daphnia magna resulted in EC_{50} values of 11,600 and 79,000 µg/l, respectively (Dill, et al.; U.S. EPA, 1978b). The 96-hour LC_{50} values for the sheepshead minnow, Cyprinodon variegatus, and the tidewater silverside, Menidia beryllina, are 249,000 and 250,000 µg/l, respectively (U.S. EPA, 1978b; Dawson, et al. 1977). The 96-hour LC_{50} for the mysid shrimp, Mysidopsis bahia, is reported to be 224,000 µg/l (U.S. EPA, 1978b).

B. Chronic Toxicity

An embryo-larval test with the fathead minnow resulted in no adverse effects occurring at 2,800 µg/l, the highest test concentration (U.S. EPA, 1978b).

C. Plant Effects

The 96-hour EC_{50} value based on cell numbers of the freshwater alga, Selenastrum capricornutum, is reported to be greater than 798,000 μg/l (U.S. EPA, 1978b). The effective concentration of 1,1-dichloroethylene on the saltwater alga, Skeletonema costatum, was observed to be 712,000 μg/l (U.S. EPA, 1978b).

D. Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value (TLV) for 1,1-dichloroethylene is 40 mg/m^3, with calculated daily exposure limits of 286 mg/day. 1,1-Dichloroethylene is suspected of being a human carcinogen; and using the "one-hit" model, the U.S. EPA (1979a) has estimated levels of 1,1-dichloroethylene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk Levels with Corresponding Draft Criteria		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0.013 μg/l	0.13 μg/l	1.3 μg/l
Consumption of fish and shellfish only.	0.21 μg/l	2.1 μg/l	21 μg/l

B. Aquatic

For 1,1-dichloroethylene, the drafted criterion to protect freshwater aquatic life is 530 μg/l as a 24-hour average, not to exceed 1,200 μg/l at any time. No saltwater criterion has been proposed because of insufficient data.

1,1-DICHLOROETHYLENE

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trans-1,2-Dichloroethylene

Health and Environmental Effects

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TRANS-1,2-DICHLORETHYLENE

SUMMARY

There is little specific information available on trans-1,2-dichloroethylene. This compound is quantitatively less toxic than the 1,1-dichloroethylene isomer; however, the toxicity appears qualitatively the same with depression of the central nervous system as well as liver and kidney damage. Trans-1,2-dichloroethylene has been shown to be a mutagen in bacterial systems. The teratogenicity and carcinogenicity of this compound have not been evaluated.

In the only aquatic study reported, the observed 96-hour LC_{50} value for the bluegill is 135,000 $\mu g/l$ in a static bioassay.

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TRANS-1,2-DICHLORETHYLENE

I. INTRODUCTION

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

Trans-1,2-dichloroethylene (traans 1,2-DCE; $C_2H_2Cl_2$; molecular weight 96.95) is a clear colorless liquid. Since the early 1960's trans-1,2-dichloroethylene has had no wide industrial usage (Patty, 1963). Trans-1,2-dichloroethylene has the following physical/chemical properties: water solubility of 6,300 μg/ml, a vapor pressure of 324 mm Hg, and a melting point of -50°C (Patty, 1963).

II. EXPOSURE

A. Water

Trans-1,2-dichloroethylene was found at a concentration of 1 μg/l in Miami drinking water (U.S. EPA, 1975, 1978).

B. Food

Pertinent data could not be located in the available literature on the ingestion of trans-1,2-dichloroethylene in foods. The U.S. EPA (1979) has not estimated a bioconcentration factor for trans-1,2-dichloroethylene.

C. Inhalation

Pertinent information could not be located in the available literature.

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III. PHARMACOKINETICS

A. Absorption

Animal or human studies do not appear to exist which specifically document the degree of systemic absorption of trans-1,2-dichloroethylene by any route.

B. Distribution

Pertinent data could not be located in the available literature.

C. Metabolism

Trans-1,2-dichloroethylene is metabolized through an epoxide intermediate to either a dichloroacetaldehyde or monochloroacetic acid (Liebman and Ortiz, 1977). The epoxide intermediate which is reactive, may form covalent bonds with tissue macromolecules (Henschler, 1977). Metabolism of the cis-isomer relative to the amount taken up by the liver was much greater than the trans-isomer (McKenna, et al. 1977).

D. Excretion

Pertinent data could not be located in the available literature.

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

Trans-1,2-dichloroethylene has been shown to be negative in the E. coli K12 and Salmonella mutagenicity assays (Greim, et al. 1975; Cerna and Kypenova, 1977).

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C.   Teratogenicity and Other Reproductive Effects

Pertinent information could not be located in the available literature.

D.   Chronic Toxicity

Although little data is available specifically on trans-1,2-dichloroethylene, it appears that chronic exposure results in kidney and liver damage similar to that noted with 1,1-dichloroethylene (U.S. EPA, 1979). Jenkins, et al. (1972) found trans-1,2-dichloroethylene to be considerably less potent than 1,1-dichloroethylene.

V.   AQUATIC TOXICITY

A.   Acute Toxicity

The reported 96-hour LC_{50} value for the bluegill, Lepomis macrochirus, exposed to 1,2-dichloroethylene is 135,000 µg/l (U.S. EPA, 1979) in a static test procedure.

B.   Chronic Toxicity, Plant Effects and Residues

Pertinent information could not be located in the available literature.

VI.   EXISTING GUIDELINES AND STANDARDS

A.   Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value (TLV) for 1,2-dichloroethylene is 790 mg/m^3, with calculated daily exposure limits of 5,643 mg/day. The U.S. EPA (1979) draft Water Quality Criteria Document for Dichloroethylene states that human health criterion could not be derived due to the lack of sufficient data on which to base a criterion.

B.   Aquatic

Guidelines do not exist for salt water species because of insufficient data. The draft criterion to protect freshwater aquatic life is 530 μg/l as a 24-hour average and not to exceed 1200 μg/l at any time (U.S. EPA, 1979).

TRANS 1,2-DICHLOROETHYLENE

REFERENCES

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Dichloroethylenes

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DICHLOROETHYLENES

Summary

Of the three dichloroethylene isomers, cis 1,2-dichloroethylene, trans 1,2-dichloroethylene, and 1,1-dichloroethylene, only the 1,1-dichloroethylene isomer is produced in large quantities. Most of the health effects information available is related to the 1,1-dichloroethylene isomers; however, qualitatively the toxicity of the 1,2-dichloroethylene isomers appears to be similar, with depression of the central nervous system and liver and kidney damage. Of the three isomers, 1,1-dichloroethylene is the most toxic. Both 1,1-dichloroethylene and trans 1,2-dichloroethylene are mutagenic in bacterial systems. Only 1,1-dichloroethylene has been shown to be a carcinogen.

All of the available aquatic data, with one exception, are for 1,1-dichloroethylene. Reported 96-hour LC_{50} values for the bluegill are 73,900 and 135,500 μg/l, respectively, for 1,1-dichloroehtylene and 1,2-dichloroethylene. Two observed 48-hour LC_{50} values for Daphnia exposed to 1,1-dichloroethylene range were 11,600 and 79,000 μg/l. All saltwater fish and invertebrates tested with 1,1-dichloroethylene showed 96-hour LC_{50} values over 224,000 μg/l, and all algae tested both in fresh and saltwater, had 96-hour EC_{50} values (based on cell numbers) of 716,000 μg/l and over. In the only reported chronic study, no adverse effects were observed at the highest test concentration of 2,800 μg/l for fathead minnows exposed to 1,1-dichloroethylene.

DICHLOROETHYLENES

I. INTRODUCTION

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

The dichloroethylenes ($C_2H_2Cl_2$; molecular weight 96.95) consist of the three isomers: 1,1-dichloroethylene, cis- 1,2-dichloroethylene, and trans-1,2-dichloroethylene. Dichloroethylenes are clear colorless liquids with water solubilities between 2,500 and 6,300 µg/l, vapor pressures between 591 and 208 mm Hg, and melting points between -50°C and -122°C (U.S. EPA, 1979). The 1,1-dichloroethylene isomer is the most extensively used in industry, with annual production prior to 1976 of approximately 120,000 metric tons (Arthur D. Little, Inc., 1976). The 1,1-dichloroethylene isomer is used as a chemical intermediate in the synthesis of methylchloroform and in the production of polyvinylidene chloride copolymers (PVDCs).

II. EXPOSURE

A. Water

The National Organic Monitoring Survey (U.S. EPA, 1978a) reported detecting 1,1-dichloroethylene in finished drinking waters; however, neither the amount nor the occurrence was quantified. Both cis and trans-1,2-dichloroethylene were found at concentrations of 16 and 1 µg/l, respectively, in Miami drinking water (U.S. EPA, 1975, 1978b).

B. Food

Pertinent data could not be located on the ingestion of dichloro-ethylene in foods. The U.S. EPA (1979) has estimated the weighted bioconcen-tration factor for 1,1-dichloroethylene to be 6.9 for the edible portions of

fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficients of 1,1-dichloroethylene. There is no estimate for a bioconcentration factor for the other isomers.

C.   Inhalation

The population at risk due to vinylidene chloride exposure is composed primarily of workers in industrial or commercial operations manufacturing or using it. Airborne emissions of vinylidene chloride are not likely to pose a significant risk to the general population. Emissions during production, storage, and transport can be controlled by methods similar to those planned for control of vinyl chloride (Hushon and Kornreich, 1978)

III. PHARMACOKINETICS

A.   Absorption

Specific data on the absorption of dichloroethylenes are unavailable. However, a recent study by McKenna, et al. (1978b) suggests that in rats most, if not all, of the orally administered dose is absorbed at two dose levels: 1 and 50 mg/kg.

B.   Distribution

Distribution of 1,1-dichloroethylene was studied in rats following inhalation (Jaeger, et al. 1977). The largest concentrations were found in kidney, followed by liver, spleen, heart, and brain; and fasting made no difference in the distribution pattern. At the subcellular level 1,1-dichloroethylene or its metabolites appear to bind to macromolecules of the microsomes and mitochondria (Jaeger, et al. 1977). There is also some association with the lipid fraction. Distl,2-dichloroethylene isomers are not available.

C.   Metabolism

The essential feature of all dichloroethylene metabolism is the presence of epoxide intermediates which are reactive and may form covalent

bonds with tissue macromolecules (Henschler, 1977). In rats and mice, covalently bound metabolites of 1,1-dichloroethylene are found in the kidney and liver (McKenna, et al. 1978b). Interaction of dichloroethylenes with the microsomal mixed function oxidase system is not clear, since both inhibitors (dithiocarbamate) and inducers (phenobarbital) decreased the toxic effects of 1,1-dichloroethylene (Anderson and Jenkins, 1977; Reynolds, et al. 1975; Jenkins, et al. 1972). Carlson and Fuller (1972), however, reported increased mortality from 1,1-dichloroethylene in rats following phenobarbital pretreatment. There is evidence that the 1,1-dichloroethylene metabolites are conjugated with gluthathione, which presumably represents a detoxification step (McKenna, et al. 1978b).

B. Excretion

The only information available on elimination pertains to the 1,1-dichloroethylene isomer. It is postulated that the 1,1-dichloroethylene isomer has a rapid rate of elimination since a substantial fraction of the total absorbed dose may be recovered in urine within 26 to 72 hours (Jaeger, et al. 1977; McKenna, et al. 1978a). Also, disappearance of covalently bonded metabolites of 1,1-dichloroethylene (measured as TCA-insoluble fractions) appears to be fairly rapid, with a reported half-life of 2 to 3 hours (Jaeger, et al. 1977).

IV. EFFECTS

A. Carcinogenicity

There is only data on the carcinogenicity of the 1,1-dichloroethylene isomer. This isomer has been shown to produce kidney adenocarcinomas in male mice and mammary adenocarcinomas in female mice upon inhalation of 100 mg/m^3 (Maltoni, et al. 1977; Maltoni, 1977). In

similar experiments with Sprague-Dawley rats exposed as high as 800 mg/m^3, no significant increase in tumor incidence was noted. Hamsters exposed to the same conditions as the mice failed to exhibit an increased tumor incidence (Maltoni, et al. 1977). In rats exposed to 1,1-dichloroethylene in their drinking water (200 mg/l) there was no evidence of increased tumors (Rampy, et al. 1977). There was an increased incidence of mammary tumors in rats receiving 20 mg of 1,1-dichloroethylene by gavage 4 to 5 days a week for 52 weeks. The incidence was 42 percent in the treated animals and 34 percent in the controls; however, the data was not analyzed statistically (Maltoni, et al. 1977).

B.   Mutagenicity

1,1-Dichloroethylene has been shown to be mutagenic in S. typhimurium (Bartsch, et al. 1975) and E. coli K12 (Greim, et al. 1975); however, both the cis and trans isomers of 1,2-dichloroethylene were non-mutagenic when assayed with E. coli K12. In order to demonstrate mutagenic activity, 1,1-dichloroethylene needed microsomal activation. In addition, cis 1,2-dichloroethylene was mutagenic in Salmonella tester strains, and promoted chromosomal aberrations in cytogenic analysis of bone marrow cells (Cerna and Kypenova, 1977). In mammalian systems, 1,1-dichloroethylene was negative in the dominant lethal assay (Short, et al. 1977b; Anderson, et al. 1977).

C.   Teratogenicity

A study by Murray, et al. (1979) failed to show teratogenic effects in rats or rabbits inhaling concentrations of up to 160 ppm 1,1-dichloroethylene for 7 hr/day or in rats given drinking water containing 200 ppm 1,1-dichloroethylene.

D.   Other Reproductive Effects

Pertinent data could not be located in the available literature.

E.   Chronic Toxicity

In animal studies, liver damage is associated with exposure either in the air or water, to dichloroethylenes (6 mg/m^3 or 0.79 mg/l) with transitory damage appearing as vacuolization in liver cells (U.S. EPA, 1979).   Jenkins, et al. (1972) found both cis and trans 1,2-dichloro-ethylene to be considerably less potent than 1,1-dichloroethylene as a hepatotoxin.   Less attention has been paid to the renal toxicity of the dichloroethylenes despite the occurrence of histologically demonstrated damage at 1,1-dichloroethylene exposures equal to or less than those required for hepatoxicity (Prendergast, et al. 1967; Short, et al. 1977a).

F.   Other Relevant Information

Alterations in tissue glutathione concentrations affect the hepatotoxicity of 1,1-dichloroethylene, with decreased tissue glutathione associated with greater toxicity and elevated gluthathione associated with decreased toxicity (Jaeger, et al. 1973, 1977).

V.   AQUATIC TOXICITY

A.   Acute Toxicity

All of the available data for dichloroethylene, with one exception, are for 1,1-dichloroethylene.   The data on acute static tests with bluegill, Lepomis macrochirus, under similar conditions show a correlation between the degree of chlorination and toxicity.   The 96-hour LC$_{50}$ values for the bluegill are 73,900 and 135,000 ug/l for 1,1- and 1,2-dichloroethylene, respectively.   Additional data for other ethylene chlorides are as follows: 44,700 ug/l for trichloroethylene, and 12,900 ug/l for tetrachloroethylene (U.S. EPA, 1978c).   These results indicate an increase in the lethal effect on bluegills with an increase in chlorine content.

The 96-hour LC_{50} value for the sheepshead minnow, _Cypuimocen variegatus_, tidewater silverside, _Menidia beryllina_, and mysid shrimp, _Mysidepsis behia_, following exposure to 1,1-dichloroethylenes are all over 224,000 ug/l (U.S. EPA, 1978c).

B.   Chronic Toxicity

In the only reported chronic study, an embryo-larval test in fathead minnows, no adverse effects were observed at the highest test concentration of 1,1-dichloroethylene, 2800 μg/l (U.S. EPA, 1979).

C.   Plant Effects

The 96-hour EC_{50} values based on cell numbers of the freshwater algae, _Salenestrum capricornutum_ and the saltwater algae, _Skeletonema costatum_, are 798,000 and 712,000 μg/l, respectively, for exposure to 1,1-dichloroethylene (U.S. EPA, 1978c).

D.   Residues

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A.   Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit values (TLV) are 40 mg/m^3 (1,1-dichloro-ethylene) and 790 mg/m^3 (1,2-dichloroethylene). These values allow daily exposures of 286 mg 1,1-dichloroethylene per day and 5,643 mg 1,2-di-chloroethylene per day. The U.S. EPA (1979) draft water criteria document for dichloroethylene states that no human health criterion could be derived for cis- and trans-1,2-dichloroethylene due to the lack of sufficient data on which to base a criterion. 1,1-dichloroethylene is suspected of

being a human carcinogen, and using the "one-hit" model, the U.S. EPA

(1979) has estimated levels of 1,1-dichloroethylene in ambient water

which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk levels and Corresponding Draft Criteria		
	10^7	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish	0.013 ug/l	0.13 ug/l	1.3 ug/l
Consumption of fish and shellfish only.	0.11 ug/l	2.1 ug/l	21 ug/l

B.   Aquatic

The proposed draft criterion to protect freshwater species

from dichloroethylene toxicity are as follows (U.S. EPA, 1979):

Compound	24-hr. Average	Concentration not to be exceeded at anytime
1,1-dichloroethylene	530 ug/l	1,200 ug/l
1,2-dichloroethylene	620 ug/l	1,400 ug/l

For saltwater species:

1,1-dichloroethylene	1,700 ug/l	3,900 ug/l
1,2-dichloroethylene	Not available	Not available

DICHLOROETHYLENES

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Dichloromethane

Health and Environmental Effects

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U.S. ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C.   20460

October 30, 1980

DISCLAIMER

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

DICHLOROMETHANE (DCM)

SUMMARY

In humans, DCM is a central nervous system depressant resulting in narcosis at high concentrations, and impaired task performance. Dichloromethane is metabolized to carbon monoxide and causes an increase in carboxyhemoblogin, placing persons with cardiovascular disease, and perhaps those who are pregnant, at increased risk of disease. On the basis of present evidence, DCM cannot be firmly identified as an animal or human carcinogen. DCM has been shown to be mutagenic to _Salmonella_, but not to _S. cerevisia_ and _Drosophila_, and causes cell transformation.

Aquatic organisms are fairly resistant to dichloromethane, with acute toxicity values ranging from 193,000 to 331,000 ug/l.

DICHLOROMETHANE

I. INTRODUCTION

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

Dichloromethane (CH_2Cl_2, methylene chloride, methylene dichloride, and methylene bichloride; molecular weight 84.93) is a colorless liquid with a melting point of -95.1°C, a boiling point of 40°C, a specific gravity of 1.327 g/ml at 20°C, a vapor pressure of 362.4 mm Hg at 20°C, and a solubility in water of 13.2 g/l at 25°C. Dichloromethane is a common industrial solvent found in insecticides, metal cleaners, paints, and paint and varnish removers (Balmer, et al., 1976). In 1976, 244,129 metric tons were imported (U.S. EPA, 1977). For additional information regarding the halomethanes as a class, the reader is referred to the Hazard Profile on Halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

The U.S. EPA (1975) has identified dichloromethane in finished drinking waters in the U.S. in 8 of 83 sites, with a maximum level of 0.007 mg/l and a median of less than 0.001 mg/l. The dichloromethane in drinking water is not a product of water chlorination (U.S. EPA, 1975; Morris and McKay, 1975). In the national organics monitoring survey, dichloromethane was detected in 15 of 109 sites, with a mean concentration (positive results only) of 0.0061 mg/l (U.S. EPA, 1978).

B.   Food

Pertinent information could not be located in the
available literature.

C.   Inhalation

Reported background concentrations of dichloromethane
in both continental and saltwater atmospheres were about 0.00012
mg/m^3, and urban air concentrations ranged from less than 0.00007
to 0.00005 mg/m^3. Local indoor concentrations can be high due to
the use of aerosol sprays or solvents (Natl. Acad. Sci., 1978).

III. PHARMACOKINETICS

A.   Absorption

Efficiences of absorption of dichloromethane by the
lungs are between 30 to 75 percent, depending on length of
exposure, concentration, and activity level (Natl. Acad. Sci.,
1978; Natl. Inst. Occup. Safety and Health, 1976).

B.   Distribution

Upon inhalation and absorption, dichloromethane levels
increase rapidly in the blood to equilibrium levels that depend
primarily upon atmosphere concentration (Natl. Acad. Sci., 1978).
Carlsson and Hultengren (1975) reported that dichloromethane
and its metabolites were in highest concentrations in white
adipose tissue, followed in descending order by levels in brain
and liver.

C.   Metabolism

Dichloromethane is metabolized to carbon monoxide.
Some of this carbon monoxide is exhaled, but a significant amount

is involved in the formation of carboxyhemoglobin (Natl. Inst. Occup. Safety and Health, 1976). Cardiorespiratory stress from elevated carboxyhemoglobin may be greater as a result of dichloromethane exposure than from exposure to carbon monoxide alone due to the continued formation of carbon monoxide following cessation of dichloromethane exposure (Stewart and Hake, 1976). As shown by animal experiments, other possible human metabolites of dichloromethane include carbon dioxide, formaldehyde, and formic acid (Natl. Acad. Sci., 1978).

D. Excretion

A large proportion of absorbed dichloromethane is ex-creted unchanged, primarily via the lungs, with some in the urine. DiVincenzo, et al. (1972) have reported that about 40 percent of absorbed dichloromethane undergoes some reaction and decomposition process in the body.

IV. EFFECTS

A. Carcinogenicity

Friedlander et al. (1978) analyzed the mortality of Eastman-Kodak male employees exposed to low levels of methylene chloride. No significant neoplastic risk factors were identified.

Theiss and coworkers (1977) examined the tumorigenic activity of dichloromethane in strain A mice. Dichloromethane at the low dose (1:5 dilution of the maximum tolerated dose) produced marginally significant increases in tumor response. Shimkin and Stoner (1975) did not report a positive carcinogenic response for the strain A mouse bioassay system.

Although the data base is inadequate, there is a basis to suspect the potential carcinogenicity of DCM based on the (marginally positive) pulmonary adenoma response in strain A mice, on positive responses for mutagenicity in the Ames test, and on the ability to transform rat embryo cells (see below).

B.   Mutagenicity

Simmon, et al. (1977) reported that dichloromethane was mutagenic to _Salmonella_ _typhimurium_ strain TA100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required, and the number of revertants per plate was directly dose-related. A linear dose response curve was observed. Dichloromethane did not increase mitotic recombination in _S._ _cerevisia_ D3 (Simmon, et al., 1977), and it was reported negative on testing for mutagenicity in _Drosophila_ (Filippova, et al., 1967). Positive results for dichloromethane in the Ames assay were recently confirmed by Jongen, et al. (1978) with vapor phase exposures (5,700 ppm) of strains TA98 and TA100.

C.   Teratogenicity

Schwetz et al., (1975) showed that DCM can affect embryonal and fetal development in rats and mice as evidenced by the increased incidence of extra sternebrae. DCM also affects the development of chick embryos, causing a 2 to 3-fold increase in malformation frequencies (Elsavaara et al., 1979).

D.   Other Reproductive Effects

Gynecologic problems in femal workers exposed for

long period to gasoline and dichloromethane vapors were reported
by Vozovaya (1974). Also, inhalation exposures of rats and mice
to vapor levels of 4,342 mg/m^3 for seven hours daily on gestation
days 6 to 15 produced evidence of feto- or embryotoxicity (Schwetz,
et al., 1975; Natl. Inst. Occup. Safety and Health, 1976).

   E.   Chronic Toxicity

      Acute exposures to dichloromethane produce central
nervous system disfunction, are irritating to mucous membranes,
and increase the level of carboxyhemoglobin (Natl. Acad. Sci.,
1978). Price, et al. (1978) reported that Fischer rat embryo
cells (F1706) were transformed by dichloromethane at high
concentrations (1.6 x 10^{-3}M) in the growth medium. However,
Sivak (1978) indicated the presence of carcinogenic contaminants
in the dichloromethane and could not demonstrate transformation
in the BALB/C-3T3 assay system with highly purified food grade
dichloromethane.

V. AQUATIC TOXICITY

   A.   Acute Toxicity

      Acute toxicity values have been obtained for two species
of freshwater fish and one species of freshwater invertebrates.
LC$_{50}$ values for the fathead minnow (Pimephales promelas) ranged
from 193,000 ug/l in a flowthrough assay to 310,000 ug/l in a
static assay. An LC$_{50}$ value of 224,000 ug/l was obtained for the
bluegill (Lepomis Macrochirus) in a static assay. Daphnia magna
were reported as having an LC$_{50}$ value of 224,000 ug/l (U.S. EPA,

1979a). For the marine fish, the sheepshead minnow (Cyprinodon variegatus), an LC_{50} of 331,000 ug/l was obtained. The marine mysid shrimp was reported as having an LC_{50} value of 256,000 ug/l.

B.   Chronic Toxicity

Chronic tests for freshwater or marine species could not be located in the available literature.

C.   Plant Effects

Both species of freshwater algae, Selenastrum capricor-nortum and marine algae, Skeletonema cornutum, were equally resistant to dichloromethane, with LC_{50} values in excess of 662,000 ug/l.

VI.   EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by the 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

OSHA (1976) has established an eight-hour, time-weighted average for dichloromethane of 1,737 mg/m^3; however, NIOSH (1976) has recommended a ten-hour, time-weighted average exposure limit of 261 mg/m^3. The U.S. EPA (1979a) draft water quality criterion for dichloromethane is 2 ug/l. The reader is referred to the Halomethanes Hazard Profile for discussion of criteria derivation (U.S. EPA, 1979b).

B. Aquatic

The criterion for protecting freshwater aquatic life has been drafted as 4,000 ug/1, not to exceed 9,000 ug/1, while the marine criterion has been drafted as 1,900 ug/1, not to exceed 4,400 ug/1.

DICHLOROMETHANE

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2,4 - Dichlorophenol

Health and Environmental Effects

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

October 1, 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 reflect all
available information impacts presented by the subject chemical.
This document has undergone scrutiny to ecsure its technical accuracy.

2,4-DICHLOROPHENOL

Summary

Insufficient data exist to indicate that 2,4-dichlorophenol is a carcinogenic agent. 2,4-Dichlorophenol appears to act as a nonspecific irritant in promoting tumors in skin painting studies. No information on mutagenicity, teratogenicity, or chronic toxicity is available. In a subacute study, the only adverse effect noted in mice was microscopic nonspecific liver changes. 2, 4-Dichlorophenol appears to be a weak uncoupler of oxidative phosphorylation.

Acute and chronic toxic effects of 2,4-dichlorophenol have been observed at a concentrations as low as 2,200 and 365 ug/l respectively. Mortality to early life stages of one species of fish occurs at 70 ug/l. Flavor impairment studies indicate that the highest concentrations of 2,4-dichlorophenol in water which would not cause tainting of the edible portions of fish range from 0.4 to 14 ug/l depending on the species of fish consumed.

2,4-DICHLOROHENOL (2,4 DCP)

I. INTRODUCTION

This profile is in large part based on the Ambient Water Quality Criteria Document for 2,4-dichlorophenol (U.S. EPA,1980).

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-DCP 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. It is a product resulting from degradation of many commercial products by plants, micro-organisms, and sunlight. Its low vapor pressure cause it to be only slowly removed from surface water via volatilization (U.S. EPA, 1980). Studies have indicated low absorption of 2,4-DCP from natural surface waters by various clays (Aly and Faust, 1964). 2,4-DCP is photolabile in aqueous solutions (Aly and Faust, 1964; Crosby and Tutass, 1966) and can be degraded to succinic

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acid by microorganisms in soil and water (Alexander and Aleem,
1961; Ingols, et al., 1966; Loos, et al., 1967). In lake water,
under laboratory conditions, the half life of 2,4-DCP is 8-9
days in aerated waters and 17 days under anaerobic conditions
(U.S. EPA 1980).

II. EXPOSURE

A. Water

Sources of 2,4-DCP in water are agricultural run-off (as a
contaminant and metabolic breakdown product of biocides) and
manufacturing waste discharges (U.S. EPA, 1980). 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). The worst-case exposure
to 2,4 DCP from drinking water, as calculated from 2,4-DCP level
in water downstreams from a 2,4-DCP manufacturing facility,
has been estimated as 36 ug/kg body weight/day.

B. Food

Contamination of food with 2,4-DCP could be an indirect
result from use of the herbicide 2,4-D (U.S. EPA, 1980). The
worst use estimate for the degree of human exposure to 2,4-DCP from
consumption of contaminated meat is about 4 ug 2,4-DCP/kg body
weight.

The U.S. EPA (1980) has estimated the weighted average
bioconcentration factor for 2,4-dichlorophenol to be 41 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-dichlorohenol
through inhalation has not been found in the available literature.

III. 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 ug/g feed) to cattle
and sheep (Clark, et al. 1975) and Nemacide (50 - 800 ug/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

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or beta benzene hexachloride (hexachlorocylohexane) included 2,4-dichorophenol 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

Existing data are not sufficient to indicate whether 2,4-dichlorophenol is a carcinogen. The only study performed (Boutwell and Bosch, 1959) indicate that 2,4-dichlorophenol may promote skin cancer in mice after initiation with dimethylbenz-anthracene. An analysis of the data of Boutwell and Bosch using the Fisher Exact Test indicated that the incidence of papillomas. in 2,4-DCP-treated groups was significantly elevated over controls, while the incidence of carcinomas was not (U.S. EPA, 1980).

B. Mutagenicity, Teratogenicity and Other Reproductive Effects

No studies addressing the mutagenicity, teratogenicity or other reproductive effects of 2,4-DCP in mammaliam systems were found in the available literature. However, genotoxic effects of 2,4-DCP have been reported in plants. Exposure of

flower buds or root cells of vetch (<u>Vicia</u> <u>fabia</u>) to solutions of 2,4-DCP, 01M 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, 1980).

C.   Chronic Toxicity

One report (Bleiberg, et al. 1964) suggested that 2,4-dichlorophenol was involved in the induction of chloracne and porphyria cutanea tarda in workers manufacturing 2,4-dichlorophenol and 2,4,5-trichlorophenol. Since various chlorinated dioxins (powerful chloracnegens) have been implicated as contaminants of 2,4,5-trichlorophenol, the specific 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 nonspecific 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-DCP is a weak uncoupler of oxidative phosphorylation (Farquharson, et al. 1958; Mitsuda, et al. 1963). Values on odor

threshold for 2,4-DCP in water range from 0.65 to 6.5 ug/l, depending on the temperature of water (Hoak, 1957).

V.   AQUATIC TOXICITY

A. Acute Toxicity (U.S. EPA, 1980)

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 ug/l for the bluegill, Lepomis macrochirus, and an LC_{50} value of 8,230 ug/l for the juvenile fathead minnow, Pimpephales promelas, 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 ug/l.

Only one marine fish or invertebrate species has been tested for the acute effects of 2,4-DCP: the mountain bass, a species endemic to Hawaii is poisoned at 20 mg 2,4-DCP/l.

B.   Chronic Toxicity

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

C.   Plant Effects

Concentrations of 2,4-DCP causing a 56 percent reduction in photosynthetic oxygen production or a complete destruction of chlorophyll were 50 or 100 mg/l, respectively, in algal assays with Chlorella pyrenoidosa. An earlier study reported that 58.3 mg 2,4-D/l caused a 50 percent reduction in Chlorophyll 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 bioconcentraion factor for the edible portion of aquatic organisms is 41.

E. Miscellaneous

Flavor impairment studies indicated that the highest concentration of 2,4-DCP in the exposure water which would not cause tainting of the edible portion of fish ranged from 0.4 ug/l for the largemouth bass (<u>Microbterus</u> <u>salmoides</u>), to 14 ug/l for the bluegill (<u>Lepomis</u> <u>marcrochirus</u>). The value for the rainbow trout (<u>Salmo</u> <u>gairdneri</u>) was 1 ug/l.

A. Human

Based upon the prevention of adverse organoleptic effected, the criterior for 2,4-DCP in water recommended by the U.S. EPA (1980) is 0.3 ug/l. This level is far below minimal no-effect concentrations determined in laboratory animals (U.S. EPA, 1980). 3.09 mg/l is the criterion based on toxicity data (U.S. EPA, 1980).

B. Aquatic

The criterion for protecting freshwater organisms is 2020 ug/l (acute) and 365 ug/l as a chronic exposure value. No criterion was derived for marine organisms (U.S. EPA, 1980).

2,4-DICHLOROPHENOL

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2,6-Dichlorophenol

Health and Environmental Effects

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

OCTOBER 30, 1980

76-1

DISCLAIMER

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

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 fo 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 metachlorophenol, 2,4,5-trichlorophenol, and 2,3,4,6-tetrachlorophenol.

I.   INTRODUCTION

2,6-Dichlorophenol (2,6-DCP), 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:	$68^{a}C - 69°C$
Boiling Point:	$219°C - 220°C$ (740 torr)
Vapor Pressure:	1 torr @ 59.5°C
pH:	6.79
Production:	unknown

2,6-DCP 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 (Hoak, 1957). 2,6-DCP has a taste and odor threshold of 0.002 mg/1 and 0.003 mg/1, respectively (McKee and Wolf, 1963). Piet and DeGrunt (1975) found unspecified dichlorophenols in Dutch surface waters at 0.01 to 1.5 ug/1, and Burttschell, et al. (1959) demonstrated that chlorination of phenol-containing water produced, among other products, 2,6-DCP 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-DCP is absorbed through the skin and from the gastrointestinal tract, and rapidly eliminated (U.S. EPA, 1980).

B. Distribution

Pertinent data could not be located in the available literature. The high lipid solubility of the compound would suggest that the unexcreted and unmetabolized 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-DCP is rapidly eliminated from the body, primarily as urinary sulfate and glucuronide conjugates (U.S. EPA, 1980).

IV.   EFFECTS

    A.   Carcinogencity

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

    B.   Mutagenicity

        2,6-DCP 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-DCP 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-DCP inhibits liver mitochondrial respiration (level not specified) (Chung, 1978). At relatively high concentrations 2,6-DCP affects the nervous system (U.S. EPA, 1980).

V.   AQUATIC TOXICITY

   A.   Acute

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

   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-DCP, a
water quality criterion of 0.2 ug/l has been recommended by
the U.S. EPA (1980).

   B.   Aquatic

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

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

Health and Environmental Effects

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

APRIL 30, 1980

77-1
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DISCLAIMER

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

2,4-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.
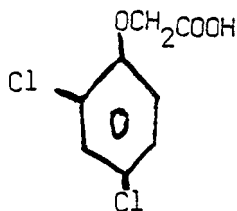
Toxicity tests on a variety of aquatic organisms generally have demonstrated that various esters of 2,4-D are more toxic than the 2,4-D acid, dimethyl amine, or sodium salt. Freshwater trout and bluegill sunfish were adversely affected by the propylene glycol butylether (PGBE) ester at concentrations 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 benzehe, 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/1).

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 iso-octyl 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 isooctyol 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 (<u>Rasbora heteromorpha</u>) 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 (<u>Fundulus diaphanus</u>), white perch (<u>Roccus americanus</u>), stripped bass (<u>Morone sazatilis</u>), guppies (<u>Libistes reticulatus</u>), pumpkinseed sunfish (<u>Lepomis gibbosus</u>), carp (<u>Cyprinus carpio</u>), and American eel (<u>Anguilla rostrata</u>), 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 (<u>Orconectes nails</u>) 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 (<u>Daphnia magna</u>) and seed shrimp (<u>Cypridopsis vidua</u>) were most sensitive to the PGBE ester, with 48-hour LC_{50} values of 100 and 320 µg/l, respectively. Scuds (<u>Gammarus fasciatus</u>), sowbugs (<u>Ascellus brevicaudus</u>), and freshwater grass shrimp (<u>Palaemonetes kadiakensis</u>) 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 (<u>Pteronarcy californica</u>) 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 (<u>Cyclops vernalis</u>) nauplii exposed to 2,4-D as free acid. The range of 96-hour LC_{50} values for nauplii 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 $\mu g/l$ for the PGBE ester of 2,4-D. The 2,4-D acid had no detectable effect at exposures of 2,000 $\mu g/l$ for 96-hours. Butler (1963) observed paralysis of brown shrimp (Penaeus aztecus) exposed to 2,4-D acid at a concentration of 2,000 $\mu g/l$ for 48-hours. Sudak and Claff (1960) found a 96-hour LC_{50} value of 5,000,000 $\mu g/l$ 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 $\mu g/l$ 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.

2.   Chronic Toxicity

Rehwoldt, et al. (1970) exposed several species of fish to 100 $\mu g/l$ 2,4-D for ten months and observed no overt effects to any tested species. The percent reduction of brain acetylcholinesterase ranged from 16 percent in white perch to 35 percent in American eels. In breeding experiments with guppies, a 100 $\mu g/l$ 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 $\mu g/l$. 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 (1952). Poorman (1973) treated cultures of Euglena gracilis with concentrations of 50,000 µg/l 2,4-D for 24 hours and observed decreased growth rates. Valentine and Bingram (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 (Canoi 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 depletion 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 130 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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1,2-Dichloropropane

Health and Environmental Effects

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.

78-2

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.

<u>1,2-DICHLOROPROPANE</u>

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^{o}C, a density of 1.156 g/ml, a vapor pressure of 40 mm Hg at

19.4^{o}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 dichloro-

propane in commerical foodstuffs; therefore, the amount of this compound in-

gested by humans through food is not known. The U.S. EPA (1979) has esti-

mated the bioconcentration factor (BCF) of dichloropropane to be 20. This

estimate is based on the octanol/water partition coefficients of dichloro-

propane. The weighted average BCF for edible portions of all aquatic organ-

isms 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 dichloropropane 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 macna is 52,500 μg/l (U.S. EPA, 1979). Tidewater silverside, (Menidia bevvllina), 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).

1,2-DICHLOROPROPANE

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Profile.

Dichloropropanes/Dichloropropenes

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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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 97,900, 280,000, and greater than 520,000 $\mu g/l$, respectively. For Daphnia magna, the corresponding reported 48-hour LC_{50} values are 23,000, 52,000, and 282,000 $\mu g/l$, 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 $\mu g/l$ compared to 520,000 $\mu g/l$ for 1,3-dichloropropane. For Daphnia magna, the corresponding values are 6,150 and 282,000 $\mu g/l$, respectively. The EC_{50}, based on chlorophyll a for a freshwater alga, is 4,950 $\mu g/l$ 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-dichloropro-
pene are mutagenic to S. typhimurium strains TA 1535 and TA 100,
as are the individual compounds. The mixture, but not the in-
dividual 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 pro-
duced cloudy swelling in renal tubular epithelium which disap-
peared 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 4,950 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 pro-
pene 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 coef-
ficients of dichloropropanes and dichloropropenes, the U.S. EPA.
(1979) has estimated the bioconcentration factors for these com-
pounds to range between 10 and 35.

VI.   Other Pertinent Information

In the non-aquatic environment, movement of 1,2-dichloro-
propane 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 volatiliza-
tion (Roberts and Staydin, 1976).

Following field application, movement of 1,3-dichloropro-
pene 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 car-
bon 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 di-
chloropropenes 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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Dichloropropanol

Health and Environmental Effects

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

APRIL 30, 1980

-955

80-1

DISCLAIMER

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

-956

80-2

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.

80-3

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 di-
chloropropanol intoxication as being similar to carbon tetrachloride poison-
ing, 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; Gos-
selin, 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 pro-
duction 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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1,3-Dichloropropene

Health and Environmental Effects

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

APRIL 30, 1980

81-1

DISCLAIMER

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and environmental hazards from exposure to the subject chemi-
cal. 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.

1,3-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 6150 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 promeles) 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.

81-3

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 $104.3^{\circ}C$ for the trans-isomer and $112^{\circ}C$ 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, 1979b).

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).

<u>1,3-DICHLOROPROPENE</u>

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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 salt-water 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 µg/l for steel head trout (<u>Salmo</u> <u>guirdnes</u>) in an embryolarval study and 0.4 µg/l for the guppy (<u>Poecilia reticulata</u>) 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 freshwater alga, 1395 for <u>Daphnia magna</u>, 2993 for the channel catfish, and 8000 for the edible tissues of the Eastern oyster.

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82-4

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 x 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).

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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

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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

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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 dicarboxylic acid (both of which are products of the transformation of the epoxy group), the syn-12-hydroxy-dieldrin (a mono-hydro deriva-tive), 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, 1979).

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 dur-
ing 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 ferti-
lity, 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,

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1979) and induce a greater number of tumors in mice when admini-
stered 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

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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 obliquus (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 $\mu g/l$ (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 $\mu g/l$ 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 $\mu g/l$ as a 24-hour average; the concentration should not exceed 0.16 $\mu g/l$ at any time.

DIELDRIN

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

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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.

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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 (Vettorazzi, 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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o,o-Diethyl-S-methyl Phosphorodithioate

Health and Environmental Effects

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

APRIL 30, 1980

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o,o-DIETHYL-S-METHYL PHOSPHORODITHIOATE

Summary

There is no available information on the possible carcinogenic, muta-genic, teratogenic or adverse reproductive effects of o,o-diethyl-S-methyl phosphorodithioate. Pesticides containing the o,o-diethyl phosphoro-dithioate 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: $100^{\circ}C$ to $102^{\circ}C$ (4 torr)
(CA 55:8335h)

Density: 1.192420
(CA 55:8335h)

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-di-ethyl-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,

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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. In-
jection of phorate into developing chick embryos has been reported to pro-
duce 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 ef-
fects (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 onosphorodithioate, 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.

References

American Cyanamid. 1966. Toxicity data on 15 percent Thimet granules. Unpublished report. In: Initial Scientific and Minieconomic Review of Phorate (Thimet) Washington, DC: Office of Pesticide Programs.

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Diethyl Phthalate

Health and Environmental Effects

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

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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 fol.owing i.p. administration of diethyl phthalate to pregnan rats. This same study has also indicated fetal toxicity an increased resorptions after i.p. administration of DEP.

Evidence that diethyl phthalate prc uces carcinogenic effects has not been found.

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

Diethyl phthalate appears to be mor toxic for marine species acutely tested, with a concentra .on of 7,590 µg/l being reported as the LC_{50} in marine i vertebrates. The data base for the toxic effects of die iyl phthalates to aquatic organisms is insufficient to d ift criterion for their protection.

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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: 3.75×10^3 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).

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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).

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DIETHYL PHTHALATES

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Dimethylnitrosamine

Health and Environmental Effects

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

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 dimethyl-nitrosamine 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 concen-
tration 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 produc-
tion 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

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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 expo-
sures 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 in-
duced 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 dimethyl-
nitrosamines.

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 dimethyl-
nitro-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. Addition-
ally, 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 hepato-
cellular carcinoma during a range of exposures from 200
to 300 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

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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 life-time 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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2,4-Dimethylphenol

Health and Environmental Effects

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

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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^{O}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

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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 $30^{o}C$, the odor threshold for 2,4-DMP was 55.5 $\mu g/l$.

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).

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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 loca-
ted 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, methyl-
phenols 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 literature1(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,

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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

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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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Dimethyl Phthalate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

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DISCLAIMER

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

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DIMETHYL PHTHALATE

SUMMARY

Dimethyl phthalate has been shown to produce mutagenic effects in the Ames <u>Salmonella</u> 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 <u>in vitro</u> 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 <u>Salmonella</u> 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.

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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).

DIMETHYL PHTHALATES

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and environmental hazards from exposure to the subject chemi-
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from secondary sources and available reference documents.
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adverse health and environmental impacts presented by the
subject chemical. This document has undergone scrutiny to
ensure its technical accuracy.

Dinitrobenzenes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

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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.

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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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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 <u>Proteus mirabilis</u> but failed to show mutagenic effects in the Ames assay or in <u>E</u>. <u>coli</u>. 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.

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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 res-
piratory tract, and the gastrointestinal tract (NIOSH,
1978).

B.   Distribution

DNOC has been found in several body tissues; how-
ever, the compound may be bound to serum proteins, thus pro-
ducing 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 de-
toxification 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 ex-
creted 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).

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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 12.3 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).

2,4-Dinitrophenol

Health and Environmental Effects

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

APRIL 30, 1980

91-1

DISCLAIMER

     This report represents a survey of the potential health
and environmental hazards from exposure to the subject chemi-
cal. 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.

2,4-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 $\mu g/l$ for the bluegill to 16,700 $\mu g/l$ 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 vari-
ous 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 sol-
uble 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 pro-
duction of 2,4-dinitrophenol was 4.3 x 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 Nitro-
phenols (1979b).

II. EXPOSURE

The lack of monitoring data for the nitrophenols makes it
difficult to assess exposure from water, inhalation, 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 biocon-
centration factor for 2,4-dinitrophenol to be 2.4 for the edible

portions of fish and shellfish consumed by Americans. This esti-
mate 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 tis-
sue sites (U.S. EPA, 1979a).

C.   Metabolism

Metabolism of the nitrophenols occurs through conjuga-
tion 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 development-al 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 criter-
ia 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 cri-
terion 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).

2,4-DINITROPHENOL

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Dinitrotoluene

Health and Environmental Effects

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92-1

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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 $71^{\circ}C$, a boiling point of $300^{\circ}C$ with decomposition, and a solubility in water of 270 mg/l at $22^{\circ}C$. It is readily soluble in ether, ethanol, and carbon disulfide (U.S. EPA, 1979). 2,6-Dinitrotoluene has a melting point of $66^{\circ}C$ 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 litera-
ture 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 dinitrotol-
uene after oral administration to rats was essentially com-
plete 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 adminis-
tration 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 experi-
ment 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 dinitro-
toluene 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-di-
nitrotoluene in mammals would be either toxic and/or car-
cinogenic.

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 radioactiv-
ity 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., 1976).

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).

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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, <u>Selenastrum</u> <u>capricornutum</u>, were

1,370 or 1,620 µg/l, respectively. These same effects mea-

sured in the marine algae, <u>Skeletonema</u> <u>costatum</u>, 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:

<u>Exposure Assumptions</u> (per day)	<u>Risk Levels and Corresponding Draft Criteri</u>			
	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.

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DINITROTOLUENE

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2,4-Dinitrotoluene

Health and Environmental Effects

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

APRIL 30, 1980

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DISCLAIMER

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

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 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.

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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^OC, a boiling point of 300^OC with decomposition, and a solubility in water of 270 mg/l at 22^OC. 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:

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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.

2,4-DINITROTOLUENE

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2,6-Dinitrotoluene

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

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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 bio-assay to determine the carcinogenicity of 2,4-DNT by administer-ing 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 carcinogen-icity. 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 activa-tion.

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 muscu-lar coordination primarily in the hind legs, rigidity in exten-sion 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 reticu-
locytosis. The tissue lesions seen were extramedullary hemato-
poeisis 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 adminis-
tered 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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Di-n-octyl Phthalate

Health and Environmental Effects

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

APRIL 30, 1980

95-1

DISCLAIMER

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cal. The information contained in the report is drawn chiefly
from secondary sources and available reference documents.
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ensure its technical accuracy.

95-2

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.

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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.

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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 criterion 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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1,2-Diphenylhydrazine

Health and Environmental Effects

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DISCLAIMER

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

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 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.

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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.

DIPHENYLHYDRAZINE

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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.

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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 0,0-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

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TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF DISULFOTON

Synonyms: 0,0-Diethyl S-(2-(ethylthio)ethyl) phosphorodithioate;
           0,0-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.

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

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.

$\mathcal{2}$

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-

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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/1 (McKee and Wolf, 1963).

VI. EXISTING GUIDELINES AND STANDARDS

    A.   Human

The occupational threshold limit value for air has been estab-
lished as 100 μg/m³. 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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Endosulfan

Health and Environmental Effects

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ENDOSULFAN

Summary

Endosulfan is an insecticide and is a member of the organochlorocyclo-diene insecticides. Endosulfan does not appear to be carcinogenic, mutagen-ic 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 hyperpla-sia, 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 Organiza-tion 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 poly-cyclic 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-Thio-dan, 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

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and Mahfouz, 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 Dobbs, 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, Eschericia 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 ∼ 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-

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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 µg/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).

B.   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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Endrin

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health
and environmental hazards from exposure to the subject chemi-
cal. 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 µg/m^3 in 1971 to a maximum level of 0.5 µg/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/1; 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).

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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, 1968). 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 ug/l for carp fry (Cyprinus carpio) fry to 140.00 ug/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 µg/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 fresh-
water aquatic life is 0.0020 µg/l as a 24 hour average con-
centration 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.

ENDRIN

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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 all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

· U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 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^oC, and its vapor pressure is 20 mm Hg at 29^oC. 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 epichlorohy-
drin 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 epichloro-
hydrin in foodstuffs has been generated.

C. Inhalation

Numerous environmental sources of epichlorohydrin have been identi-
fied (SRC, 1979). Epichlorohydrin is released into the atmosphere through
waste ventilation processes from a number of industrial operations which re-
sult in volatilization of the chemical. ' No quantitative monitoring informa-
tion is available on ambient epichlorohydrin concentrations. High concen-
trations have been observed in the immediate vicinity of a factory discharg-
ing 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 exposuré 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).

1-CHLORO-2,3-EPOXYPROPANE(EPICHLOROHYDRIN)

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100-14

Ethyl Methacrylate

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

101-1

DISCLAIMER

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

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101-2

ETHYL METHACRYLATE

Summary

Information on the carcinogenic and mutagenic effects of ethyl methac-
rylate 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 re-
ported 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 $75^{\circ}C$, has a boiling point of $117^{\circ}C$, a density of 0.9135, and an index of refraction of 1.4147. It is insoluble in water at $25^{\circ}C$ 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.

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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.

ETHYL METHACRYLATE

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Ferric Cyanide

Health and Environmental Effects

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

APRIL 30, 1980

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DISCLAIMER

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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.

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VI. EXISTING GUIDELINES AND STANDARDS

Pertinent data could not be located in the available literature.

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Fluoranthene

Health and Environmental Effects

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

APRIL 30, 1980

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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, $111^{\circ}C$; boiling point, $375^{\circ}C$; water solubility, 265 $\mu g/l$ (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 in-
crease in smoked or cooked foods (pyrolysis of fats) (U.S.
EPA, 1979). Borneff (1977) has estimated that dietary in-
take 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 bioconcen-
tration factor of 890 for fluoranthene for the edible por-
tion 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).

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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

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

B.   Mutagenicity

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

C.   Teratogenicity

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

D.   Other Reproductive Effects

Pertinent information could not be located in the available literature.

E.   Chronic Toxicity

Pertinent information could not be located in the available literature.

V.   AQUATIC TOXICITY

A.   Acute Toxicity

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

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

B.   Chronic Toxicity

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

C.   Plant Effects

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

D.   Residues

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

VI. EXISTING GUIDELINES AND STANDARDS

A.   Human

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

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

total PAH compounds is expected to have precedence for fluor-anthene.

B.   Aquatic

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

FLUOROANTHENE

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Formaldehyde

Health and Environmental Effects

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

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FORMALDEHYDE

SUMMARY

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

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

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

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

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

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

I.   INTRODUCTION

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

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

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

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

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

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

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

II. EXPOSURE

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

A. Environmental Fate

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

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

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

B. Bioconcentration

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

C. Environmental Occurrence

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

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

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

III. PHARMACOKINETICS

A.   Absorption

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

B. Distribution

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

C. Metabolism

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

D. Excretion

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

IV. HEALTH EFFECTS

A. Carcinogenicity

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

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

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

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

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

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

B.   Mutagenicity

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

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

C.   Teratogenicity

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

D.   Other Reproductive Effects

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

E.   Other Chronic Toxicity

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

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

F.   Other Relevant Information

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

V.   AQUATIC EFFECTS

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

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

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

VI. EXISTING GUIDELINES

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

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Formic Acid

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

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FORMIC ACID

Summary

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

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

Formic acid is toxic to freshwater organisms at concentrations ranging from 120,000 to 2,500,000 ug/l. _Daphnia magna_ was the most sensitive fresh-water species tested. Marine crustaceans were adversely affected by expo-sure to formic acid at concentrations from 80,000 to 90,000 ug/l.

FORMIC ACID

I. INTRODUCTION

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

Property	Pure	90%	85%
Formula:	CH_2O_2	---	---
Molecular Weight:	46.02	---	---
Melting Point:	8.4^oC	-4^oC	-12^oC
Boiling Point:	100.5^oC	---	---
Density:	1.220^{20}_4	1.202^{25}_{25}	1.194^{25}_{25}
Vapor Pressure:	33.1 torr @ 20^oC		
Solubility:	Miscible in water, alcohol, and ether; soluble in acetone, benzene, and toluene		
Demand (1979):	67.5 million lbs. (CMR, 1979)		

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

II. EXPOSURE

   A.   Water

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

   B.   Food

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

   C.   Inhalation

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

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

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

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

B. Distribution

Pertinent data were not found in the available literature.

C. Metabolism

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

D. Excretion

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

IV. EFFECTS

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

B. Chronic Toxicity

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

C. Other Pertinent Information

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

V. AQUATIC TOXICITY

A. Acute Toxicity

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

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

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

B. Chronic Toxicity

Pertinent data were not found in the available literature.

C. Plant Effects

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

D. Residue

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

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

B. Aquatic

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

FORMIC ACID

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Fumaronitrile

Health and Environmental Effects

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APRIL 30, 1980

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FUMARONITRILE

Summary

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

x

FUMARONITRILE

I. INTRODUCTION

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

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

II. EXPOSURE

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

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

III. PHARMACOKINETICS

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

IV. EFFECTS

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

Pertinent data could not be located in the available literature.

B. Acute Toxicity

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

V. AQUATIC TOXICITY

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

VI. EXISTING GUIDELINES AND STANDARDS

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

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Halomethanes

Health and Environmental Effects

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107-1

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HALOMETHANES

Summary

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

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

I. INTRODUCTION

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

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

II. EXPOSURE

A. Water

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

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

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

Source: U.S. EPA, 1975

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

B. Food

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

C. Inhalation

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

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

III. PHARMACOKINETICS

A. Absorption

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

B. Distribution

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

C. Metabolism

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

D. Excretion

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

IV. EFFECTS

A. Carcinogenicity

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

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

B. Mutagenicity

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

C. Teratogenicity

Pertinent information could not be located in the available literature.

D. Other Reproductive Effects

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

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

E. Chronic Toxicity

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

F. Other Relevant Information

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

V.   AQUATIC TOXICITY

A. Acute Toxicity

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

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

B. Chronic Toxicity

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

C. Plant Effects

Effective concentrations for chlorophyll a and cell numbers in freshwater algae <u>Selenastrum</u> <u>capricornutum</u> ranged from 112,000 to 116,000 µg/l for bromoform and 662,000 µg/l for methylene chloride, while effective concentrations for the marine algae (<u>Sketonema</u> <u>costatum</u>) were reported as 11,500 to 12,300 µg/l for bromoform and 662,000 µg/l for methylene chloride (U.S. EPA, 1979).

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

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

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

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

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

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

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

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

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

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

B. Aquatic

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

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

HALOMETHANES

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No. 108

Heptachlor

Health and Environmental Effects

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

APRIL 30, 1980

1084

DISCLAIMER

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

SPECIAL NOTATION

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

HEPTACHLOR

Summary

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

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

I. INTRODUCTION

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

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

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

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

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

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

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

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

II. EXPOSURE

    A. Water

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

    B. Food

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

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

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

C. Inhalation

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

D. Dermal

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

III. PHARMACOKINETICS

   A. Absorption

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

   B. Distribution and Metabolism

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

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

C. Excretion

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

IV. EFFECTS

A. Carcinogenicity

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

B. Mutagenicity

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

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

C. Teratogenicity

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

D. Other Reproductive Effects

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

E. Chronic Toxicity

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

F. Other Relevant Information

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

V. AQUATIC TOXICITY

A. Acute Toxicity

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

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

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

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

B. Chronic Toxicity

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

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

C. Plant Effects

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

O. Residues

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

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

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

Based on the data for the carcinogenicity of heptachlor epoxide in mice (Davis, 1965), and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of heptachlor/heptachlor epoxide in ambient water which will result in risk levels of human cancer as specified in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.0023 ng/l	0.023 ng/l	0.23 ng/l
Consumption of fish and shellfish only.	0	0.0023 ng/l	0.023 ng/l	0.23 ng/l

Existing Guidelines and Standards

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

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

*Time-weighted average

B. Aquatic

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

HEPTACHLOR

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Heptachlor Epoxide

Health and Environmental Effects

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

APRIL 30, 1980

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DISCLAIMER

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

HEPTACHLOR EPOXIDE

SUMMARY

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

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

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

HEPTACHLOR EPOXIDE

I. INTRODUCTION

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

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

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

II. EXPOSURE

A. Water

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

B. Food

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

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

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

C.   Inhalation

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

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

D. Dermal

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

III. PHARMACOKINETICS

A. Absorption

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

B. Distribution

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

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

C.   Metabolism and Elimination

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

IV. EFFECTS

A.   Carcinogenicity

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

B.   Mutagenicity

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

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

   C.   Teratogenicity, Other Reproductive Effects and Chronic Toxicity

   Pertinent data could not be located in the available literature.

   D.   Other Relevant Information

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

V.   AQUATIC TOXICITY

   A.   Acute Toxicity

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

   B.   Chronic Toxicity

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

   C.   Plant Effects

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

   D.   Residues

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

tration factor for heptachlor in all species of fish tested

is 11,400 (U.S. EPA, 1979a). As explained in the "Distri-

bution" section of this text, the bioconcentration factor

for heptachlor epoxide would be as least as great as that

for heptachlor.

VI. EXISTING GUIDELINES AND STANDARDS

    A.   Human

        The existing guidelines and standards for hepta-

chlor and heptachlor epoxide are:

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

*   Time weighted average

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

        The U.S. EPA (1979a) is in the process of establish-

ing ambient water quality criteria for heptachlor and hepta-

chlor epoxide. Based on potential carcinogenicity of hepta-

chlor epoxide, the draft criterion is calculated on the esti-

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

B. AQUATIC

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

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Hexachlorobenzene

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

HEXACHLOROBENZENE

Summary

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

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

I. INTRODUCTION

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

Hexachlorobenzene (HCB; C_6Cl_6; molecular weight 284.79) is a color-less solid with a pleasant aroma. Hexachlorobenzene has a melting point of $230^{O}C$, a boiling point of $322^{O}C$, a density of 2.044 g/ml, and is vir-tually insoluble in water. Hexachlorobenzene is used in the control of fungal diseases in cereal seeds intended solely for planting, as a plasti-cizer for polyvinyl chloride, and as a flame retardant (U.S. EPA, 1979).

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

II. EXPOSURE

A. Water

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

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

B. Food

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

C. Inhalation

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

D. Dermal

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

III. PHARMACOKINETICS

A. Absorption

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

B. Distribution

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

C. Metabolism

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

D. Excretion

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

IV. EFFECTS

A. Carcinogenicity

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

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

B. Mutagenicity

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

C. Teratogenicity

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

D. Other Reproductive Effects

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

E. Chronic Toxicity

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

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

F. Other Relevant Information

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

V. AQUATIC TOXICITY

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

B. Residues

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

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

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

Exposure Assumption (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.0125 ng/l	0.125 ng/l	1.25 ng/l
Consumption of fish and shellfish only.	0	0.0126 ng/l	0.126 ng/l	1.26 ng/l

B. Aquatic

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

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Hexachlorobutadiene

Health and Environmental Effects

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

APRIL 30, 1980

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III-1.

DISCLAIMER

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

SPECIAL NOTATION

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

HEXACHLOROBUTADIENE

SUMMARY

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

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

III-4

HEXACHLOROBUTADIENE

I. INTRODUCTION

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

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

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

II. EXPOSURE

A. Water

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

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

B.   Food

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

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

C.   Inhalation

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

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

III. PHARMACOKINETICS

A.   Absorption

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

B.   Distribution

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

C.   Metabolism

Pertinent data were not found in the available
literature.

D.   Excretion

Pertinent data were not found in the available
literature.

IV.   EFFECTS ON MAMMALS

A.   Carcinogenicity

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

No carcinomas were observed in controls, however, a nephro-blastoma developed in one male and one female.

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

B.   Mutagenicity

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

C.   Teratogenicity

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

D.   Other Reproductive Effects

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

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

E.   Chronic Toxicity

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

F.   Other Relevant Information

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

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

V.   AQUATIC TOXICITY

A.   Acute Toxicity

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

B.   Chronic Toxicity

Pertinent information was not found in the avail-
able literature.

C.   Plant Effects

Pertinent data was not found in the available
literature.

D.   Residues

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

VI.   EXISTING GUIDELINES AND STANDARDS

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

A.   Human

Standards or guidelines for exposure to HCBD are not available.

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

B.   Aquatic

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

HEXACHLOROBUTADIENE

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Hexachlorocyclohexane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

DISCLAIMER

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

SPECIAL NOTATION

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

HEXACHLOROCYCLOHEXANE

Summary

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

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

I. INTRODUCTION

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

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

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

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

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

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

II. EXPOSURE

A. Water

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

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

B. Food

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

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

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

C. Inhalation

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

D. Dermal

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

III. PHARMACOKINETICS

A. Absorption

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

B. Distribution

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

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

C. Metabolism

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

D. Excretion

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

IV. EFFECTS

A. Carcinogenicity

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

B. Mutagenicity

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

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

C. Teratogenicity

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

D. Other Reproductive Effects

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

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

E. Chronic Toxicity

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

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

F. Other Relevant Information

Hexachlorocyclohexane is a convulsant.

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

V. AQUATIC TOXICITY

A. Acute Toxicity

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

values obtained for lindane in 96-hour studies of the freshwater goldfish (Carassius auratus) ranged from 152 µg/l for 100 percent lindane to 8,200 µg/l for BCH (15.5 percent gamma isomer) (Henderson, et al. 1959). Static tests on freshwater invertebrates revealed a range of LC_{50} values of from 4.5 µg/l (96-hour test) (Sanders and Cope, 1968) for the stonefly (Pteronarcys californica) to 880 µg/l (48-hour test) (Sanders and Cope, 1968) for the clado- ceran (Simocephalus serralatus) for lindane. Canton and Slooff (1977) re- ported an LC_{50} value for the pond snail (Lymnaea stagnalis) of 1,200 µg/l for alpha-HCH in a 48-hour static test.

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

B. Chronic

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

C. Plant Effects

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

D. Residues

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

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

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

VI. EXISTING STANDARDS AND GUIDELINES

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

A. Human

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

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

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

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

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

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

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

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

B. Aquatic

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

HEXACHLOROCYCLOHEXANE

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gamma-Hexachlorocyclohexane

Health and Environmental Effects

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

APRIL 30, 1980

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

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GAMMA-HEXACHLOROCYCLOHEXANE (Lindane)

Summary

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

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

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X

GAMMA-HEXACHLOROCYCLOHEXANE (Lindane)

I. INTRODUCTION

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

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

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

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

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

II. EXPOSURE

A. Water

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

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

B. Food

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

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

C. Inhalation

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

D. Dermal

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

III. PHARMACOKINETICS

A. Absorption

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

B. Distribution

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

C. Metabolism

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

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

D. Excretion

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

IV. EFFECTS

A. Carcinogenicity

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

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

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

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

B. Mutagenicity

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

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

C. Teratogenicity

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

D. Other Reproductive Effects

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

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

E. Chronic Toxicity

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

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

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

F. Other Relevant Information

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

V. AQUATIC TOXICITY

A. Acute Toxicity

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

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

B. Chronic

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

C. Plant Effects

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

D. Residues

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

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

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

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

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

B. Aquatic

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

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Hexachlorocyclopentadiene

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.

HEXACHLOROCYCLOPENTADIENE

Summary

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

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

HEXACHLOROCYCLOPENTADIENE

I. INTRODUCTION

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

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

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

II. EXPOSURE

A. Water

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

B. Food

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

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

C. Inhalation

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

III. PHARMACOKINETICS

A. Absorption

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

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

B. Distribution

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

C. Metabolism

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

D. Excretion

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

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

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

IV. EFFECTS

A. Carcinogenicity

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

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

B. Mutagenicity

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

C. Teratogenicity

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

D. Other Reproductive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

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

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

V. AQUATIC TOXICITY

A. Acute Toxicity

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

B. Chronic Toxicity

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

C. Plant Effects

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

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

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

B. Aquatic

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

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No. 115

Hexachloroethane

Health and Environmental Effects

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APRIL 30, 1980

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DISCLAIMER

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

HEXACHLOROETHANE

SUMMARY

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

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

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

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

HEXACHLOROETHANE

I. INTRODUCTION

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

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms are replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. Hexachloroethane (Perchloroethane; M.W. 236.7) is a solid at room temperature with a boiling point of $186^\circ C$, specific gravity of 2.091; and is insoluble in water (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds. Hexachloroethane does not appear to be commercially produced in the U.S., but 730,000 kg were imported in 1976. (U.S. EPA, 1979a).

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

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

II. EXPOSURE

The chloroethanes are present in raw and finished waters due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water or treatment of sewage. Air levels are produced by evaporation of volatile chloroethanes.

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. Fish and shellfish have shown

levels of chloroethanes in the nanogram range (Dickson and Riley, 1976). Information on the levels of hexachloroethane in foods is not available.

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

III. PHARMOKINETICS

Pertinent data could not be located in the available literature on hexachloroethane for absorption, distribution, metabolism, and excretion. However, the reader is referred to a more general treatment of chloroethanes (U.S. EPA, 1979b) which indicates rapid absorption of chloroethanes following oral or inhalation exposure; widespread distribution of the chloroethanes through the body; enzymatic dechlorination and oxidation to the alcohol and ester forms; and excretion of the chloroethanes primarily in the urine and in expired air.

IV. EFFECTS

A. Carcinogencitiy

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

B. Mutagenicity

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

C. Teratogenicity

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

D. Other Reproductive Effects

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

E. Chronic Toxicity

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

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

V. AQUATIC TOXICITY

A. Acute Toxicity

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

B. Chronic Toxicity

Pertinent data could not be located in the available literature.

C. Plant Effects

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

D. Residues

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

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

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

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

B. Aquatic Toxicity

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

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No. 116

Hexachlorophene

Health and Environmental Effects

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DISCLAIMER

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

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HEXACHLOROPHENE

Summary

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

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

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

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

I. INTRODUCTION

Hexachlorophene ($C_{13}H_6O_2Cl_6$, molecular weight 406.9) is a white powder which melts between 166°C and 167°C. The compound is practically insoluble in water but is soluble in ethanol, ether, and other organic solvents. Under alkaline conditions, hexachlorophene forms water-soluble salts (IARC, 1979).

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

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

II. EXPOSURE

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

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

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

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

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

III. PHARMACOKINETICS

A. Absorption

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

B. Distribution

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

C. Metabolism

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

D. Excretion

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

IV. EFFECTS

A. Carcinogenicity

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

B.   Mutagenicity

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

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

C.   Teratogenicity

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

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

D.   Other Reporductive Effects

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

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

E.   Chronic Toxicity

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

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

V.   AQUATIC TOXICITY

A.   Acute and Chronic Toxicity and Plant Effects

Pertinent data were not found in the available literature.

B.   Residues

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

VI.   EXISTING GUIDELINES

A.   Human

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

B.   Aquatic

Pertinent data were not found in the available literature.

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Hydrofluoric Acid

Health and Environmental Effects

117-1

DISCLAIMER

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

HYDROFLUORIC ACID

Summary

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

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

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

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

HYDROFLUORIC ACID

I. INTRODUCTION

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

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

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

II. EXPOSURE

A. Water

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

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

B. Food

Pertinent data were not found in the available literature.

C. Inhalation

HF occurs in the atmosphere from coal fires and from manufacturing and production facilities (see above), as well as from the photochemical reaction of CCl_2F_2 with NO and humid air (Saburo, et al. (1977). It is present in the stratosphere (Zander, et al. 1977; Drayson, et al. 1977; Farmer and Raper, 1977). The extent and amounts of HF in the atmosphere could not be determined from the available literature.

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

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

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

B.   Distribution

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

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

C.   Metabolism

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

D.   Excretion

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

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

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

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

IV. EFFECTS

A. Carcinogenicity

Pertinent data were not found in the available literature.

B. Mutagenicity

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

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

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

C. Teratogenicity

Pertinent data were not found in the available literature.

D. Other Reproductive Effects

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

E. Chronic Toxicity

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

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

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

F. Other Relevant Information

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

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

V. AQUATIC TOXICITY

A. Acute Toxicity

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

B. Chronic Toxicity, Plant Effects, and Residue

Pertinent data were not found in the available literature.

C. Other Relevant Information

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

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

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

B. Aquatic

Pertinent data were not found in the available literature.

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Hydrogen Sulfide

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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118-2

~~1977~~-

Hydrogen Sulfide

Summary

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

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

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

118-3
T572

I. INTRODUCTION

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

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

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

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

II. EXPOSURE

   A. Water

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

   B. Food

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

   C. Inhalation

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

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

D.   Dermal

Pertinent information could not be found in the available literature.

III. PHARMACOKINENTICS

A.   Absorption

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

B.   Distribution

Pertinent information could not be found in the available literature.

C.   Metabolism and Excretion

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

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

IV. EFFECTS

   A.   Carcinogenicity

   Pertinent information could not be found in the
available literature.

   B.   Mutagenicity

   Pertinent information could not be found in the
available literature.

   C.   Teratogenicity

   Pertinent information could not be found in the
available literature.

   D.   Other Reproductive Efforts

   Pertinent information could not be found in the
available literature.

   E.   Chronic Toxicity

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

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

F.   Other Relevant Information

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

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

V.   AQUATIC TOXICITY

A.   Acute Toxicity

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

to H_2S at concentrations ranging from 1 to 100 ppm.

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

B.   Chronic Toxicity, Plant Effects and Residues

Pertinent information could not be located in the available literature.

C.   Other Relevant Information

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

VI. EXISTING GUIDELINES AND STANDARDS

A.   Human

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

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

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

B.   Aquatic

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

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118-10

1399

Indeno (1,2,3-cd)pyrene

Health and Environmental Effects

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

APRIL 30, 1980

119-1

DISCLAIMER

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and environmental hazards from exposure to the subject chemi-
cal. The information contained in the report is drawn chiefly
from secondary sources and available reference documents.
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subject chemical. This document has undergone scrutiny to
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119-2

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated indeno(1,2,3-c,d)pyrene and has found sufficient evidence to indicate that this compound is carcinogenic.

INDENO[1,2,3-cd]PYRENE

Summary

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

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

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria

Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the

Multimedia Health Assessment Document for Polycyclic Organic Matter (U.S.

EPA, 1979b).

Indeno[1,2,3-cd]pyrene (IP; $C_{22}H_{12}$) is one of the family of polycyclic

aromatic hydrocarbons (PAH) formed as a result of incomplete combustion

of organic material. Its physical and chemical properties have not been

well-characterized.

PAH, including IP, are ubiquitous in the environment. They have

been identified in ambient air, food, water, soils, and sediments (U.S.

EPA, 1979b). The PAH class contains several potent carcinogens (e.g.,

benz[b]fluoranthene), weak carcinogens (benz[a]anthracene), and cocarcinogens

(e.g., fluoranthene), as well as numerous non-carcinogens (U.S. EPA,

1979b).

PAH which contain more than three rings (such as IP) are relatively

stable in the environment, and may be transported in air and water by

adsorption to particulate matter. However, biodegradation and chemical

treatment are effective in eliminating most PAH in the environment. The

reader is referred to the PAH Hazard Profile for a more general discussion

of PAH (U.S. EPA, 1979c).

II. EXPOSURE

A. Water

Basu and Saxena (1977, 1978) have conducted monitoring surveys

of U.S. drinking water for the presence of six representative PAH, including

IP. They found the average total level of the six PAH (fluoranthene,

benzo[k]fluoranthene, benzo[j]fluoranthene, benzo[a]pyrene, benzo[g,h,i]-

perylene, and indeno[1,2,3-cd]pyrene) to be 13.5 ng/l.

B.   Food

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

C.   Inhalation

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

III. PHARMACOKINETICS

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

A.   Absorption

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

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B.   Distribution

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

C.   Metabolism

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

D.   Excretion

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

IV. EFFECTS

   A. Carcinogenicity

      IP is regarded as only a weak carcinogen (U.S. EPA, 1979b). LaVoie

and coworkers (1979) reported that IP had slight activity as a tumor initiator

and no activity as a complete carcinogen on the skin of mice which is known

to be highly sensitive to the effects of carcinogenic PAH.

   B. Mutagenicity

      LaVoie and coworkers (1979) reported that IP gave positive results

in the Ames Salmonella assay.

   C. Teratogenicity and Other Reproductive Effects

      There are no data available concerning the possible teratogenicity

or other reproductive effects as a result of exposure to IP. Other related

PAH are apparently not significantly teratogenic in mammals (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

   Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

   Neither the human health nor aquatic criteria derived by U.S. EPA (1979a),

which are summarized below, have not gone through the process of public

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

   A. Human

      There are no established exposure criteria for IP. However, PAH,

as a class, are regulated by several authorities. The World Health Organization

(1970) has recommended that the concentration of PAH in drinking

water (measured as the total of fluoranthene, benz[g,h,i]perylene, benz[b]-

fluoranthene, benz[h]fluoranthene, indeno[1,2,3-cd]pyrene, and benz[a]pyrene)

not exceed 0.2 µg/l. Occupational exposure criteria have been established

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

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

B. Aquatic

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

INDENO[1,2,3-cd]PYRENE

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Isobutyl Alcohol

Health and Environmental Effects

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

APRIL 30, 1980

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DISCLAIMER

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

Isobutyl Alcohol

I. Introduction

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

II. Exposure

No data were readily available.

III. Pharmacokinetics

A. Absorption

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

B. Distribution

No data were readily available.

C. Metabolism

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

D. Elimination

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

IV. Effects

A. Carcinogenicity

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

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

    B.   Teratogenicity

        No data were readily available.

    C.   Other Reproductive Effects

        No data were readily available.

    D.   Chronic Toxicity

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

    E.   Other Relevent Information

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

V.   Aquatic Toxicity

    A.   Acute Toxicity

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

VI. Existing Guidelines and Standards

    OSHA   - 100 ppm
    NIOSH - None
    ACGIH - 50 ppm

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Lead

Health and Environmental Effects

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

APRIL 30, 1980

121-1

DISCLAIMER

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LEAD

SUMMARY

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

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

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

LEAD

I.   INTRODUCTION

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

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

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

II. EXPOSURE

   A.   Water

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

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

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

   B.   Food

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

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C.   Inhalation

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

III. PHARMACOKINETICS

A.   Absorption

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

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

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

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

B.   Distribution

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

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

C.   Excretion

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

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

IV. EFFECTS

    A. Carcinogenicity

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

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

    B. Mutagenicity

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

    C. Teratogenicity

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

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

D. Other Reproductive Effects

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

E. Other Chronic Toxicity

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

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

V.   AQUATIC TOXICITY

A.   Acute Toxicity

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

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

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

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

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

B.   Chronic Toxicity

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

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

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

C.   Plant Effects

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

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

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

D.   Residue

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

Schulz-Baldes (1972) reported that mussels (Mytilus edulis) could bioconcentrate lead 2,568-fold. Two species of algae bioconcentrate lead 933 and 1,050-fold (Schulz-Baldes, 1976).

VI   EXISTING GUIDELINES AND STANDARDS

A.   Human

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

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

B. Aquatic

For lead, the draft criterion to protect fresh-water aquatic life is:

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

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

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

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

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

LEAD

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Maleic Anhydride

Health and Environmental Effects

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

APRIL 30, 1980

122-1

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MALEIC ANHYDRIDE

SUMMARY

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

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

I. INTRODUCTION

A. Chemical Characteristics

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

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

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

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

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

II. EXPOSURE

A. Environmental Fate

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

B. Bioconcentration

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

C. Environmental Occurrence

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

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

III. PHARMACOKINETICS

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

IV. HEALTH EFFECTS

A. Carcinogenicity

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

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

B. Other Toxicity

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

V. AQUATIC EFFECTS

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

VI. EXISTING GUIDELINES

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

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Malononitrile

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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123-1

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MALONONITRILE

Summary

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

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

MALONONITRILE

I. INTRODUCTION

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

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

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

II. EXPOSURE

A. Water and Food

Pertinent data were not found in the available literature.

B. Inhalation

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

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

C. Dermal

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

III. PHARMACOKINETICS

A. Absorption

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

B. Distribution

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

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

C. Metabolism

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

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

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

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

D. Excretion

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

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity and Reproductive Effects

Pertinent data were not found in the available literature.

B. Chronic Toxicity

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

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

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

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

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

F. Acute Toxicity

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

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

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

V.   AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A.   Human

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

B.   Aquatic

Pertinent data were not found in the available literature.

MALONONITRILE

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Mercury

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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MERCURY

SUMMARY

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

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

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

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

mercury from their tissues. In general, the methylmercury compounds are more toxic than the inorganic forms of mercury. Toxicity varies widely among species. Concentrations as low as 0.1 µg/1 have been shown to be toxic to freshwater crayfish.

I. INTRODUCTION

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

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

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

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

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

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

II. EXPOSURE

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

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

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

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

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

III. PHARMACOKINETICS

A. Absorption

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

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

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

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

B.   Distribution

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

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

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

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

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

C.   Metabolism

Methylmercury undergoes cleavage of the carbon mercury bond, resulting in the production of inorganic mercury _in vivo_.

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

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

D. Excretion

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

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

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

IV. EFFECTS

A. Carcinogenicity

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

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

B. Mutagenicity

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

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

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C. Teratogenicity

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

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

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

D. Other Reproductive Effects

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

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

E.   Chronic Toxicity

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

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

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

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

V. AQUATIC TOXICITY

A. Acute Toxicity

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

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

B. Chronic Toxicity

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

C. Plant Effects

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

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

D.   Residues

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

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

VI.   EXISTING GUIDELINES

A.   Human

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

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

B.   Aquatic

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

tive criterion is 0.025 µg/l as a 24-hour average not to exceed

2.6 µg/l at any time (U.S. EPA, 1979).

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

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No. 125

Methomyl

Health and Environmental Effects

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

APRIL 30, 1980

125-1

DISCLAIMER

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

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METHOMYL

Summary

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

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

METHOMYL

I. INTRODUCTION

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

II. EXPOSURE

A. Water

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

B. Food

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

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TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF METHOMYL

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

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

Molecular Weight: 162.2

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

Specific Gravity and/or Density$^{24}_4$ d $= 1.2946$

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

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

        Half-life approximately 50 days

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

                $\dfrac{sediment}{H_2O} : \dfrac{.5}{1}$

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

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

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

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

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

C.   Inhalation and Dermal

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

III. PHARMACOKINETICS

A.   Absorption and Distribution

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

B.   Metabolism

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

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

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C.   Excretion

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

IV. EFFECTS

A.   Carcinogenicity

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

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

B.   Mutagenicity

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

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

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

C. Teratogenicity and Other Reproductive Effects

Methomyl was fed to pregnant New Zealand White rabbits on days 8 to 16 of gestation. Teratogenic effects were not found at any of three dietary levels, 0, 50, and 100 ppm (Kaplan and Sherman, 1977). The same authors also reported on a 3-generation, 6-litter reproduction study with rats with the same dietary levels. Methomyl did not have adverse effects on reproduction and lactation performance; in addition, pathological changes were not observed in the third-generation weanling pups. Using a model ecosystem, Howe (1978) did not see effects on quail egg production or egg fertility from a diet of 10, 40, and 80 ppm methomyl.

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

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D. Chronic Toxicity

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

E. Other Relevant Information

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

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

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

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

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

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

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

V.   AQUATIC TOXICITY

A.   Acute and Chronic Toxicity

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

B.   Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI.   EXISTING GUIDELINES AND STANDARDS

A.   Human

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

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

mustard greens, parsley, swiss chard, turnip greens, and watercress; 10 ppm

for wheat, rye, barley, and oats used as hay, straw, or forage; and 40 ppm

for bermuda grass hay (Federal Register [43(98): 21700, 1978; 43 and (112):

25120, 1978; 44(63): 18972; 44(83): 24846; 44(129): 38844; 44(160): 47934,

and 44(227): 67117, 1979]).

B. Aquatic -

Guidelines or standards to protect aquatic life could not be lo-

cated in the available literature.

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Methyl Alcohol

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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

Extent of Exposure

Methyl alcohol, CH3OH, also called methanol, is the first member of a homologous series of monohydric aliphatic alcohols. At room temperature, methyl alcohol is a colorless, neutral liquid possessing a mild distinctive odor. [1] Additional chemical and physical properties of methyl alcohol are presented in Table XIII-1. [2,3,4]

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

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

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

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

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

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

EFFECTS ON HUMANS

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

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

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

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

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

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

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

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

ANIMAL TOXICITY

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

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

Correlation of Exposure and Effect

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

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

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

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

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

Basis for the Recommended Environmental Standard

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

TABLES AND FIGURE

TABLE XIII-1

PHYSICAL AND CHEMICAL PROPERTIES OF METHYL ALCOHOL

Molecular formula	CH_3OH
Formula weight	32.04
Apparent specific gravity at 20 C	0.7910
Boiling point at 760 mmHg	64.5 C
Vapor pressure at 20 C	96 mmHg
Melting point	-97.6 C
Solubility in water	Miscible
Solubility in alcohols, ketones, esters, and halogenated hydrocarbons	Miscible
Flash point, Tag open cup	16 C
Flash point, Tag closed cup	12 C
Flammable limits (% in air)	6.72-36.50
Vapor density (air=1)	1.11
Corrosivity	Noncorrosive at normal atmospheric temperatures. Exceptions: lead and aluminum
Conversion factors (760 mmHg and 25 C)	1 ppm=1.310 mg/cu m 1 mg/cu m=.763 ppm

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

TABLE XIII-2

US METHYL ALCOHOL CONSUMPTION, 1973

	Million Pounds	Million Gallons
Formaldehyde	2,778	420
Dimethyl terephthalate	435	66
Solvent usage	565	85
Methyl halides	435	66
Methylamines	232	35
Methyl methacrylate	265	40
Inhibitor for formaldehyde	66	10
Exports	824	124
Glycol methyl ethers	81	12
Acetic acid	240	36
Miscellaneous	1,207	181
Total	7,128	1,075

From Blackford [5]

=501=

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TABLE XIII-3

POTENTIAL OCCUPATIONAL EXPOSURES TO METHYL ALCOHOL

Acetic acid makers
Adhesive workers
Alcohol distillery workers
Alcohol lamp users
Aldehyde pumpmen
Antifreeze workers
Art glass workers
Automobile painters
Aviation fuel handlers
Bookbinders
Bronzers
Brushmakers
Denatured alcohol workers
Dimethyl sulfate makers
Drug makers
Drycleaners
Dye makers
Dyers
Ester makers
Explosives workers
Feather workers
Felt-hat makers
Flower makers, artificial
Formaldehyde makers
Foundry workers
Furniture polishers
Gilders
Glassmakers, safety
Hectograph operators
Incandescent lamp makers
Inkmakers
Japan makers
Japanners
Jet fuel workers
Lacquerers
Lacquer makers
Lasters
Leather workers
Linoleum makers
Lithographers
Metal polishers
Methyl acrylate makers

Methyl alcohol workers
Methyl amine makers
Methylation workers
Methyl bromide makers
Methyl chloride makers
Methyl methacrylate makers
Millinery workers
Motor fuel blenders
Organic chemical synthesizers
Painters
Paintmakers
Paint remover workers
Patent leather makers
Perfume makers
Photoengravers
Photographic film makers
Polish makers
Printers
Rayon makers
Resin makers
Rocket fuel handlers
Rocket fuel makers
Rubber shoe cementers
Rubber workers
Shellackers
Shellac makers
Shoe factory workers
Shoe finishers
Shoe heel coverers, wood
Shoe stitchers
Soapmakers
Straw-hat makers
Sugar refiners
Textile printers
Type cleaners
Vacuum tube makers
Varnish workers
Vulcanizers
Wood alcohol distillers
Wood stainers
Wood stain makers

From Gafafer [6]

TABLE XIII-4

ANIMAL EXPERIMENTATION RESULTS
OF METHYL ALCOHOL EXPOSURE

Species	Route of Exposure	Dose	Effect	Reference
Monkeys	Inhalation	5,000 ppm duration unknown	The monkey survived for an unstated period of time.	47
"	"	1,000 ppm duration unknown	The monkey died promptly upon exposure at this level.	47
Dogs	"	450-500 ppm 8 hr/day 7 days/week for 379 days	Blood levels of methyl alcohol were found to range from 10 to 15 mg/100 ml of blood and on occassion went as high as 52 mg/100 ml. No abnormal eye findings were reported.	41
"	Oral	2.5 to 9.0 g/kg body weight	Of the 9 treated dogs, 2 died at doses of 4 and 9 g/kg. CO_2 combining capacities dropped below normal in 2 dogs, and no ophthalmoscopic changes were noted.	42

TABLE XIII-4 (CONTINUED)

ANIMAL EXPERIMENTATION RESULTS
OF METHYL ALCOHOL EXPOSURE

Species	Route of Exposure	Dose	Effect	Reference
Monkeys	Oral	1.0 to 8.0 g/kg	Acidosis developed in monkeys receiving doses ranging from 3.0 to 6.0 g/kg. The animal receiving 1.0 g/kg did not develop acidosis. Definite eyeground change occurred to 2 of the acidotic monkeys.	42
Rats	"	4.75 g/kg	70% mortality	42
"	"	4.5 g/kg	None of the 9 tested rats developed acidosis.	42
Rabbits	"	3.5 g/kg	One animal receiving this dose died in less than 24 hours. No eye fundus changes were reported.	42
Rabbits	"	2.1 g/kg	Of the 3 animals tested at this dose, all died between 24 hours and 3 days after dosing.	42
"	Intra-cutaneous	10 mg and 35 mg	At 10 mg, there was no skin reaction, whereas at 35 mg, a 9-sq mm skin reaction occurred.	49

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TABLE XIII-4 (CONTINUED)

ANIMAL EXPERIMENTATION RESULTS
OF METHYL ALCOHOL EXPOSURE

Species	Route of Exposure	Dose	Effect	Reference
Monkeys	i.p. inj	0.5 g/kg of 14 C-methyl alcohol with an equimolar amount of ethyl alcohol	The ethyl alcohol reduced the oxidation of methyl alcohol 90%.	52
"	"	1.0 g/kg 14 C-methyl alcohol and 6.0 g/kg 14C-methyl alcohol	The methyl alcohol was oxidized at a rate of 37 mg/kg/hour between the first and fourth hour. The CO_2 formation was linear at the high dose; the oxidation rate was 47 mg/kg/hour which is a significant difference.	52
Rats	"	1.0/kg 14C-methyl alcohol	The oxidation rate of the methyl alcohol was 24 mg/kg/hr for the first 28 hours. At the end of 36 hours 77% of the methyl alcohol had been oxidized to 14C-labled CO_2 and 24% was excreted unchanged in approximately equal amounts by the pulmonary and combined urinary and fecal routes.	51

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S,S'-Methylene - o,o,o',o'-Tetraethyl Phosphorodithioate

Health and Environmental Effects

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

APRIL 30, 1980

127-1

DISCLAIMER

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

PHOSPHORODITHOIC ACID,
S,S'-METHYLENE,O,O,O',O'-TETRAETHYL ESTER (ETHION)

Summary

The S,S'-methylene,O,O,O',O'-tetraethyl ester of phosphorodithoic acid, ethion, has not shown mutagenic effects in mice or teratogenic effects in fowl. Subcutaneous injection of the compound into atropinized chickens produced neurotoxic effects. There is no available information on the possible carcinogenic effects of ethion.

Ethion has shown acute toxicity in stonefly naiads at a 96-hour LC_{50} range from 1.8 to 4.2 µg/l.

I.   INTRODUCTON

O,O,O',O'-Tetraethyl-S,S'-methylene bisphosphorodithioate (CAS registry number 563-12-2), also called ethion, is an insecticide and miticide made from phosphorus pentasulfide (SRI, 1976). Ethion has the following physical and chemical properties (Windholz, 1976; FAO, 1969):

Formula:	$C_9H_{22}O_4P_2S_4$
Molecular Weight:	384.48
Melting Point:	-12^oC to -13^oC
Density:	$1.220\frac{20}{4}$
Vapor Pressure:	Practically non-volatile at ordinary temperatures
Solubility:	Insoluble in water, soluble in organic solvents
Consumption:	0.7 million lbs/year (SRI, 1976)

Ethion is a pre-harvest topical insecticide used primarily on citrus fruits, deciduous fruits, nuts and cotton (SRI, 1976). It is also used as a cattle dip for ticks and as a back-line treatment for buffalo flies (FAO, 1969).

II.   EXPOSURE

A.   Water

Pertinent data could not be located in the available literature. Water contamination from ethion manufacturing may be minimal due to the common use of industrial wastewater treatment plants (U.S. EPA, 1977).

B.   Food

Residues on a variety of foods have been reported (FAO, 1969). A sampling shows the residues on fruits and vegetables range from 10.4 ppm for raisins to less than 0.1 ppm for almonds. The majority are less than 1 ppm. Treated cotton showed no residue in the seed. Tea at harvest showed residues of up to 7 ppm; since tea is blended prior to sale, residues are lower

when consumed. Lactating cows fed up to 20 ppm radioactive ethion showed no residues in their milk. In meat, the highest radioactivity was in the liver; however, chemical analysis showed these residues were not ethion but metabolites. When animals were dipped, residues from skin absorption of ethion were found in the body fat.

    C.   Inhalation and Dermal

    Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

    A.   Absorption

    Results of acute toxicity studies in animals indicate that ethion is absorbed following oral and dermal exposure (Gaines, 1969).

    B.   Distribution

    Following feeding of dairy cattle with ethion, small amounts of the unchanged compound were found in milk and fatty tissues (Vettorazzi, 1976).

    C.   Metabolism

    Rao and McKinley (1969) have reported that in vitro metabolism of ethion occurs through oxidative desulfuration of the compound by chicken liver homogenates.

    D.   Excretion

    Pertinent data could not be located in the available literature. Based on studies of other organophosphorous insecticides, it may be anticipated that ethion metabolites would be eliminated primarily in the urine (Matsumura, 1975).

IV. EFFECTS

    A.   Carcinogenicity

    Pertinent data could not be located in the available literature.

B. Mutagenicity

Vettorazzi (1976) has cited an unpublished study which found no dominant lethal effects in mice administered ethion.

C. Teratogenicity

Oral administration of ethion (100 ppm) to chickens, chukars, and quail failed to produce teratogenic or adverse reproductive effects (Abbott and Walker, 1972).

D. Other Reproductive Effects

Oral feeding of ethion to chickens, chukar, and quail failed to affect egg hatch (Abbott and Walker, 1972).

E. Chronic Toxicity

Subcutaneous injection of atropinized chickens with 400 mg/kg ethion produced neurotoxic effects (flaccid paralysis) (Gaines, 1969). Ethion will produce anti-cholinesterase effects in mammals (Vettorazzi, 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

Sanders and Cope (1968) observed 96-hour LC_{50} values ranging from 1.8 to 4.2 µg/l for stonefly naiads (Pteronarcys californica) exposed to ethion.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The World Health Organization (FAO, 1969) has established an ADI level of 0.005 mg/kg for ethion based on cholinesterase inhibition studies.

B. Aquatic

Pertinent data could not be located in the available literature.

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127-7

No. 128

Methyl Ethyl Ketone

Health and Environmental Effects

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

APRIL 30, 1980

128-1

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ensure its technical accuracy.

128-2

Methyl Ethyl Ketone

I.   INTRODUCTION

   Methyl ethyl ketone or (MEK) as it is commonly referred
to is a clear, colorless, volatile liquid (VP of 100 mm at 25°C)
with a molecular weight of 72.12. It has a melting point of
-86.35°C and a boiling point of 76.6°C. It is very soluble
in water (25.5 g/loo at 2 percent) and soluble in all
proportions in alcohol, ether, acetone and benzene.[2] It is
also highly flammable (22°F - open cup).[3]

   MEK is produced and used as a solvent in nitrocellulose
coatings and vinyl films; in the synthesis of colorless
resins; in the manufacture of smokeless powder; in paint
removers, cements, adhesives, and cleaning fluids; in printing
industry; as a catalyst carrier; in lube oil dewaxing and in
acrylic coatings.[2]

II. ROUTES OF EXPOSURE

   MEK is rapidly absorbed through the skin by inhalation.

III. PHARMACOKINETICS

   MEK occurs in trace amounts in normal human urine and
may have a dietary origin.[1] Most probable precursor is

   - methylacetoacetic acid.[1]

   Urine of rabbits exposed to MEK reported to contain
glucuronide of 2-butanol.[1]

IV. EFFECTS ON MAMMALS

   The chief effect of MEK is narcosis but is also a strong
irritant of the mucous membranes of the eyes and nose. The
oral LD50 for rats is 3.3 g/kg and the inhalation LC50 is

around 700 ppm.[1]

Repeated exposure of guinea pigs for 12 weeks to 235 ppm caused no symptoms.[1]

Lethal doses in animals caused marked congestion of internal organs and slight congestion of brain. Lungs showed emphysema (see Table 1).

Slight throat irritation in humans occured at 100 ppm and in eyes at 200 ppm.

Dermatoses among workers having direct contact and exposed to vapors are not uncommon. Some workers complained of numbness of fingers and arms.[1]

Table 1

Effects of Methyl Ethyl Ketone on Animals

	Concentration/ Duration	Animal	Effects
Methyl Ethyl Ketone	33,000-100,000 ppm/200 min.	Guinea Pigs	Gasping, death, emphysema, slight congestion of the brain, marked congestion of the systemic organs especially the lungs and corneal opacities
	3,300 ppm/810 min.	Guinea Pigs	No abnormal signs
	1,125 ppm/24 hr/3,55d	Rats	No evidence of peripheral neuropathy
	1,126 or 2,618 ppm/7 hr/d on d 6-15 of gestation	Pregnant Rats	Embryotoxicity, fetotoxicity and possible teratogenicity

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No. 130

Methyl Methacrylate

Health and Environmental Effects

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

APRIL 30, 1980

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130-2

METHYL METHACRYLATE

Summary

Oral or skin painting studies in rats have failed to show carcinogenic effects of administration of methyl methacrylate. Implantation of the compound in mice also failed to produce tumors.

Exposure of rats to a mixture of chloroprene and methyl methacrylate produced an increase in lymphocyte chromosome aberrations. Increased chromatid breaks and chromosome breaks have been reported in workers exposed to this same chemical mixture.

Teratogenic effects (hemangiomas) have been reported following intraperitoneal administration of methyl methacrylate to pregnant rats. Inhalation exposure of pregnant rats to an acrylic cement containing methyl methacrylate failed to produce significant teratogenic effects.

Ninety-six hour LC_{50} values for four species of fish range from 159 to 368 ppm. Inhibition of cell multiplication of an alga begins at 120 ppm.

I. INTRODUCTION

Methyl methacrylate, CAS registry number 80-62-6, is a colorless, clear, volatile liquid. It is made from acetone cyanohydrin which is hydrolyzed in sulfuric acid to yield methacrylamide sulfate, which is then treated with methanol to yield methyl methacrylate. It has the following physical and chemical properties (Windholz, 1976; Hawley, 1971; Weast, 1972; Verschueren, 1977):

Formula:	$C_5H_8O_2$
Molecular Weight:	100.12
Melting Point:	$-48.2^{\circ}C$
Boiling Point:	$101^{\circ}C$
Density:	0.9440^{20}_{4}
Vapor Pressure:	28 torr @ $20^{\circ}C$
Solubility:	Sparingly soluble in water, miscible in alcohol, benzene, ether, etc.
Production:	706 million lbs (1973) (Gruber, 1975)

Virtually all the methyl methacrylate produced in this country is used for polymers, e.g., surface coating resins and plastics (plexiglass, lucite), ion exchange resins, dentures, etc.

II. EXPOSURE

A. Water

According to Gruber (1975), about 1.8 g of methyl methacrylate per kilogram final product (methyl methacrylate) is present in wastewater. The amount of methyl methacrylate entering domestic water supplies is probably small.

B. Food

Polymethyl methacrylate is used for food storage. A very small amount of residual monomer may migrate into food from the polymer.

C.   Inhalation

Fugitive emissions from production, storage, and transportation probably constitute the only major sources of methyl methacrylate in the air. The concentration would most likely be highest in production facilities. Production was estimated to be 7.9 million pounds in 1974 (U.S. EPA, 1976). A 550-million pound-per-year production facility with 0.5 percent loss emits 39.6 grams of methyl methacrylate per second. If this is considered to be a virtual point source, the downwind concentration 500 meters away would be 1.5 ppm one-hour average (U.S. EPA, 1976).

D.   Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A.   Absorption and Distribution

Pertinent data could not be located in the available literature.

B.   Metabolism

Bratt and Hathway (1977) found that up to 88 percent of a single methyl(^{14}C)methacrylate dose of 5.7 mg/kg body weight was expired as CO_2 within 10 days. Neither the route of administration nor the specific labelling of the propylene residue changed this value. Small amounts of several metabolites were excreted in the urine, including ^{14}C-methylmalonate, ^{14}C-succinate, 2-formylpropionate, and possibly ^{14}C-β-hydroxybutyrate.

Corkill, et al. (1976) found that the disappearance of methyl methacrylate in human blood in vitro showed a first order dependence on methyl methacrylate concentration. The calculated half-life was 20 to 40 minutes, irrespective of the sex or age of the blood donor. More than 40 percent of the initial dose of methyl methacrylate was converted to methacrylic acid within 90 minutes.

C. Excretion

Pertinent data could not be located in the available literature.

IV. EFFECTS

A. Carcinogenicity

The International Agency for Research on Cancer (IARC, 1979) has evaluated the available data and concluded that there is not enough information to determine the potential carcinogenicity of methyl methacrylate to humans. Borzelleca, et al. (1964) observed no treatment-related tumors in male and female Wistar rats administered 6, 60, or 2,000 mg/l methyl methacrylate in their drinking water for two years. Oppenheimer, et al. (1955) found no local tumors in ten Wistar rats painted with methyl methacrylate three times per week for four months and observed for their entire life span.

Another study, by Spealman, et al. (1945), in which male and female mice received implants consisting of 0.075 gm of methyl methacrylate in a gelatin capsule also yielded negative results.

B. Mutagenicity

The only data available on the mutagenic effects of methyl methacrylate are two studies involving exposure to a mixture of chloroprene and methyl methacrylate (Bagramjan, et al. 1976; Bagramjan and Babajan, 1974). In both studies, an increased frequency of chromosomal aberrations were found in rats exposed to the mixture. Bagramjan, et al. (1976) also measured a significant increase in chromatid breaks and chromosome breaks in the lymphocytes of workers exposed to a mixture of chloroprene and methyl methacrylate.

C. Teratogenicity

Singh, et al. (1972a,b) and Autian (1975) injected intraperitoneally three groups of pregnant Sprague-Dawley rats with methyl methacrylate at doses of 0.1, 0.2, or 0.4 g/kg body weight on days 5, 10, and 15 of ges-

tation. In animals administered the two higher doses, a significantly greater number of hemangiomas were seen at various sites. All three groups exhibited reduced fetal weights, but no significant increase in skeletal defects was observed in any group.

McLaughlin, et al. (1978) exposed pregnant mice to a vapor concentration of 1,330 ppm methyl methacrylate (as acrylic cement, Simplex p) for two hours two times per day for days 6 through 15 of gestation. No fetotoxic or teratogenic effects were noted other than a slight decrease in the average fetal weight.

D.   Other Reproductive Effects

Pertinent data could not be located in the available literature.

E.   Chronic Toxicity

Spealman, et al. (1945) conducted a series of subchronic inhalation ex- periments involving guinea pigs and dogs. Guinea pigs exposed to 39.0 mg/l methyl methacrylate for two hours per day for three days exhibited significant liver degeneration, while dogs exposed to 46.8 mg/l methyl methacrylate for two hours per day for 8 to 15 days exhibited liver degeneration and tubular degeneration of the kidneys.

Borzelleca, et al. (1964) administered 6, 60, and 2,000 ppm of methyl methacrylate in drinking water to male and female rats for a period of two years. Weight gain was decreased for the first few weeks in animals given the highest dose. No changes in hematological values or urine concentrations of protein and reducing agents were noted. Females receiving the highest dose level exhibited an increase in kidney to body weight ratios.

Blagodatin, et al. (1970) reported symptoms of headache, pain in the extremities, fatigue, sleep disturbance, loss of memory, and irritability in 152 workers exposed to concentrations of 0.5 to 50 ppm methyl methacrylate. Most of the workers had been employed for longer than 10 years.

F.   Acute Toxicity

No detectable acute effects were noted in workers employed in manufacturing polymethyl methacrylate sheets (Cromer and Kronoveter, 1976). The airborne concentrations of methyl methacrylate varied from 4 to 49 ppm.

V.   AQUATIC TOXICITY

A.   Acute Toxicity

Pickering and Henderson (1966) observed the following 96-hour LC_{50} values for fish exposed to methyl methacrylate: fathead minnow (Pimephales promelas) - 159 ppm in soft water (20 mg/l); fathead minnow - 311 ppm in hard water (360 mg/l); bluegill (Lepomis macrochirus) - 357 ppm in soft water (20 mg/l); goldfish (Carassius auratus) - 277 ppm in soft water (20 mg/l); guppies (Lebistes reticulatus) - 368 ppm in soft water (20 mg/l).

B.   Chronic Toxicity

Pertinent data could not be located in the available literature.

C.   Plant Effects

Inhibition of cell multiplication of the alga, Microcystis aerugi-nosa, by methyl methacrylate begins at 120 ppm (Bringmann and Kuhn 1976).

D.   Residues

Pertinent data could not be located in the available literature.

VI.   EXISTING GUIDELINES AND STANDARDS

A.   Human

Guidelines have been established for exposure to methyl methacry-late by the American Conference of Governmental Industrial Hygienists and OSHA. Both the TLV and the federal standard have been set at 100 ppm (or 410 mg/m^3) (ACGIH, 1977; 29 CFR 1910).

8. Aquatic

No guidelines have been established for the protection of aquatic organisms from acute or chronic methyl methacrylate toxicity because of the lack of pertinent data.

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Naphthalene

Health and Environmental Effects

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

APRIL 30, 1980

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DISCLAIMER

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

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NAPHTHALENE

Summary

Naphthalene is present in ambient water as well as drinking water. Naphthalene can be absorbed by any route, although the efficiency of absorption has not been determined. The toxicological properties are due to the formation of highly reactive metabolites. Chronic exposure produces cataracts, hemolytic anemia, and kidney disease. Naphthalene can cross the placenta and produce these effects on newborns. Naphthalene has been found to be nonmutagenic in several microsomal/bacterial assay systems. Chronic toxicity studies of naphthalene have shown it to be noncarcinogenic.

Naphthalene has been shown to be acutely toxic in freshwater fish with LC_{50} values of 150,000 µg/l being reported in one static bioassay. Freshwater invertebrates were more sensitive with LC_{50} values of 8,570 µg/l, as were marine fish with LC_{50} values ranging from 2,350 to 2,600 µg/l.

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INTRODUCTION

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

Naphthalene ($C_{10}H_8$; molecular weight 128.16) is a bicyclic, aromatic hydrocarbon which in a pure grade, forms a white crystalline solid at room temperature (Windholz, 1976). Pure naphthalene has a melting point of 80.2^oC, a boiling point of 217.96^oC (Manufacturing Chemists Assoc., 1956) and a vapor pressure of 0.0492 mm Hg at 19.8^oC (Gil'denblat, et al. 1960). Naphthalene is water soluble, with solubility ranging from 30,000 µg/l (Mitchell, 1926) to 40,000 µg/l (Josephy and Radt, 1948). Naphthalene vapor and dust can form explosive mixtures with air (Windholz, 1976). Naphthalene is used as an intermediary in the production of dye compounds, in the formulation of solvents, lubricants and motor fuels, and as a feedstock in the synthesis of phthalic anhydride. Naphthalene is also used directly as a moth repellant, insecticide, antihelminthic, vermicide, and an intestinal antiseptic (U.S. EPA, 1979). In 1974, production of naphthalene was approximately 2.9×10^5 metric tons (U.S. EPA, 1976).

II. EXPOSURE

A. Water

The two major sources of naphthalene in the aquatic environment are from industrial effluents and from oil spills. The final effluents of sewage treatment plants receiving discharges from these industrial facilities have been noted to have up to 22 µg/l naphthalene, while natural waters have up to 2.0 µg/l, and drinking water supplies have up to 1.4 µg/l naphthalene (U.S. EPA, Region IV, unpublished data).

B.   Food

The U.S. EPA (1979) has estimated the weighted average bio-
concentration factor for naphthalene to be 60 for the edible portions of
fish and shellfish consumed by Americans. This estimate was based on
octanol/water partition coefficients.

C.   Inhalation

In the ambient air, inhalation of naphthalene is negligible
with vapor concentrations ranging from 0.00005 to 0.0001 $\mu g/m^3$ and
particulate concentrations ranging from 0.000003 to 0.00025 $\mu g/m^3$
(Krstulovic, et al. 1977). Industrial exposure can range from 0.72 $\mu g/m^3$
to 1.1 x 10^6 $\mu g/m^3$ in the vapor phase (Bjrseth, et al., 1978b; Robbins,
1951) and from 0.09 $\mu g/m^3$ to 4.40 $\mu g/m^3$ in particulates (Bjrseth, 1978a,
1978b). Naphthalene has also been found in cigarette smoke condensate
(Akin, et al. 1976).

III. PHARMACOKINETICS

A.   Absorption

Little detailed information is available on the absorption of
naphthalene in man or animals. Adequate amounts of naphthalene can be
absorbed when ingested as a solid, or by inhalation, to cause significant
toxicity (U.S. EPA, 1979). Absorption seems to be facilitated if naphthalene
is dissolved in oil (Solomon, 1957), and hindered if naphthalene is bound
to protein (Sanborn and Malins, 1977).

B.   Distribution

Naphthalene distributes widely after absorption. In mallards,
the relative distribution of naphthalene was as follows: greatest in
skin, followed by liver, brain, blood, muscle, and heart (Lawler, et al.
1978).

C. Metabolism

Naphthalene is first metabolized by hepatic mixed-function oxidases to an epoxide, which is an obligatory step in the metabolism of naphthalene. Further metabolism can occur leading to the formation of a variety of compounds. Most of these compounds are enzymatically conjugated with glucuronic acid or sulfate. During metabolism a number of highly reactive compounds are formed such as 1,2-dihydroxynaphthalene and 1,2-naphthoquinone (U.S. EPA, 1979).

Naphthalene metabolites undergo further conversions in the eye. This multi-step pathway can lead to the formation of 1,2-naphthaquinone which can irreversibly bind to lens protein and amino acids (Van Heyningen and Pirie, 1966).

D. Excretion

Naphthalene has not been identified in urine after absorption. With sufficient absorption of naphthalene to result in toxicity to an 18 month old infant, Mackell, et al. (1951) noted metabolites of naphthalene in the urine that were still identifiable two weeks after exposure but which had disappeared 18 days after exposure.

1-Napthol is the predominant spontaneous decomposition product of the epoxide of napohthalene. 1-Napthol is excreted unchanged as well as congugated with glucuronic acid or sulfate prior to excretion. The finding of 1,4-nathoquinone in the urine of a child poisoned with naphthalene (Mackell, et al. 1951) suggests that 1-napthol can also be further oxidized in mammals (Cerniglia and Gibson, 1977).

IV. EFFECTS

A. Carcinogenicity

In attempts to demonstrate its carcinogenicity, naphthalene has been given orally, subcutaneously, implanted in the bladder, and painted

on the backs of a number of animal species (U.S. EPA, 1979). In these
experiments naphthalene caused no increase in tumor formation. Two
experiments have produced increases in lymphosarcoma and lymphatic
leukemia after treatment with coal tar derived naphthalene. The first of
these studies (Knake, 1956) was complicated by the presence of 10 percent
impurities in the naphthalene and the painting of the injection site with
carbolfuchsin, a known experimental carcinogen, prior to injection. In
the second study (Knake, 1956) where excess leukemia was noted, naphthalene
was dissolved in benzene, a known human leukemogenic agent, and painted on
the backs of mice. Benzene treatment resulted in no leukemia. Skin
papillomas have been produced on mice following painting with 1,4-naphtha-
quinone, a metabolite of naphthalene (Takizawa, 1940). Also, Pirie (1968)
noted abnormal mitotic figures in metaphase and cell overgrowth in the
epithelial cells of the lens of rabbits given 1 g/kg/day of naphthalene
by gavage.

B. Mutagenicity

Naphthalene has been found to be nonmutagenic in several microsomal/
bacterial assay systems (McCann, et al. 1975; Kraemer, et al. 1974).

C. Teratogenicity

Pertinent data could not be located in the available literature.

D. Other Reproductive Effects

Naphthalene or its metabolites can cross the placenta in sufficient
amounts to cause fetal toxicity (Zinkham and Childs, 1958; Anziulewicz,
et al. 1959). When a metabolite of naphthalene, 2-naphthol, was admin-
istered to pregnant rabbits, their offspring were born with cataracts and
evidence of retinal damage (Van der Hoeve, 1913).

E.   Toxicity

Oral administration of two percent naphthalene or 2-napthol to rats for at least 60 days resulted in the development of cataracts (Fitzhugh adn Busckke, 1949). Van Heyningen and Pirie (1976) dosed rabbits daily by gavage with 1000 mg/kg of naphthalene for a maximum of 28 days. Lens changes developed after the first dose, and retinal changes developed after the second dose. Rabbits fed 1000 mg/kg/day developed cataracts between day 3 and 46. Topical application of a 10 percent solution in oil to the eyes of rabbits did not produce cataracts after a period of 50 days. Intraperitoneal injection of 500 mg/kg of naphthalene in an oily solution produced weight loss over a period of 50 days (Ghetti and Mariani, 1956). Hemolytic anemia with associated jaundice and occasionally renal disease from precipitated hemoglobin has been described in newborn infants, children and adults after exposure to naphthalene by ingestion, inhalation, or possibly by skin contact (U.S. EPA, 1979). The extent or duration of exposure was not given. Mahvi, et al. (1977) noted a dose related damage to bronchiolar epithelial cells in mice given intraperintoneal injections of naphthalene in corn oil. Bronchiolar epithelial changes were not noted in two control groups. The authors noted minor bronchiolar epithelial changes in the treated group receiving 67.4 mg/kg of naphthalene. Those mice receiving higher doses (128 and 256 mg/kg of naphthalene) developed reversible necrosis of bronchiolar cells.

F.   Other Relevent Information

Alexandrov and Frayssinet (1973) demonstrated that naphthalene administered intraperitoneally to rats could inhibit the mixed-function microsomal oxidase enzyme system, and could also inhibit the induction of these enzymes by 3-methylcholanthrene.

V. AQUATIC TOXICITY

A. Acute

For the freshwater mosquitofish (Gambusia affinis) a 96-hour static bioassay provided an LC_{50} value of 150,000 µg/l (Wallen, et al. 1957), while the freshwater cladoceran (Daphnia magna) was shown to have an 48-hour LC_{50} value of 8,570 µg/l (U.S. EPA, 1978). Marine organisms tended to be somewhat more sensitive to naphthalene with an 24-hour static LC_{50} value of 2,400 µg/l for the sheepshead minnow (Cyprinodon variegatus). Two 24-hour static LC_{50} values of 2,500, 2,600 were obtained for two species of marine shrimp, (Penaeus aztecus) and (Palaemonetes pugio), respectively (Anderson, et al. 1974). A 96-hour LC_{50} value of 2,350 µg/l was obtained for grass shrimp (Palaemonetes pugio) (Tatem, 1976).

B. Chronic Toxicity

A single embryo-larval test on the fathead minnow (Pimephales promelas) stated that no effects were observed at concentrations as high as 440 µg/l (U.S. EPA, 1978).

Data pertaining to the chronic toxicity of naphthalene for any marine species could not be located in the available literature.

C. Plant Effects

A 48-hour EC_{50} value of 33,000 µg/l for reduced cell numbers has been reported for the freshwater algae (Chlorella vulgaris) exposed to naphthalene. Data pertaining to the effects of naphthalene to marine plants could not be located in the available literature.

D. Residues

Using the octanol/water partition coefficient of 2,300 for naphthalene, a bioconcentration factor for aquatic organisms with an 8 percent lipid content has been estimated as 210. Bioconcentration

factors determined for marine invertebrates ranged from 50 to 60 in the marine copepod Calanus helgolandicus after one day (Harris, et al. 1977a, 1977b) to 5,000 in the copepod Eurytemora affinis, after nine days, (Harris, et al. 1977b) indicating that equilibrium may not occur rapidly. Bioconcentration factors of 32 to 77 after 1 to 24 hours were reported for these 3 species of marine fish and one species of mussel (Lee, et al. 1972a; 1972b).

VI.   EXISTING GUIDELINES AND STANDARDS

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

A.   Human

The Occupational Safety and Health Administration standard for exposure to vapor for a time-weighted industrial exposure is 50 mg/m^3. The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) threshold limit value is 75 mg/m^3, while at present the ACGIH also suggests a maximum 15 minute exposure value of 75 mg/m^3 (ACGIH, 1978). The acceptable daily intake for naphthalene is 448 μg/day for a 70 kg person. The U.S. EPA (1979) draft ambient water criterion for naphthalene is 143 μg/l.

B.   Aquatic

Criterion can not be derived for naphthalene for either freshwater or marine organisms, because of the lack of sufficient toxicological data.

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1,4-Naphthoquinone

Health and Environmental Effects

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

APRIL 30, 1980

132-1

DISCLAIMER

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

SUMMARY

1,4-Naphthoquinone is used as a polymerization regulator and an
intermediate. Some data are available which indicate that 1,4-naphtho-
quinone is biodegradable.

The most consistent findings reported in the literature for health
effects of 1,4-naphthoquinone involve hematological changes, irritant and
allergenic activity, and inhibition of biochemical oxidation processes.
One study found 1,4-naphthoquinone to be oncogenic. Some evidence of
inhibition of _in vitro_ endocrine function and of nerve activity was re-
ported.

I. INTRODUCTION

1,4-Naphthoquinone (1,4-naphthalenedione; $C_{10}H_6O_2$; molecular weight 158.15)
is a solid at room temperature. It occurs as a greenish yellow powder or
as yellow triclinic needles. It has a melting point of 123–126°C and begins
to sublime at 100°C; its density is 1.422. 1,4-Naphthoquinone is only
slightly soluble in water; it is soluble in a variety of organic solvents
(Windholz 1976; Hawley 1971).

Current production (including importation) statistics for 1,4-naphtho-
quinone (CAS No. 130-15-4) listed in the initial TSCA Inventory (U.S. EPA 1979)
show that between 1,000,000 and 9,000,000 pounds of this chemical were
produced/imported in 1977.*

1,4-Naphthoquinone is used as a polymerization regulator for rubber
and polyester resins, in the synthesis of dyes and pharmaceuticals, and as
a fungicide and algicide (Hawley 1971).

II. EXPOSURE

A. Environmental Fate

No specific information on the biological, chemical or photochemical
transformation of 1,4-naphthoquinone under environmental conditions was
identified in the literature. Napthoquinones undergo few substitution

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

reactions (Thirtle 1965). Like other quinones, 1,4-naphthoquinone can interconvert with its corresponding hydroquinone in an oxidation-reduction system.

Talakin (1964) reported that 1,4-naphthoquinone in river water apparently undergoes slow biochemical oxidation, based on an observed increase in BOD. Verschueren (1977) reports that the BOD_5 is 0.81, using the standard dilution technique with normal sewage as seed material, and that the theoretical oxidation demand is 2.1.

B. Bioconcentration

No information was found on the bioconcentration potential of 1,4-naphthoquinone. Based on its low water solubility and its solubility in organic solvents, 1,4-naphthoquinone could be expected to bioconcentrate to some extent.

C. Environmental Occurrence

No information was found on the presence of 1,4-naphthoquinone in environmental media.

In addition to its potential entry into the environment from its manufacture, processing and uses, 1,4-naphthoquinone may also enter the environment as a degradation product of certain naphthalene derivatives. For example, the U.S. EPA (1975) reported studies showing that the pesticide carbaryl (1-naphthyl-n-methyl-carbamate) undergoes hydrolysis to 1-naphthol, which is then converted by bacteria to 1,4-naphthoquinone and other products.

III. PHARMACOKINETICS

No information was obtained.

IV. HEALTH EFFECTS

A. Carcinogenicity

1,4-Naphthoquinone was found to induce neoplasm when applied dermally to mice for 28 weeks. The total dose applied was 2000 mg/kg. (Proceedings of the Imperial Academy of Tokyo 16:309, 1940, as cited in NIOSH 1975).

B. Reproductive Effects

1,4-Naphthoquinone completely inhibited the gametokinetic effect of human chorionic gonadotropin in toads (Pakrashi 1963).

C. Other Toxicity

The oral LD_{50} for rats was reported as 190 mg/kg (NIOSH, 1975). The LD_{100} of 1,4-naphthoquinone in rats was 0.5 g/kg, 0.25 g/kg, and 0.5 g/kg for intraventricular, subcutaneous, and intraperitoneal administrations, respectively. The LC_{100} in air was 0.45 mg/L for a one-hour exposure. Acute (0.5 g/kg) and subchronic (0.3 g/kg for 4 days) exposure of rats resulted in the formation of 39 and 18% methemoglobin, respectively, followed by the appearance of Heinz bodies and development of hemolytic anemia. A decrease in total respiration and hypothermia due to disturbances in oxidation-reduction processes was also observed. According to the authors, "threshold concentrations of 1,4-naphthoquinone detected for rats and rabbits in single-exposure and chronic experiments were 0.0004 and 0.0007 mg/L with respect to their irritant and toxic effects" (Slyusar et al. 1964).

D. Other Relevant Information

1,4-Naphthoquinone exerted an allergenic effect in guinea pigs (Kryzhanovskaya et al. 1966). A possible role for 1,4-naphthoquinone in drug-induced thrombocytopenia was suggested by Niewig et al. (1973) as 1,4-naphthoquinone was found to be involved in the destruction of normal blood platelets by serum antibodies in vitro. 1,4-Naphthoquinone blocks the biosynthesis of adrenal steroids by bovine adrenal cortex in vitro (Kahnt and Neher 1966), and has an inhibitory effect on mixtures of cytochrome c and dehydrated succinate oxidase from beef heart (Heymann and Feiser 1966). 1,4-Naphthoquinone inhibited ATPase and nerve activity in the (American) cockroach. (Baker and Norris 1971, Baker 1972).

V. AQUATIC TOXICITY

Very little information was available. For 1,4-naphthoquinone, a median threshold limit value (TLM:24-28 hr) of 0.3-0.6 mg/L was listed for an unspecified species of fish (Verschueren 1977).

VI. GUIDELINES

No guidelines for exposure to 1,4-naphthoquinone were located.

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Nickel

Health and Environmental Effects

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

APRIL 30, 1980

~~1563~~
133-1

DISCLAIMER

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

133-2
-1564-

SPECIAL NOTATION

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

NICKEL

Summary

Nickel is a ubiquitous multi-media environmental contaminant. Although nickel is toxic and appears to be a carcinogen to man, there is an increasingly strong indication that nickel is an essential element. The route of exposure to nickel is very important, since oral intake of nickel metal is comparatively nontoxic. However, exposure to nickel by inhalation or parenteral administration as well as cutaneous contact can produce toxic effects. In terms of human health effects, probably the most acutely toxic nickel compound is nickel carbonyl. Nickel in several chemical forms has been associated with lung cancer in man and experimental animals upon inhalation; carcinogenic effects, however, are not indicated by the oral route. The acceptable daily intake (ADI) of nickel is 294 μg per day for a 70 kg man.

The toxicity of nickel to aquatic life is affected by water hardness. In the aquatic environment nickel is acutely toxic to freshwater fishes at a concentration of 2,480 μg/l (26 mg/l hardness). Chronic toxicity to fishes has been reported at 527 μg/l (210 mg/l hardness). Nickel toxicity is affected by water hardness. Algae appears to be more sensitive to nickel than fish. Based on the limited number of studies performed, the bioconcentration factor for fish is 61, for algae the factor is 9.8, and the weighted average bioconcentration factor is 11 for fish and shellfish.

NICKEL

I. INTRODUCTION

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

Nickel (Ni; atomic weight 58.71), a bright, silver metal of the iron-cobalt-nickel triad, is a hard and malleable metal with a high tensile strength used in virtually all areas of metallurgy. Nickel does not readily form chloro-complexes under environmental conditions and would not be expected to form significant amounts of sulfate complexes (U.S. EPA, 1979).

In 1972, U.S. consumption of nickel, exclusive of scrap, was estimated to total about 160,000 tons (Reno, 1974). The estimate consisted mainly of commercially pure nickel (about 110,000 tons) which is used in stainless steel, electroplating, and various other alloys.

II. EXPOSURE

The route by which most people in the general population receive the largest portion of daily nickel intake is through foods. Total daily dietary intake values may range up to 900 μg nickel, depending on the nature of the diet, with average values of 300 to 500 μg daily (NAS, 1975). The U.S. EPA (1979) has estimated a weighted average bioconcentration factor for nickel to be 11 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in fathead minnow larvae (Pimephales promelas) (Lind, et al. Manuscript). The values for nickel levels in 969 U.S. public water supplies for 1969-1970 was 4.8 μg/l, with only 11 systems of this total exceeding 25 μg/l (NAS, 1975). The levels of nickel in the air are also low, with a 1974 arithmetic mean level for urban air of 9 ng/m^3 (U.S. EPA, 1976).

III. PHARMACOKINETICS

A. Absorption

The major routes of nickel absorption are inhalation and ingestion
via the diet. Percutaneous absorption is a less significant factor for
nickel's systemic effects but important in the allergenic responses to nick-
el. Collectively the data of Tedeschi and Sunderman (1957), Perry and Perry
(1959), Nomoto and Sunderman (1970), Nodiya (1972), and Horak and Sunderman
(1973) indicate that 1 to 10 percent of dietary nickel is absorbed. Skin
penetration of nickel has been demonstrated with nickel entering at sweat-
duct and hair-follicle ostia (Wells, 1956). The extent to which nickel en-
ters the bloodstream by way of the skin cannot be stated at the present time
(U.S. EPA, 1979).

Respiratory absorption of various forms of nickel is probably the
major route of nickel entry into man under conditions of occupational expo-
sure. Pulmonary absorption into the bloodstream is probably greatest for
nickel carbonyl vapor, with animal studies suggesting that as much as half
of the inhaled amount is absorbed (Sunderman and Selin, 1968). Nickel in
particulate matter is absorbed from the pulmonary tract to a lesser degree
than nickel carbonyl (Leslie, et al. 1976). Based on animal studies, nickel
appears to have a half-life of several days in the body, yet there is little
evidence for tissue accumulation.

B. Distribution

Blood is the main vehicle for transport of absorbed nickel, with
serum albumin being the main carrier protein, although a specific nickelrich
metalloprotein has been identified in man (NAS, 1975). Tissue distribution
of absorbed nickel appears to be dependent on the route of intake. Inhaled
nickel carbonyl leads to highest levels in the lung, brain, kidney, liver,

and adrenals (Armit, 1908; Sunderman and Selin, 1968; Mikheyev, 1971). Par-
enteral administration of nickel salts usually results in highest levels in
the kidney, with significant uptake shown by endocrine glands, liver and
lung (Wase, et al. 1954; Smith and Hackley, 1968).

C. Metabolism

A number of disease states and other physiological stresses are
reported to alter the movement and tissue distribution of nickel in man as
well as experimental animals. In man, increased levels of serum nickel are
seen in cases of acute myocardial infarction (D'Alonzo and Pell, 1963; Sun-
derman, et al. 1972), acute stroke and extensive burn injury (McNeely, et
al. 1971). Reduction is seen in hepatic cirrhosis or uremia, possibly sec-
ondary to hypoalbuminemia.

Nickel appears to be an essential element, at least in experimental
animals. Nickel deficient diets have produced decreased growth rates and
impaired reproduction in swine (Anke, et al. 1974) and rats (Schnegg and
Kirchgessner, 1975).

D. Excretion

The routes of elimination for nickel in man and animals depend in
part on the chemical forms of nickel and the mode of nickel intake. Dietary
nickel, due to the low extent of gastrointestinal absorption, is simply lost
in the feces (U.S. EPA, 1979). Urinary excretion in man and animals is usu-
ally the major clearance route for absorbed nickel. In some instances sweat
can constitute a major route of nickel elimination (Hohnadel, et al. 1973).
Nodiya (1972) reported a fecal excretion average of 258 μg in Russian stu-
dents. Horak and Sunderman (1973) determined fecal excretion of nickel in
10 healthy subjects and arrived at a value identical to that found in the
Russian study.

IV. EFFECTS

   A. Carcinogenicity

      A carcinogenic response to various nickel compounds upon injection
has been observed in a number of animal studies (Lau, et al. 1972; Stoner,
et al. 1976; IARC, 1976). In nickel refinery workers, an excess risk of
nasal and lung cancer has been demonstrated (IARC, 1976). However, there is
no evidence at present to indicate that orally ingested nickel is tumori-
genic.

      The qualitative and quantitative character of the carcinogenic effects
of nickel as seen in experimental animal models has been shown to vary with
the chemical form of the nickel, the route of exposure, the animal model em-
ployed, and the amounts of the substance administered (U.S. EPA, 1979).

   B. Mutagenicity

      Pertinent information could not be located in the available litera-
ture.

   C. Teratogenicity

      While Ferm (1972) has claimed unspecified malformations in surviv-
ing hamster embryos when mothers were exposed to parenteral nickel (0.7 to
10.0 mg/kg), Sunderman, et al. (1978) found no teratogenic effects from oral
administration of either nickel chloride (16 mg/kg) or nickel subsulfide (80
mg/kg) in rats. Exposure of pregnant rats by inhalation to nickel carbonyl
on days 7 or 8 of gestation frequently caused the progeny to develop ocular
anomalies, including anophthalmia and microphthalmia. The incidence of ex-
traocular anomalies is very low. The specificity of nickel carbonyl for in-
duction of ocular anomalies in rats appears to be unique among known terato-
genic agents (Sunderman, et al. 1979).

D. Other Reproductive Effects

Schroeder and Mitchner (1971) have demonstrated adverse affects in a three generation study with rats at a level of 5 mg/l (5 ppm) nickel in drinking water. In each of the generations, increased numbers of runts and enhanced neonatal mortality were seen. A significant reduction in litter size and a reduced proportion of males in the third generation were also observed. Nickel sulfate (25 mg/kg) has been demonstrated to be gametotoxic in rats, with complete obliteration of spermatozoa following exposure for 120 days (Hoey, 1966; Waltschewa, et al. 1972).

E. Chronic Toxicity

Chronic exposure to nickel has resulted in injury to both the upper and lower respiratory tract in man (Tolot, et al. 1956; McConnell, et al. 1973). Inhalation of nickel particulate matter is likely to play a role in chronic respiratory infections by effects on alveolar macrophages. Contact dermatitis in man with nickel sulfate has been observed (Fregert, et al. 1969; Brun, 1975). Also, dietary nickel can elicit a dermatitic response (Kaaber, et al. 1978).

F. Other Relevant Information

There are experimental data that demonstrate that nickel has a synergistic effect on the carcinogenicities of polycyclic hydrocarbons (Toda, 1962; Maenza, et al. 1971; Kasprzak, et al. 1973). Nickel and other elements are known to be present in asbestos and may possibly be a factor in asbestos carcinogenicity (Cralley, 1971). Also, a synergistic action between nickel and viruses has been suggested (Treagon and Furst, 1970).

V. AQUATIC TOXICITY

A. Acute Toxicity

Water hardness significantly influences the acute toxicity of nickel to freshwater fish. For fish, observed LC_{50} values range from 2,480

µg/l for the rock bass (Ambloohites rupestris) (hardness = 26 mg/l) to 110,385 µg/l for the bluegill (Lepomis macrochirus) (hardness = 42 mg/l). At a hardness of 20-29 mg/l, six freshwater species have LC_{50} values of between 2,916 and 5,360 µg/l (Pickering and Henderson, 1966; Lind et al., manuscript). At a hardness of 360 µg/l, values range from 39,600 to 44,500 µg/l. In comparison, acute tests with freshwater invertebrate species have a greater range of LC_{50} values at a fixed hardness. The stonefly (Acroneuria lycorias) exhibited the highest LC_{50} of 33,500 µg/l (Warnick and Bell, 1969) and Daphnia magna gave the lowest value of 510 µg/l (Biesinger and Christensen, 1972). Lind, et al. (1979) provide the only data obtained under relatively high hardness conditions (244 mg/l), an LC_{50} value of 2409 µg/l for Daphnia pulicaria.

Data on the acute toxicity of nickel to saltwater fishes is limited. The LC_{50} values range from 29,000 µg/l for the Atlantic Silverside (Menidia menidia) to 350,000 µg/l for the mummichog (Fundulus heteroclitus) (Eisler and Hennekey, 1977). The invertebrate acute toxicity data base consists of 14 results, with a range of LC_{50} values from· 310 µg/l for larvae of the hard clam (Mercenaria mercenaria) (Calabrese and Nelson, 1974) to 500,000 µg/l for adults of the cockle Cardium edule (Portmann, 1968).

B. Chronic Toxicity

A life cycle test (Pickering, 1974) and an embryo-larval test (Lind, et al., manuscript) have been conducted with the fathead minnow (Pimephales promelas). The chronic values are 527 µg/l· (210 mg/l hardness) and 109 µg/l (44 mg/l hardness) respectively. Biesinger and Christensen (1972) conducted a life cycle test with Daphnia magna resulting in a chronic value of 53 µg/l at a hardness of 45 mg/l. There are no chronic saltwater data available (U.S. EPA, 1979).

C. Plant Effects

Hutchinson (1973) and Hutchinson and Stokes (1975) observed reduced growth of several algae species at concentrations ranging from 100 to 700 µg/l. A decrease in diatom diversity was observed by Patrick, et al. (1975) to occur at concentrations as low as 2 µg/l.

D. Residues

Bioconcentration data is limited to the fathead minnow, Pimephales promelas, (Lind, et al., manuscript) and the alga, Scenedesmes acuminata (Hutchinson and Stokes, 1975). The bioconcentration factor for the whole body of the fathead minnow is 61 and for the alga the factor is 9.8.

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 American Conference of Governmental Industrial Hygienists (ACGIH, 1971) has adopted a threshold limit value (TLV) for a workday exposure of 1 ppb. The acceptable daily intake (ADI) for man has been determined to be 294 µg/day (U.S. EPA, 1979). The U.S. EPA (1979) draft water quality criterion for nickel is 133 µg/l.

B. Aquatic

For nickel, the draft criterion (U.S. EPA, 1979) to protect freshwater aquatic life is:

$$e^{(1.01 \cdot \ln (hardness) - 1.02)}$$

as a 24-hour average, and the concentration should not exceed at any time:

$$e^{(0.47 \cdot \ln (hardness) + 4.19)}.$$

The draft criterion to protect saltwater aquatic life is 220 µg/l as a 24-hour average, not to exceed 510 µg/l at any time (U.S. EPA, 1979).

NICKEL

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133-16

Nitrobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

134-1

DISCLAIMER

This report represents a survey of the potential health
and environmental hazards from exposure to the subject chemi-
cal. 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.

NITROBENZENE

Summary

Nitrobenzene is a pale yellow oily liquid with an almond-like odor. There is little or no information available on its teratogenic, mutagenic or carcinogenic effects. Nitrobenzene yielded negative results in the Ames assay for mutagenicity. Gross abnormalities were observed in 4 fetuses of 30 rats administered nitrobenzene.

Chronic exposure to nitrobenzene produces cyanosis, methemoglobinemia, jaundice, anemia, and sulfhemoglobinemia in man.

Static tests with the bluegill, sunfish, Daphnia magna, and an alga, Selenestrum capricornutum, indicates little difference in sensitivity with no 50 percent effective concentration lower than 27,000 ug/l. An embryo-larval test with the fathead minnow demonstrated no adverse chronic effects at the highest concentration tested (32,000 μg/l). Static tests with salt-water fish, shrimp, and alga gave repeated 96-hour LC_{50} or EC_{50} values of 58,538 μg/l, 6,676 μg/l and 9,600 μg/l, respectively.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrobenzene (U.S. EPA, 1979). The principal uses of nitrobenzene are for reduction to aniline (97 percent), solvent for Friedel-Crafts reaction, metal polishes, shoe black, perfume, dye intermediates, crystallizing solvent for some substances, and as a combustible propellant (Dorigan and Hushon, 1976).

Nitrobenzene ($C_6H_5NO_2$) is a pale yellow oily liquid with an almond-like odor. Its physical properties include: melting point, 6^oC; vapor pressure, 0.340 mm Hg at 25^oC; and solubility in water of 1000 mg/l at 20^oC (U.S. EPA, 1979). Nitrobenzene is miscible with most organic solvents, a fairly strong oxidizing agent, and undergoes photoreduction when irradiated with ultraviolet light in organic solvents that contain abstractable hydrogen atoms.

II. EXPOSURE

A. Water

Levels of nitrobenzene in wastewater are monitored by plants producing and using the chemical, but nitrobenzene levels in city water systems are usually too low to measure (Pierce, 1979).

B. Food

Nitrobenzene is not an approved food additive (Dorigan and Hushon, 1976). There have been reports of nitrobenzene poisoning resulting from its contamination of alcoholic drinks and food (Nabarro, 1948).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for nitrobenzene to be 4.3 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on octanol/water partition coefficients.

C. Inhalation

Atmospheric nitrobenzene levels outside a plant are not monitored by industry. Since inner plant levels are below the Threshold Limit Value (TLV) of 5 mg/m^3 and nitrobenzene vapors accumulate at the floor level due to their high density, the external concentrations are expected to be very low (Dorigan and Hushon, 1976).

III. PHARMACOKINETICS

A. Absorption

· Nitrobenzene absorption can occur by all possible routes, but it takes place mainly through the respiratory tract and skin. On the average, 80 percent of the nitrobenzene vapors are retained in the human respiratory tract (Piotrowski, 1977).

Nitrobenzene, as liquid and vapor, will pass directly through the skin. The rate of vapor absorption depends on the air concentration, ranging from 1 mg/hr at 5 mg/m^3 concentration to 9 mg/hr at 20 mg/m^3. Maximal cutaneous absorption of liquid nitrobenzene is 0.2 to 3 $mg/cm^2/hr$ depending on skin temperature.

B. Distribution

Upon entry into the body, nitrobenzene enters the bloodstream. Nitrobenzene is a very lipid soluble with an oil to water coefficient of 800. In a rat study, the ratio of concentration of nitrobenzene in adipose tissue versus blood in internal organs and muscle was approximately 10:1 one hour after an intravenous injection (Piotrowski, 1977). Dorigan and Hushon (1976) found that 50 percent of the nitrobenzene administered to rabbits accumulated unchanged in tissues within two days after intubation.

C. Metabolism

There are two main pathways for the metabolism of nitrobenzene: 1) reduction to aniline followed by hydroxylation to aminophenols, and 2) direct hydroxylation of nitrobenzene to form nitrophenols. Further reduction of nitrophenols to aminophenols may also occur (Piotrowski, 1977). The first pathway proceeds via the unstable intermediates, nitrosobenzene and phenylhydroxylamine, both of which are toxic and have pronounced methemoglobinemic capacity. These reactions occur in the cytoplasmic and microsomal fractions of liver cells by the nitro-reductase enzyme system (Fouts and Brodie, 1957). The aniline is then excreted as an acetyl derivative, or hydroxylated and excreted as an aminophenol. The second pathway does not occur in the microsomal fraction. This reaction proceeds via peroxidase in the presence of oxygen (Piotrowski, 1977).

Robinson, et al. (1951) found p-aminophenol to be the main metabolic product of nitrobenzene metabolism in rabbits. Little unchanged nitrobenzene was excreted in the urine and only 1 percent was expired as carbon dioxide. Together with nitrophenols and nitrocatechol, p-aminophenol constituted 55 percent of the urinary metabolites. Metabolites were detected in the urine up to one week after dosing.

D. Excretion

In man, the primary known excretion products of nitrobenzene are p-aminophenol and p-nitrophenol which appear in the urine after chronic or acute exposure. In experimental inhalation exposure to nitrobenzene, p-nitrophenol was formed with the efficiency of 6 to 21 percent. The efficiency of p-aminophenol formation is estimated from acute poisoning

cases where the molar ratio of excreted p-nitrophenol to p-aminophenol is two to one, since p-aminophenol is not formed at a detectable level in short subacute exposure (Piotrowski, 1977).

Ikeda and Kita (1964) found the rate of excretion of these two metabolites to parallel the level of methemoglobin in the blood.

Nitrobenzene remains in the human body for a prolonged period of time. The excretion coefficient of urinary p-nitrophenol (followed for three weeks) in man is about 0.008 per hour. The extended systemic retention and slow excretion of metabolites in man is determined by the low rates of metabolic transformation (reduction and hydroxylation) of the nitrobenzene itself. The conjugation and excretion of the metabolites, p-nitrophenol and p-aminophenol, is rapid (Piotrowski, 1977). The urinary metabolites in man account for only 20 to 30 percent of the nitrobenzene dose; the fate of the rest of the metabolites is not known (Piotrowski, 1977).

IV. EFFECTS

A. Carcinogenicity

The available literature does not demonstrate the carcinogenicity of nitrobenzene, although it is suspect (Dorigan and Hushon, 1976).

Some nitrobenzene derivatives have demonstrated carcinogenic capacities. Pentachloronitrobenzene (PCNB) induced hepatomas and papillomas in mice (Courtney, et al. 1976).

1-Fluoro-2,4-dinitrobenzene (DNFB) was found to be a promoter of skin tumors in mice, although it does not induce them when administered alone (Bock, et al 1969).

B. Teratogenicity

There is a paucity of information on the teratogenic effects of nitrobenzene. In one study, 125 mg/kg was administered to pregnant rats

during preimplantation and placentation periods (Kazanina, 1968). Delay of embryogensis, alteration of normal placentation, and abnormalities in the fetuses were observed. Gross morphogenic defects were seen in 4 of 30 fetuses examined.

C. Mutagenicity

Nitrobenzene was not found to be mutagenic in the Ames Salmonella assay (Chiu, et al., 1978). Trinitrobenzene and other nitrobenzene derivatives have demonstrated mutagenicity in the Ames Salmonella microsome assay and the mitotic recombination assay in yeast (Simmon, et al. 1977), thus raising questions concerning the mutagenicity of nitrobenzene.

D. Other Reproductive Effects

Changes in the tissues of the chorion and placenta of pregnant women who worked in the production of a rubber catalyst that used nitrobenzene were observed. No mention was made of the effects on fetal development or viability (Dorigan and Hushon, 1976). Menstrual disturbances after chronic nitrobenzene exposure have been reported.

Garg, et. al. (1976) tested substituted nitrobenzene derivatives for their ability to inhibit pregnancy in albino rats. Two of the compounds tested (p-methoxy and p-ethoxy derivatives) inhibited implantation and pregnancy 100 percent when administered on days 1 through 7 after impregnation.

E. Chronic Toxicity

Symptoms of chronic occupational nitrobenzene absorption are cyanosis, methemoglobinemia, jaundice, anemia, sulfhemoglobinemia, presence of Heinz bodies in the erythrocytes, dark colored urine, and the presence of nitrobenzene metabolites (e.g., nitrophenol) in the urine (Pacseri and Magos, 1958; Hamilton, 1919; Wuertz, et al. 1964; Browning, 1950; Malden, 1907; Piotrowski, 1967).

Chronic exposure of laboratory animals to nitrobenzene (via inhalation, ingestion or subcutaneous injection) produced symptoms similar to those mentioned above for humans as well as tissue degeneration of the heart, liver, and kidney, and reductions in erythrocytes and hemoglobin levels in the blood (U.S. EPA, 1979).

F. Other Relevant Information

Alcohol ingestion has been found to act synergistically with nitrobenzene in man and animals (Dorigan and Hushon, 1976; Smyth, et al., 1969).

Kaplan, et al. (1974) showed that caffeine, an inducer of microsomal enzymes, increases the rate of metabolism and excretion of nitrobenzene thus causing a rapid decline in nitrobenzene induced methemoglobin levels.

Metabolism and excretion of nitrobenzene in humans is slower by an order of magnitude than in rats or rabbits (Piotrowski, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

The 96-hour LC_{50} reported value for the bluegill (Lepomis macrochirus) is 42,600 µg/l and the observed 48-hour LC_{50} for Daphnia magna is 27,000 µg/l. Saltwater species tested are the sheepshead minnow, Cyprinodon variegatus, which has a reported 96-hour LC_{50} of 58,539 µg/l and the mysid shrimp, Mysidopsis bahia, with a reported 96-hour LC_{50} of 6,676 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

In the only chronic data available, no adverse effects were observed during an embryo-larval test with the fathead minnow (Pimephales promelas) at nitrobenzene test concentrations as high as 32,000 µg/l (U.S. EPA, 1978).

C. Plant Effect

Based on cell numbers and chlorophyll a concentration, reported EC_{50} values for the freshwater alga, Selenastrum capricornutum, are 42,000 and 44,100 µg/l; and for the marine alga, Skeletonema costatum, there are reported EC_{50} values of 9,600 and 10,300 µg/l (U.S. EPA, 1979).

D. Residues

A bioconcentration factor of 15 was estimated for aquatic organisms that contain 8 percent lipids.

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 TLV for nitrobenzene is 5 mg/m^3. This is the OSHA Federal standard, the value set by the ILO/WHO committee on Occupational Health, and the TLV suggested by the American Conference of Governmental and Industrial Hygienists (Goldstein, 1975, ACGIH, 1977).

The draft water quality criteria for nitrobenzene is 30 µg/l (U.S. EPA, 1979). This value is based on the TLV and organoleptic level (minimum detectable odor limit in water) of nitrobenzene.

B. Aquatic

For nitrobenzene the drafted criterion to protect freshwater aquatic life is 480 µg/l as a 24-hour average concentration not to exceed 1,100 µg/l at any time. To protect saltwater aquatic life, the 24-hour average is 53 µg/l and this concentration should not exceed 120 µg/l at any time (U.S. EPA, 1979).

NITROBENZENE

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4-Nitrophenol

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

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4-NITROPHENOL

SUMMARY

There is no evidence to indicate that 4-nitrophenol is carcinogenic.

Weak mutagenic effects in Saccharomyces and in Proteus have been observed. Results from the Ames assay, the E. coli, and the dominant lethal assay failed to show mutagenic effects from 4-nitrophenol.

No information on the teratogenic or adverse reproductive effects of 4-nitrophenol is available.

A single animal study indicates cumulative chronic toxicity; the methodology of this study was not available for review.

For freshwater organisms, acute values for the toxic effects of 4-nitrophenol ranged from 8,280 to 60,500 µg/l, and 7,170 to 27,100 µg/l for marine organisms. Effective concentrations for aquatic plants fall within these ranges of concentrations.

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4-NITROPHENOL

I. INTRODUCTION

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

The mononitrophenols are a family of compounds composed
of the isomers resulting from nitro group substitution at the
2,3, and 4 position of phenol (the ortho, meta, and para isomers,
respectively). The para isomer, 4-nitrophenol, has a molecular
weight of 139.11, a boiling point of 279°C, a melting point of
113-114°C, a density of 1.479 g/ml; it is soluble in water (U.S.
EPA, 1979).

Uses of the mononitrophenols include the following: produc-
tion of dyes, pigments, pharmaceuticals, rubber chemicals, lumber
preservatives, photographic chemicals, and pesticidal and fungici-
dal agents (U.S. EPA, 1979). Production was 17.5 x 10^3 tons
per year in 1976 (Chem. Market. Reporter, 1976).

The nitrophenols may be formed via microbial degradation
or photodegradation of pesticides (e.g., parathion) containing
the nitrophenol moiety. 4-Nitrophenol may be produced in the
atmosphere through the photochemical reaction between benzene
and nitrogen monoxide (U.S. EPA, 1979). Partial microbial degrada-
tion of certain nitrophenols has been shown, particularly by
acclimated microorganisms. Mononitrophenols appear to be effi-
ciently degraded by unacclimated microorganisms (Haller, 1978).

II. EXPOSURE

The lack of monitoring data on the mononitrophenols makes
it difficult to assess exposure from water, inhalation, and foods.

Mononitrophenols in water have been detected in the effluents of chemical plants (U.S. EPA, 1976, 1979). 4-Nitrophenol has been shown to penetrate the skin and to produce damage at threshold concentrations of 0.8 and 0.9 percent (w/v), respectively (U.S. EPA, 1979).

Exposure to nitrophenols appears to be primarily through occupational contact (chemical plants, pesticide applications). Contaminated water may result in isolated poisoning incidents.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for 4-nitrophenol to be 4.9 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 and Distribution

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

B. Metabolism

Metabolism of the mononitrophenols occurs primarily by conjugation. Other possible routes are reduction of the nitro group to an amino group or oxidation to dihydric-nitrophenols (U.S. EPA, 1979). These reactions are mediated primarily by liver enzyme systems, although other tissues show lower metabolizing activity (U.S. EPA, 1979).

B. Excretion

An animal study has indicated that oral or intraperitoneal administration of 4-nitrophenol leads to rapid elimination in all species tested, and that the total elimination period is not likely to exceed one week (Lawford, et al. 1954).

IV. EFFECTS

A. Carcinogenicity

There is no evidence available regarding the carcinogenicity of mononitrophenols.

B. Mutagenicity

A weak mutagenic effect was detected in Saccharomyces cerevisiae by 4-nitrophenol (Fahrig, 1974); this was also indicated by testing 4-nitrophenol for growth inhibition in a DNA repair deficient strain of Proteus mirabilis (Adler, et al., 1976). This compound has also induced chromosome breaks in plants (U.S. EPA, 1979). 4-Nitrophenol has failed to show mutagenic effects in the Ames assay, in E. coli, or in the dominant lethal assay (U.S. EPA, 1979).

C. Teratogenicity and Other Reproductive Effects

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

D. Chronic Toxicity

A single Russian study (Makhinya, 1969) reported that chronic administration of mononitrophenol to mammals produced hepatitis, splenic hyperplasia, and neurological symptoms. Methodology of this study was not available for review.

V. AQUATIC TOXICITY

A. Acute Toxicity

LC$_{50}$ values have been obtained for two species of freshwater fish: 8,280 µg/l for bluegills, Lepomis macrochirus, in a 96-hour static assay (U.S. EPA, 1978), and 60,510 µg/l for the fathead minnow, Pimephales promelas, in a 96-hour flow-through assay (Phipps, et al. unpublished manuscript). For the fresh-

water invertebrate, Daphnia magna, determined LC$_{50}$ values range from 8,396 to 21,900 µg/l (U.S. EPA, 1979). The marine fish, sheepshead minnow, Cyprinodon variegatus, has produced determined LC$_{50}$ value of 27,100 816 µg/l in a 96-hour static assay, while the marine mysid shrimp, Mysidopis bahia, was more sensitive, with a reported LC$_{50}$ value of 7,170 µg/l.

B. Chronic Toxicity

No chronic studies on freshwater organisms are available. In an embryo-larval test of the marine fish, sheepshead minnow, a chronic value of 6,325 µg/l was obtained. No chronic testing for marine invertebrates was available.

C. Plant Effects

Four species of freshwater plants have been tested with 4-nitrophenol. The algae, Selenastrum capricornutum and Chlorella vulgaris, and the duckweed, Lemna minor, were most sensitive with effective concentrations of 4,190, 6,950, and 9,452 µg/l, respectively; while the alga, Chlorella pyrenoidosa, was much more resistant, with an effective concentration of 25,000 µg/l. The marine alga, Skeletonema costatum, provided effective concentrations of 7,370 to 7,570 µg/l (U.S. EPA, 1979).

D. Residues

No bioconcentration factors for either freshwater or marine species were available.

VI. EXISTING GUIDELINES AND STANDARDS

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

A.   Human

Available data pertaining to 4-nitrophenol is insuffi-
cient for deriving a criterion to protect human health.

B.   Aquatic

A criterion for protecting freshwater organisms has
been drafted as 240 µg/l, for a 24-hour average concentration,
not to exceed 550 µg/l.   For marine life, a criterion has been
drafted as 53 µg/l for a 24-hour average, not to exceed 120 µg/l
(U.S. EPA, 1979).

4-NITROPHENOL

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Nitrophenols

Health and Environmental Effects

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

APRIL 30, 1980

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DISCLAIMER

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

NITROPHENOLS

SUMMARY

None of the nitrophenols have shown carcinogenic activity.

Mutagenicity testing has indicated positive effects of: 2,4-dinitrophenol in mouse bone marrow cells and E. coli; 2,4,6-trinitrophenol in E. coli and Salmonella; and 4,6-dinitro-ortho-cresol in Proteus. Weak mutagenic effects of 4-nitrophenol have been reported in Saccharomyces and in Proteus. Other mutagenic test assays have shown negative results for these compounds.

Teratogenic effects have been reported in the developing chick embryo following administration of 2,4-dinitrophenol. This compound did not produce teratogenic effects in mammalian studies. Adverse reproductive effects (embryo toxicity) were seen in rats exposed to 2,4-dinitrophenol.

The chronic effects of 2,4-dinitrophenol ingestion have included cases of agranulocytosis, neuritis, functional heart damage, and cataract formation. Ingestion of 4,6-dinitro-ortho-cresol has also produced cataracts in humans.

One Russian study has reported cumulative toxic effects in animals produced by the mononitrophenols; methodology of this study was not available for review.

Freshwater fish appeared to be the most sensitive organism to the action of nitrophenols, with acute values ranging from 230 to 167,000 μg/l. The reactivities of various nitrophenols in order of decreasing toxicity are, in general: 2,4-dinitro-6-methylphenol, 2,4-dinitrophenol, 2-nitrophenol, 4-nitrophenol, and 2,4,6-trinitrophenol.

NITROPHENOLS

I.   INTRODUCTION

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

The nitrophenols are a family of compounds which, depending on the extent and position of nitro group substituents, include the mononitrophenols, dinitrophenols, and trinitrophenols. Dinitrocresols are related compounds bearing an additional 2-position methyl group. The mononitrophenols (molecular weight 139.11) show boiling points from 194-279°C (depending on the isomeric form) and melting points of 44-114°C. They have a density of 1.485 and are soluble in water. The dinitrophenols (molecular weight 184.11) have melting points from 63.5-144°C and show a density of 1.67 to 1.70. Water solubility is from 0.42 to 2.3 g/l. Tri-nitrophenols (molecular weight 229.11) have melting points from 96-123°C; they are slightly soluble in water. 2,4,6-Trinitrophenol, the most widely used isomer, has a density of 1.763 g/ml and a solubility of 1.28 g/l. Of the six isomers of dinitrocresol, 4,6-dinitro-o-cresol is the only one of any commercial importance. The physical properties of 4,6-dinitro-o-cresol, hereafter referred to as dinitro-ortho-cresol, include a molecular weight of 198.13, a melting point of 85.8°C and a solubility of 100 mg/l in water (U.S. EPA, 1979).

Uses of the mononitrophenols include the following: production of dyes, pigments, pharmaceuticals, rubber chemi-

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cals, lumber preservatives, photographic chemicals, and
pesticidal and fungicidal agents. The dinitrophenols are
used as chemical intermediates for sulfur dyes, azo dyes,
photochemicals, pest control agents, wood preservatives,
and explosives. 2,4,6-Trinitrophenol (picric acid) is used
for dye intermediates, germicides, tanning agents, fungi-
cides, tissue fixative, photochemicals, pharmaceuticals,
and for the etching of metal surfaces. Dinitro-ortho-cresol
is used primarily as a blossom-thinning agent on fruit trees
and as a fungicide, insecticide, and miticide on fruit trees
during the dormant season (U.S. EPA, 1979).

Current Production: 2-nitrophenol $5-.7.5 \times 10^3$ tons/year (1976)

4-nitrophenol 17.5×10^3 tons/year (1976)

2,4-dinitrophenol 4.3×10^2 tons/year (1968)

The nitrophenols may be formed via microbial degrada-
tion or photodegradation of pesticides (e.g., parathion)
containing the nitrophenol moiety (U.S. EPA, 1979). Partial
microbial degradation of certain nitrophenols has been shown,
particularly by acclimated microorganisms. Mononitrophenols
appear to be efficiently degraded by unacclimated microorgan-
isms (Haller, 1978).

II. EXPOSURE

The lack of monitoring data on the nitrophenols makes
it difficult to assess exposure from water, inhalation,
and foods. Nitrophenols in water have been detected in

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effluents from chemical plants (U.S. EPA, 1976; 1979) or following dumping of explosives (Harris, et al. 1946). Dermal absorption of mononitrophenols, dinitrophenols, tri-nitrophenols (picric acid), and dinitro-ortho-cresol (DNOC) has been detected (U.S. EPA, 1979).

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

The U.S. EPA (1979) has estimated weighted average bioconcentration factors for the following nitrophenols: 2-nitrophenol, 4.0; 4-nitrophenol, 4.9; 2,4-dinitrophenol, 2.4; 2,4,6-trinitrophenol, 6.0; and 4,6-dinitrocresol, 7.5 for fish and shellfish consumed by Americans. This estimate is based on octanol/water partition coefficients.

III. PHARMACOKINETICS

   A.   Absorption

      Specific data on the absorption of the mononitro-phenols is not available. The dinitrophenols are readily absorbed following oral, inhalation, or dermal administration. Data on the absorption of trinitrophenols is not available. Animal studies with oral administration of 2,4,6-trinitrophenol indicate that it is readily absorbed from the gastrointestinal tract. Dinitro-ortho-cresol is readily absorbed through the skin, the respiratory tract, and the gastrointestinal tract in humans (NIOSH, 1978).

B.   Distribution

No information on the distribution of the mono-
nitrophenols is available. Dinitrophenol blood levels rise
rapidly after absorption, with little subsequent distribu-
tion or storage at tissue sites (U.S. EPA, 1979). 2,4,6-
Trinitrophenol and dinitro-ortho-cresol have been found
to stain several body tissues; however, the compounds may
be bound to serum proteins, thus producing non-specific
organ distribution (U.S. EPA, 1979).

C.   Metabolism

Metabolism of the nitrophenols occurs through
conjugation, reduction of nitro groups to amino groups,
or oxidation to dihydric-nitrophenols (U.S. EPA, 1979).
These reactions are mediated primarily by liver enzyme systems,
although other tissues show lower metabolizing activity
(U.S. EPA, 1979). The metabolism of dinitro-ortho-cresol
is very slow in man as compared to that observed in animal
studies (King and Harvey, 1953).

D.   Excretion

Evidence from human poisoning with parathion indi-
cates that excretion of 4-nitrophenol in the urine is quite
rapid (Arteberry, et al. 1961). Experiments with urinary
clearance of dinitrophenols in several animal species indi-
cate rapid elimination of these compounds (Harvey, 1959).
2,4,6-Trinitrophenol has been detected in the urine of ex-
posed human subjects indicating at least partial urinary
elimination (Harris, et al. 1946). The experiments of Parker

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and coworkers (1951) in several animal species indicate
that dinitro-ortho-cresol is rapidly excreted following
injection; however, Harvey, et al. (1951) have shown slow
excretion of dinitro-ortho-cresol in human volunteers given
the compound orally.

IV. EFFECTS

A. Carcinogenicity

There are no available data to indicate that the
mononitrophenols are carcinogenic. Both 2- and 4-nitrophenol
failed to show promoting activity for mouse skin tumors
(Boutwell and Bosch, 1959); this same study failed to show
promoting activity for 2,4-dinitrophenol. No evidence is
available to indicate that dinitrophenols, trinitrophenols,
or dinitro-ortho-cresol produce any carcinogenic effects
(U.S. EPA, 1979).

B. Mutagenicity

A weak mutagenic effect was detected in Saccharo-
myces cerevisiae for 4-nitrophenol (Fahrig, 1974); this
was also indicated by testing 4-nitrophenol for growth in-
hibition in a DNA repair deficient strain of Proteus mirabilis
(Adler, et al. 1976). This compound has also induced chromo-
some breaks in plants (U.S. EPA, 1979). 4-Nitrophenol has
failed to show mutagenic effects in the Ames assay, in E.
coli, or in the dominant lethal assay (U.S. EPA, 1979).

Testing of 2,4-dinitrophenol has indicated muta-
genic effects in E. coli (Demerec, et al. 1951) and damage
in murine bone marrow cells (chromatid breaks) (Mitra and
Manna, 1971). 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 positive results with this compound.

2,4,6-Trinitrophenol has produced mutations in E. coli and Salmonella assays (Demerec, et al. 1951; Yoshikawa, et al. 1976). Testing in Drosophila has failed to indicate mutagenic activity.

Adler, et al. (1976) have reported that dinitro-ortho-cresol 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

No information is available to indicate that mono-nitrophenols, 2,4,6-trinitrophenol, or dinitro-ortho-cresol produce teratogenic effects.

2,4-Dinitrophenol has produced developmental abnor-malities in the chick embryo (Bowman, 1967; Miyamoto, et al. 1975). No teratogenic effects were observed 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 increased mortality in offspring (Wulff, et al. 1935); similarly, intraperitoneal administration of the compound to mice induced embryotoxicity (Gibson, 1973).

Influence of the compound on maternal health may have contributed to these effects (U.S. EPA, 1979).

E.   Chronic Toxicity

Chronic administration of mononitrophenols to mammals has been reported to produce hepatitis, splenic hyperplasia, and neurological symptoms in a single Russian study (Makhinya, 1969). Methodology of this study was not available for review.

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 cases of cataracts (Horner, 1942). Cataracts have also been reported in patients poisoned with dinitro-ortho-cresol (NIOSH, 1978).

Human effects resulting from 2,4,6-trinitrophenol exposure have been reported as temporary impairment of speech, memory, walking, and reflexes (Dennie, et al. 1929).

F.   Other Relevant Information

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).

The combination of 2,4,6-trinitrophenol and opioids or minor analgesics produced an increase in analgesia (Huidobro, 1971).

2,4-Dinitrophenol is a classical uncoupler of oxidative phosphorylation, which accounts for its marked acute toxicity. Dinitro-ortho-cresol is also well known for its activity as an uncoupler.

V.   AQUATIC TOXICITY

A.   Acute Toxicity

Freshwater fish LC_{50} values reported for the blue-gill (Lepomis macrochinus) ranged from 230 to 167,000 µg/l and for the juvenile fathead minnow (Pimephales promelas), from 2,040 to 60,510 µg/l. The order of decreasing toxicity for five nitrophenols examined was: 2,4-dinitro-6-methyl phenol, 2,4-dinitrophenol, 2-nitrophenol, 4-nitrophenol, 2,4,6-trinitrophenol (U.S. EPA, 1979). For three of the phenols tested with both the bluegill and fathead minnow, the bluegill appeared more sensitive. In static bioassays with the freshwater invertebrate, Daphnia magna, 48-hour LC_{50} values of 4,090 to 4,710; 8,396 to 21,900; and 84,700 µg/l were reported for 2,4-dinitrophenol, 4-nitrophenol and 2,4,6-trinitrophenol, respectively (U.S. EPA, 1979). The marine fish, sheepshead minnow (Cyprinodon variegatus), was the only fish species acutely tested for three nitro-phenols, with reported LC_{50} values of 29,400; 27,100 and 134,000 µg/l being obtained for 2,4-dinitrophenol, 4-nitro-phenol, and 2,4,6-trinitrophenol. Observed LC_{50} values of 4,350; 7,170 and 19,700 µg/l were reported for the mysid shrimp (Mysidopsis bahia) for the same three formulations, respectively.

B.   Chronic Toxicity

Pertinent information on the chronic effects on freshwater species could not be located in the available literature searches. The only chronic test on a marine

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species was an embryo-larval assay of the sheepshead minnow
that produced a chronic value of 6,325 µg/l (U.S. EPA, 1978).
Pertinent information relative to chronic effects on marine
invertebrates could not be located in the available literature.

C.   Plant Effects

The effects of various nitrophenols vary widely
among species of freshwater plants and according to the
formulation of nitrophenol tested. The duckweed, Lemna
minor, was the most sensitive plant tested with 2,4-dinitro-
phenol and was the most resistant with 2-nitrophenol, hav-
ing effective concentrations (50 percent growth reduction,
time unspecified) ranging from 1,472 to 62,550 µg/l for the
two respective formulations. The marine alga, Skeletonema
costatum, appeared to be slightly more resistant than fresh-
water species tested, with effective concentrations ranging
from 7,370 to 141,000 µg/l for 4-nitrophenol and 2,4,6-tri-
nitrophenol, respectively.

D.   Residues

Bioconcentration factors were not determined for
any freshwater or marine species. However, based on octanol/
water partition coefficients, bioconcentration factors were
estimated as 8.1, 21, and 26 for 2,4-dinitrophenol, 2,4,6-
trinitrophenol, and 2,4-dinitro-6-dimethylphenol, respectively.

VI. EXISTING GUIDELINES AND STANDARDS

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

A.   Human

    Eight-hour TWA exposures for 2,4,6-trinitrophenol
(0.1 mg/m^3) and 4,6-dinitro-ortho-cresol (0.2 mg/m^3) have
been established by the ACGIH (1971).

    Draft water quality criteria for the following
nitrophenols have been estimated by U.S. EPA (1979) based
on adverse effects data: dinitrophenols - 68.6 μg/l; tri-
nitrophenols - 10 μg/l; and dinitrocresols - 12.3 μg/l.

B.   Aquatic

    Criteria drafted to protect freshwater life from
nitrophenols follow: 57 μg/l as a 24-hour average concen-
tration, not to exceed 130 μg/l, for 2,4-dinitro-6-methyl-
phenol; 79 μg/l, not to exceed 180 μg/l, for 2,4-dinitro-
phenol; 240 μg/l, not to exceed 550 μg/l, for 4-nitrophenol;
2,700 μg/l, not to exceed 6,200 μg/l, for 2-nitrophenol;
and 1,500 μg/l, not to exceed 3,400 μg/l, for 2,4,6-trinitro-
phenol. For marine life the following criteria have been
drafted as 24-hour average concentrations: 37 μg/l, not
to exceed 84 μg/l, for 2,4-dinitrophenol; 53 μg/l, not to
exceed 120 μg/l, for 4-nitrophenol; and 150 μg/l, not to
exceed 340 μg/l, for 2,4,6-trinitrophenol.

NITROPHENOLS

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No. 137

Nitrosamines

Health and Environmental Effects

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

APRIL 30, 1980

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DISCLAIMER

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

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SPECIAL NOTATION

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

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NITROSAMINES

Summary

Nitrosamines and nitrosamides are widespread in the environment and can also be produced endogenously by nitrosation of constituents of food. Nitrosamines and nitrosamides are considered to be among the most potent of all carcinogenic, mutagenic, and teratogenic agents known. The livers of rats chronically exposed to nitrosamines exhibit pathological changes.

Toxicity data examining the effects of nitrosamines on aquatic organisms is scant. For freshwater life forms, acute toxicity levels of 5,850 to 7,760 µg/l were reported, while for marine fish an acute value of nearly 3,300,000 µg/l was reported (both values for N-nitrosodiphenylamine). N-nitrosodimethylamine has been shown to induce hepatocellular carcinoma in rainbow trout.

NITROSAMINES

I. INTRODUCTION

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

The nitrosamines (and nitrosamides) belong to a large group of chemicals generally called N-nitroso compounds. Because they frequently coexist with N-nitrosamines in the environment and are structurally related to nitrosamines, nitrosamides are also included in the U.S. EPA (1979) document and in this profile.

The nitrosamines vary widely in their physical properties and may exist as solids, liquids or gases. Nitrosamines of low molecular weight are volatile at room temperature, while those of high molecular weight are steam volatile. Nitrosamines are soluble in water and organic solvents (U.S. EPA, 1976).

Synthetic production of nitrosamines is limited to small quantities. The only nitrosamine produced in quantities greater than 450 kg per year is N-nitrosodiphenylamine, which is used in rubber processing and in the manufacture of pesticides. Other N-nitroso compounds are produced primarily as research chemicals (U.S. EPA, 1976).

Nitrosamines are rapidly decomposed by sunlight and thus do not persist in ambient air or water illuminated by sunlight (U.S. EPA, 1979; Fine, et al. 1977a). Some nitrosamines have been found to persist for extended periods of time in the aquatic environment (Fine, et al. 1977a; Tate and Alexander, 1975).

II. EXPOSURE

Nitrosamines are widespread in the environment. The most probable source of environmental nitrosamines is nitrosation of amine and amide precursors which are ubiquitous in the environment (Bogovski, et al. 1972).

It has been estimated that air, diet, and smoking all play a roughly equivalent role in human exposure to preformed nitrosamines, contributing a few micrograms per day; intake from drinking water is probably much less than 1 ug per day (U.S. EPA, 1976).

A. Water

Significant concentrations of nitrosamines have been reported for a limited number of samples of ocean water, river water, and waste treatment plant effluent (3 to 4 µg dimethylnitrosamine/l) adjacent to or receiving wastewater from industries using nitrosamines or secondary amines in production operations (Fine, et al. 1977b). Well water with high nitrate levels and coliform counts had nitrosamine concentrations of less than 0.015 µg/l (U.S. EPA, 1977). Non-volatile nitrosamines have been tentatively identified in New Orleans drinking water at levels of 0.1 to 0.5 µg/l (Fine, et al. 1976).

Contamination of water can occur both from industrial wastewater and from agricultural runoff.

B. Food

Nitrosamines have been found in foods, particularly in meats such as sausages, ham, and bacon which have been cured with nitrite. N-nitrosodimethylamine was present in a variety of foods in the 1 to 10 µg/kg range and occasionally at levels up to 100 µg/kg (Montesano and Bartsch, 1976). N-nitrosopyrrolidine has been consistently found in cooked bacon in the range of 10-50 µg/kg (Fine, et al. 1977a).

Many food constituents can either be converted directly to N-nitroso compounds or give rise to nitrosatable products after a metabolic intermediate step which can be involved directly or indirectly in such reactions.

Constituents include nitrate, nitrite, some amino acids, choline, phospholipids, purines, pyrimidines, some vitamins, caffeine, and some pesticides (Walters, 1977; Elsperu and Lijinsky, 1973).

Nitrate and nitrite are well supplied in the diet. Eighty-six percent of the nitrate ingested comes from vegetables; 9 percent comes from cured meats. Only 2 percent of the nitrite ingested comes from vegetables, while 21 percent comes from cured meat (White, 1975).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor to be 500 for N-nitrosodiphenylamine in the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies with bluegills. Based on the octanol/water partition coefficient for each compound, the U.S. EPA (1979) has estimated weighted average bioconcentration factors for the following compounds in the edible portions of fish and shellfish consumed by Americans: N-nitrosodimethylamine, 0.06; N-nitrosodiethylamine, 0.39; N-nitrosodi-n-butylamine, 4.9; and N-nitrosopyrrolidine, 0.12.

C. Inhalation

Due to the photolabile nature of nitrosamines, concentrations in ambient air are very low, except near sources of direct emissions of nitrosamines (i.e. chemical plants) (Fine, et al. 1977a). Nitrosamines were detected only twice at 40 collection points in New Jersey and New York City, and then only below the 0.01 $\mu g/m^3$ level.

Tobacco and tobacco smoke contain both secondary amines and nitrosamines (Hoffman, et al. 1974). The intake of nitrosamines from smoking 20 cigarettes per day has been estimated at approximately 6 $\mu g/day$ (U.S. EPA, 1979).

III. PHARMACOKINETICS

   A. Absorption

      Pertinent data could not be located in the available literature.

   B. Distribution

      Following intravenous injection into rats, nitrosamides and nitros-amines are rapidly and fairly uniformly distributed throughout the body (Magee, 1972; Stewart, et al. 1974). Both nitrosamides and nitrosamines appear to cross the placenta since they induce neoplasms in offspring if administered maternally to rats in late pregnancy (Magee, et al. 1976).

   C. Metabolism and Excretion

      Nitrosamides are rapidly metabolized in animals and excreted in the urine within 24 hours (Magee, et al. 1976).

      Nitrosamines are metabolized less rapidly and persist in the body unchanged for a longer period. The rate of metabolism depends upon the chemical structure (U.S. EPA, 1979).

      After administration of ^{14}C-labeled dimethylnitrosamine, diethyl-nitrosamine, or nitrosomorpholine, the amount of isotope appearing as $^{14}CO_2$ within 12 hours is 60, 45, and 3 percent, respectively, while the corresponding urinary excretions are 4, 14, and 80 percent. Urinary metabolites include other nitroso compounds formed by oxidation of the alkyl groups to the alcohols and carboxylic acids (Magee, et al. 1976). Dimethyl-nitrosamine is excreted in the milk of female rats (Schoental, et al. 1974).

      The liver appears to be the major site for metabolism of nitrosamines; kidney and lung also metabolize nitrosamines (Magee, et al. 1976). The metabolites of nitrosamines are thought to be the active teratogenic, mutagenic and carcinogenic forms (U.S. EPA, 1979).

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IV. EFFECTS

   A. Carcinogenicity

        The epidemiological studies conducted to date have been inadequate
to establish any correlation between exposure to N-nitroso compounds or
their precursors and human cancer (U.S. EPA, 1979).

        In animals, nitrosamines and nitrosamides are potent carcinogens,
inducing tumors in essentially all vital organs via all routes of admini-
stration (Montesano and Bartsch, 1976; Druckrey, et al. 1967).

        Many of the N-nitroso compounds which have been tested are carcino-
genic. There is a strong relationship between chemical structure and type
of tumors produced. Symmetrically substituted dialkylnitrosamines and some
cyclic nitrosamines produced carcinomas of the liver. Asymmetrical dialkyl-
nitrosamines produced carcinomas of the esophagus (Druckrey, et al. 1967).
Apparently all N,N-dialkylnitrosamines containing a tert-butyl group are
noncarcinogenic (Heath and Magee, 1962).

        There are large differences in species response to carcinogenic
nitrosamines and nitrosamides, both in type of tumor produced and in suscep-
tibility, but all animal species tested are vulnerable. The late fetus and
neonate appear to be highly susceptible (U.S. EPA, 1979). Exposure to
nitrosamides during pregnancy may result in a risk not only to the immediate
offspring, but also for at least two more generations of animals (Montesano
and Bartsch, 1976). There is no evidence to indicate that nitrosamines pose
a similar threat (U.S. EPA, 1979).

        Daily oral doses of N-nitroso compounds of 2.5 percent of the
LD_{50} values were sufficient to induce cancer in rats (Druckrey, et al.
1967).

B. Mutagenicity

The N-nitroso compounds include some of the most powerful mutagens known. Nitrosamides are mutagenic in almost all test systems, due to non-enzymic formation of active degradation products. Nitrosamines must be metabolically activated to be mutagenic in microbial assays (U.S. EPA, 1979).

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 mutations" in Drosophila; and chromosome aberrations in mammalian cells (Montesano and Bartsch, 1976). Negative results were obtained in the mouse dominant lethal test.

C. Teratogenicity

N-nitroso compounds can be potent teratogens (U.S. EPA, 1979). Nitrosamides are teratogenic over an extended period of gestation, whereas nitrosamines are active only when administered late in pregnancy (Druckrey, 1973) probably because of the inability of the embryonic tissue to metabolize nitrosamines during early pregnancy (Magee, 1973).

D. Other Reproductive Effects

Nitrosamines and nitrosamides are embryotoxic (Druckrey, 1973).

E. Chronic Toxicity

The livers of rats and other species chronically exposed to nitrosamines exhibit pathological changes including biliary hyperplasia, fibrosis, nodular parenchymal hyperplasia, and the formation of enlarged hepatic parenchymal cells with large nuclei (Magee, et al. 1976).

F. Other Relevant Information

Unlike nitrosamines, nitrosamides cause tissue injury at the site
of contact (Magee, et al. 1976). This is thought to be due to the nonenzy-
matic decomposition of nitrosamides into active products upon contact with
tissues.

Aminoacetonitrile, which inhibits the metabolism of dimethylnitros-
amine, prevented the toxic and carcinogenic effects of dimethylnitrosamine
in rat liver (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 dimethylnitrosamine (Stenback, et al. 1973; Magee, et al. 1976).

V.   AQUATIC TOXICITY

A.   Acute Toxicity

The LC_{50} value of 5,850 µg/l for bluegill sunfish (Lepomis macro-
chirus) exposed to N-nitrosodiphenylamine represents the sole acute toxicity
data for freshwater fish, while an LC_{50} value of 7,760 µg/l was obtained
for the freshwater invertebrate, Daphnia magna (U.S. EPA, 1978). The marine
mummichog (Fundulus heteroclitus) was relatively resistant to N-nitrosodi-
methylamine in a 96-hour static test, where an adjusted LC_{50} value of
3,300,000 µg/l was reported (Ferraro, et al. 1977). No additional data con-
cerning marine organisms was presented in the Ambient Water Quality Criteria
Document (U.S. EPA, 1979).

B.   Chronic Toxicity

The chronic effects of N-nitrosodiphenyl amine have been examined
in Daphnia magna, with no adverse effects being reported at a concentration
of 48 µg/l. No chronic data concerning marine organisms were found in the
available literature.

C. Plant Effects

Pertinent data could not be located in the available literature.

D. Residues

A bioconcentration factor of 217 was reported, as was a biological half-life of less than one day in the freshwater bluegill sunfish (U.S. EPA, 1978). No data on residues in marine life were found in the available literature.

E. Miscellaneous

Shasta strain rainbow trout (_Salmo gairdneri_) fed N-nitrosodimethylamine in their diet for 52 weeks developed a dose-response occurrence of hepatocellular carcinoma at doses of 200, 400, and 800 mg N-nitrosodimethylamine per kg body weight (Grieco, et al. 1978).

VI. EXISTING GUIDELINES AND STANDARDS

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

A. Human

Using the "one-hit" model, the U.S. EPA (1979) has estimated the following levels of nitrosamines in ambient water which will result in specified risk levels of human cancer.

The water concentration of dimethylnitrosamine corresponding to a lifetime cancer risk for humans of 10^{-5} is 0.026 ug/l, based on the induction of liver tumors in rats (Druckrey, 1967).

The water concentration of dibutylnitrosamine corresponding to a lifetime cancer risk for humans of 10^{-5} is 0.013 µg/l, based on induction of tumors of the bladder and esophagus in mice (Bertram and Craig, 1970).

The water concentration of N-nitroso-pyrrolidine corresponding to a
lifetime cancer risk for humans of 10^{-5} is 0.11 µg/l, based on the induc-
tion of hepatocellular carcinomas in rats (Preussman, et al. 1977).

No other guidelines or standards are available.

8. Aquatic

No criteria for freshwater or marine life have been drafted (U.S.
EPA, 1979).

NITROSAMINES

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No. 138

N-Nitrosodiphenylamine

Health and Environmental Effects

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

APRIL 30, 1980

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DISCLAIMER

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

N-NITROSODIPHENYLAMINE

SUMMARY

Formation of N-nitrosodiphenylamine (NDPhA) has been shown experimentally in the stomachs of individuals receiving nitrite and diphenylamine. N-nitrosodiphenylamine undergoes photochemical decomposition in solution or in the atmosphere in the presence of sunlight. Bacterial degradation of NDPhA has been demonstrated in soil.

Prior to the release of recent findings from the NCI bioassay program, NDPhA was considered a non-carcinogenic nitrosamine. In the NCI lifetime rat feeding study, however, NDPhA was found to induce a significant incidence of urinary bladder tumors in both males and females. Few urinary bladder tumors were observed in mice in a similar experiment, although there was a high incidence of non-neoplastic bladder lesions.

N-nitrosodiphenylamine has consistently been found negative in a variety of mutagenicity assays.

I. INTRODUCTION

This document is based on the Ambient Water Quality Criteria Document on Nitrosamines (U.S. EPA, 1979b), the Scientific and Technical Assessment Report on Nitrosamines (U.S. EPA, 1977), and other selected references. The term "N-nitrosodiphenylamine" (NDPhA) in this report refers specifically to that compound; the term "nitrosamine" when used in this report refers to nitrosamines in general.

N-nitrosodiphenylamine (NDPhA; molecular weight 198.23; molecular formula $C_{12}H_{10}N_2O$) is a yellow to brown or orange powder or flakes. It has the following physical/chemical properties (Hawley, 1977):

Melting Point:	64-66°C
Solubility:	insoluble in water; soluble in organic solvents.

NDPhA is used as a vulcanization retarder in the rubber industry (Hawley, 1977).

A review of the production range (includes importation) statistics for N-nitrosodiphenylamine (CAS No. 86-30-6) which is listed in the initial TSCA Inventory (1979a) has shown that between 400,000 and 900,000 pounds of this chemical were produced/imported in 1977.[*/]

II. EXPOSURE

A. Formation

The chemistry of formation of nitrosamines is quite complex, however, they are in general formed by the combination of amines (R_1R_2N-) with some nitrosating agent. Formation has been shown to occur with primary, secondary, and tertiary amines, as well as

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

other amino compounds. The nitrosating agent can be derived from nitric oxides (NO, NO_2, N_2O_3, or N_2O_4) or inorganic nitrite (U.S. EPA, 1977).

The _in vivo_ formation of nitrosamines following ingestion of precursors has been demonstrated in human and animal studies (U.S. EPA, 1977) Sander and Seif (1969) showed the formation of NDPhA in the stomachs of humans given nitrite and diphenylamine.

B.   Environmental Fate

In the absence of light, nitrosamines are quite stable and will decompose hydrolytically only following prolonged contact with strong acid. There is no evidence of thermal instability of nitrosamines in the gas phase; however, they do undergo photo-chemical decomposition in solution or in the atmosphere in the presence of sunlight or ultra-violet light (U.S. EPA, 1977).

Transnitrosation reactions involving direct transfer of the nitroso group from NDPhA to other amines have been demonstrated (Challis and Osborn, 1972). Such a reaction yields a new N-nitroso compound and diphenylamine.

In unamended soil, 70% of added NDPhA was lost within 30 days. In soil amended with bacteria, added NDPhA had disappeared completely at the end of day 10 (Mallik, 1979).

C.   Bioconcentration

See Section V.C.

III. PHARMACOKINETICS

Intestinal bacteria common in the gastrointestinal tract of many animals and humans have been shown capable of degrading NDPhA (Rowland and Grasso, 1975).

IV. HEALTH EFFECTS IN MAMMALS

A. Carcinogenicity

In a one-year study, Argus and Hoch-Ligeti (1961) adminis-tered NDPhA by gavage to 25 male rats for 45 weeks (total dose 244 mg/rat). No tumors were observed. In other studies (Boyland et al., 1968) no tumors were seen when 20 rats were given the test compound in the diet for 100 weeks at daily doses of 120 mg/kg, or when 24 male rats were administered DNPhA by intra-peritoneal injection once per week for 6 months at a dose of 2.5 mg/week. Both tests were terminated after 2 years. When two groups of mice (18 male and 18 female per group) were admin-istered NDPhA by gavage daily for 3 weeks at 1,000 mg/kg, then in diet at 3,769 ppm for 18 months, no significant incidences of tumors were observed. However, in another assay reticulum cell sarcomas were observed in the mice when the chemical was injected subcutaneously (NCI, 1968; Innes et al., 1969). Druckrey et al. (1967) reported a lack of tumorigenicity in rats administered 120 mg/kg/day of NDPhA for 700 days, for a total dose of 65 g/kg. Taken together, these studies were viewed as a demonstration of the non-carcinogenicity of NDPhA.

Recent results from the NCI bioassay program, however, have demonstrated that NDPhA is a carcinogen in rats (NCI, 1979; Cardy

et al., 1979). In these studies NDPhA was administered in the
diet to rats and mice at two doses, the "maximum tolerated dose"
for each species and one-half that amount. Groups of 50 animals
of each sex were tested at each dose for approximately 100
weeks. The study found that dietary exposure to NDPhA gave rise
to a significant incidence of urinary bladder tumors in both male
(40%) and female (90%) rats. Few urinary bladder tumors were
observed in the mice, although there was a high incidence of non-
neoplastic bladder lesions. The authors (Cardy et al., 1979)
ascribed the strong carcinogenic effect seen in rats in this
study to the higher doses used; they estimated that the maximum
daily intake of NDPhA was 320 mg/kg in females and 240 mg/kg in
males. These levels are somewhat higher than those used by
Druckrey et al. (1967) in the only other known chronic feeding
study done in rats.

B. Mutagenicity

NDPhA has consistently been reported negative in a variety
of mutagenicity assays: S. typhimurium (Ames test), with and
without activation (Yahagi et al., 1977; Bartsch et al., 1976;
Simmon, 1979a; Rosenkranz and Poirier, 1979); E. coli, with
activation (Nakajima et al., 1974); (Pol A⁻) E. coli (Rosenkranz
and Poirier, 1979); N. crassa (Marquardt et al., 1963); Chinese
hamster V79 (lung) cell line, with and without activation (Kuroki
et al., 1977); Saccharomyces cerevisiae D3, with activation
(Simmon, 1979b); host mediated assay (tester strains: S.
typhimurium and S. cerevisiae D3) (Simmon et al., 1979); in vivo
mouse testicular DNA synthesis assay (Friedman and Staub, 1976).

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C. Other Toxicity

The oral LD_{50} in rats is 1650 mg/kg; in mice the oral LD_{50} is 3,850 mg/kg (NIOSH, 1978).

V. AQUATIC EFFECTS

A. Acute

The 96-hour LC_{50} for NDPhA in bluegill sunfish under static test conditions is 5.9 mg/l (nominal concentration). The 48-hour EC_{50} (static conditions) in Daphnia magna is 7.7 mg/l (nominal concentration). The adjusted 96-hour LC_{50} for the mummichog (a marine fish) under static conditions is 3,300 mg/l (nominal concentration) (U.S. EPA, 1979b).

B. Chronic

No adverse effects were reported at any test concentration in a chronic toxicity study in Daphnia magna at concentrations below 0.048 mg/l (U.S. EPA, 1979b).

C. Other

Bioconcentration of NDPhA by bluegill sunfish reached equilibrium within 14 days; the bioconcentration factor was 217. The half-life of the compound in bluegill sunfish was less than one day (U.S. EPA, 1979b).

VI. EXISTING GUIDELINES

Criteria for the protection of aquatic species from excess NDPhA exposure have not been established (U.S. EPA, 1979b).

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N-Nitrosodi-n-propylamine

Health and Environmental Effects

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APRIL 30, 1980

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DISCLAIMER

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

SPECIAL NOTATION

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

N-NITROSODI-n-PROPYLAMINE

SUMMARY

The International Agency for Research on Cancer has concluded that "N-nitrosodi-n-propylamine should be regarded for practical purposes as if it were carcinogenic in humans." The conclusion is based on positive findings in several long-term animal studies with the compound. It has also been found mutagenic in several test systems with activation.

The chemistry of formation of nitrosamines is quite complex, however, they are formed in general by the combination of amines with some nitrosating agent. Nitrates, nitrites, and amines (primary, secondary, and tertiary), the precursors in the formation of nitrosamines, are ubiquitous in the environment. Significant quantities of the precursors are also produced through human activities.

The _in vivo_ formation of nitrosamines following ingestion of precursors has been demonstrated in humans and animals.

Nitrosamines degrade in the presence of sunlight; however, in the dark they are quite stable. Microorganisms can function both in the formation and degradation of nitrosamines. The half-life of aliphatic nitrosamines in the environment ranges from one hour in the atmosphere in sunlight to more than 40 days in soils and water (in the absence of light).

I.   INTRODUCTION

This document is based on the Ambient Water Quality Criteria Document for Nitrosamines (U.S. EPA, 1979a), Volume 17 of the

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans (IARC, 1978), the Scientific and Technical Assessment Report on Nitrosamines (U.S. EPA, 1977), and other selected references. The term "N-nitrosodi-n-propylamine" (NDPA) in this report refers specifically to that compound; the term "nitrosamine" when used in this report refers in general to simple aliphatic nitrosamines.

N-nitrosodi-n-propylamine (NDPA; $C_6H_{14}N_2O$; molecular weight 130.2) is a yellow liquid having the following physical chemical properties (IARC, 1978).

Boiling Point:	81°C
Density:	d_4^{20} 0.9160
Solubility:	soluble in water, organic solvents, and lipids.
Volatility:	can be steam distilled quantitatively.

A review of the production range (includes importation) statistics for NDPA (CAS No. 621-64-7) which is listed in the initial TSCA Inventory (1979b) has shown that between zero and 900 pounds of this chemical were intentionally produced/imported in 1977.*/

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

No information on the commercial uses of NDPA was located,
however, it appears likely that most, if not all, of that pro-
duced is used solely in the laboratory.

II. EXPOSURE

Nitrates, nitrites, and amines (in this case the propyl-
amines), which are precursors in the formation of nitrosamines,
are ubiquitous in the environment and occur in food, water, soil,
and air. The natural occurrence of nitrates, nitrites, and
secondary and tertiary amines results from their formation during
the nitrogen cycle. In addition to the naturally formed precur-
sors, significant quantities are produced through human activi-
ties (U.S. EPA, 1977). Some of the major man-made sources of the
precursors are listed in Table 1.

A. Formation

The chemistry of formation of nitrosamines is quite complex,
however, they are formed in general by the combination of amines
(R_1R_2N-) with some nitrosating agent. Formation has been shown
to occur with primary, secondary, and tertiary amines, as well as
other amino compounds. The nitrosating agent can be derived from
nitric oxides (NO, NO_2, N_2O_3, or N_2O_4) or inorganic nitrite.
Certain factors (catalysts) can affect the rate of nitrosation.
Depending on the reactants and catalysts that are present, nitro-
sation can occur under acidic, neutral, or alkaline conditions.
Nitrosation of amines can also occur by transnitrosation involv-
ing other, more labile N-nitroso compounds (U.S. EPA, 1977;
Mirvish, 1977).

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Table 1. Man-Made Sources of Nitrosamine Precursors (U.S. EPA, 1977)

Nitric Oxides	Amines
Transportation	Feedlots
Motor vehicles	Rendering plants
Aircraft	Antioxidants
Railroads	Vulcanization
Fuel combustion in stationary sources	accelerators
Coal	Pharmaceuticals
Fuel Oil	Self-polishing waxes
Natural gas	Synthetic detergents
Wood	Pesticides
Industrial processes	Solvents
Solid waste disposal	Corrosion inhibitors
Miscellaneous	Animal glues
Forest fires	Photographic products
Structural fires	Leather tanning
Coal refuse	Primary amine
Agricultural	production

The in vivo formation of nitrosamines following the inges-
tion of precursors has been demonstrated in human and animal
studies (U.S. EPA, 1976,).

Nitrosamines can be formed in soil, water, and sewage under
appropriate conditions (Ayanaba et al., 1973a, b; Ayanaba and
Alexander, 1974; Kohl et al., 1971). Microorganisms in soil and
water can participate in the formation of nitrosamines (Ayanaba
et al., 1973b; Mills and Alexander, 1976), although microbial
involvement in such formation reactions is not essential (Mills,
1976; Mills and Alexander, 1976).

B.   Environmental Fate

In the absence of light, nitrosamines are quite stable and
will decompose hydrolytically only following prolonged contact
with strong acid. There is no evidence of thermal instability of
nitrosamines in the gas phase; however, they do undergo photo-

chemical decomposition in solution or in the atmosphere in the presence of sunlight or ultra-violet light. There are very few quantitative studies on the rate of photochemical degradation of nitrosamines or on the rate effects of other factors (U.S. EPA, 1977; IARC, 1978). Nonetheless, it has been shown that N-nitrosodimethylamine has an atmospheric half-life (during ambient atmospheric conditions) of between 30 minutes and one hour in sunlight (Hanst et al., 1977). The atmospheric half-life of NDPA should be similar (U.S. EPA, 1979a).

N-nitrosodi-n-propylamine appears to be fairly resistant to microbial attack under environmental conditions. The soil half-life of NDPA under varying conditions has been reported as ranging between 10 and 40 days (Tate and Alexander, 1975; Saunders et al., 1979; Oliver et al., 1978). In lake water under laboratory conditions, NDPA persisted for more than 4 months (Tate and Alexander, 1975).

A laboratory soil leaching study (Saunders et al., 1979) has indicated that NDPA (which is about 1% soluble in water) will leach under heavy simulated rainfall conditions. In a field study, however, NDPA did not leach below a depth of 20 cm. The authors suggest that under field conditions, NDPA is dissipated due to volatilization and degradation.

C.   Bioconcentration

No information on the bioaccumulation potential of NDPA was located, although it should be fairly low.

D.   Environmental Occurrence

NDPA has been detected in food, alcoholic beverages, and several pesticides (IARC, 1978). It has also been detected in

the waste-water from several chemical plants (Cohen and Bachman, 1978).

III. PHARMACOKINETICS

A.   Absorption

In goats, one hour after oral administration, NDPA was found in milk and blood, indicating fairly rapid uptake. Only traces were found in the milk after 24 hours (Juszkiewicz and Kowalski, 1974).

B.   Distribution

No information was located on the distribution of NDPA; however, simple aliphatic nitrosamines tend to distribute rapidly and fairly uniformly in the body (U.S. EPA, 1979a).

C.   Metabolism

Available evidence suggests that NDPA must be metabolically activated to exert its toxic and carcinogenic effects. Urine collected during the 48 hours after oral administration of an LD_{50} dose of NDPA to rats contained the following compounds: N-nitroso-3-hydroxy-n-propyl-n-propylamine, N-nitroso-2-carboxy-ethyl-n-propylamine, and to a lesser extent, N-nitrosocarboxy-methyl-n-propylamine, and N-nitroso-2-hydroxy-n-propyl-n-propylamine (Blattman and Preussmann, 1973). The last named metabolite, N-nitroso-2-hydroxy-n-propyl-n-propylamine, has been found carcinogenic in rats (Reznik et al., 1975) and hamsters (Pour et al., 1974a,b), thus it may be the active carcinogenic metabolite (proximate and/or ultimate carcinogen) of NDPA.

IV. HUMAN HEALTH EFFECTS

A. Carcinogenicity

Groups of rats were given NDPA in the drinking water at doses of 4, 8, 15, or 30 mg/kg day. Of the 48 animals on test, 45 developed liver carcinomas, 8 developed papillomas or carcinomas of the esophagus, and 6 showed carcinomas of the tongue (Druckrey et al., 1967).

Groups of rats were injected subcutaneously with 1/5, 1/10, or 1/20 the LD_{50} of NDPA (LD_{50}: 487 mg/kg) once weekly for life. The average total dose of NDPA ranged between 0.93 and 2.7 g/kg. A high incidence of neoplasms was observed in the nasal cavities. In addition, tumors of the liver, lung, kidney, and esophagus were observed (Althoff et al., 1973a; Reznik et al., 1975).

Groups of Syrian golden hamsters were injected subcutaneously with 1.2% NDPA in olive oil once weekly for life at 5 dose levels (highest dose was 60 mg/kg). Tumors were observed in the nasal cavities, laryngobronchial tract, lungs, and a variety of other organs (Althoff et al., 1973b; Pour et al., 1973).

The International Agency for Research on Cancer (1978) has concluded:

> There is sufficient evidence of a carcinogenic effect of N-nitrosodi-n-propylamine in two experimental animal species. Although no epidemiological data were available...N-nitrosodi-n-propylamine should be regarded for practical purposes as if it were carcinogenic to humans,

B. Mutagenicity

NDPA was positive in the Ames test (S. typhimurium strains TA 1530, TA 1535, and TA 100) with activation (Barstch et al.,

1976; Camus et al., 1976; Olajos and Cornish, 1976; Sugimura et al., 1976). NDPA was also mutagenic in E. coli (Nakajima et al., 1974) and in Chinese hamster V79 cells (Kuroki et al., 1977), in both cases with activation.

C.   Other Toxic Effects

The acute oral LD_{50} of NDPA was 480 mg/kg in rats (Druckrey et al., 1967); the subcutaneous LD_{50} was 487 mg/kg in rats and 600 mg/kg in hamsters (Pour et al., 1973; Reznik et al., 1975).

V. AQUATIC EFFECTS

No data on the aquatic effects of NDPA were located.

VI.   EXISTING GUIDELINES

The class of compounds "nitrosamines" was included in the American Conference of Governmental Industrial Hygienists (1977) list of "Industrial Substances Suspected of Carcinogenic Potential for Man." No threshold limit value (TLV) was given.

As noted in Section IV.A, the International Agency for Research on Cancer (1978) has concluded that "N-nitrosodi-n-propylamine should be regarded for practical purposes as if it were carcinogenic to humans."

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No. 140

Paraldehyde

Health and Environmental Effects

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APRIL 30, 1980

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140-1

DISCLAIMER

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

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PARALDEHYDE

Summary

There is no evidence in the available literature to indicate that paraldehyde, a central nervous system depressant, is carcinogenic, muta-genic, or teratogenic.

In low doses (4-8 ml) paraldehyde has a hypnotic effect on the central nervous system. Following chronic and acute exposures at higher concen-trations, paraldehyde affects the respiratory and circulatory systems.

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

Guidelines or standards concerning air or water exposures were not found in the available literature.

PARALDEHYDE

I.   INTRODUCTION

Paraldehyde, 2,4,6-trimethyl-1,3,5-trioxane, also known as para-acetaldehyde, is a colorless liquid with a molecular weight of 132.2. This compound melts at 13°C and boils at 125°C. It has a specific gravity of 0.994 at 20°C, and its solubility in water is 120,000 mg/l at 13°C and 58,000 mg/l at 100°C (Verschueren, 1977). The odor of paraldehyde is not pungent or unpleasant, but it is characterized by a disagreeable taste (Wilson, et al. 1977).

Paraldehyde was introduced into medicine by Ceruello in 1882 as the second synthetic organic compound to be used as a sedative hypnotic (Wilson, et al. 1977). It is used frequently in delirium tremens and in treatment of psychiatric states characterized by excitement when drugs must be given over a long period of time (Wilson, et al. 1977). It also is administered for intractable pain which does not respond to opiates and for basal and obstetrical anaesthesia (Goodman and Gilman, 1970). It is effective against experimentally induced convulsions and has been used in emergency therapy of tetanus, eclampsia, status epilepticus, and poisoning by convulsant drugs (Goodman and Gilman, 1970).

It is used primarily in medicine, and therefore, the chance of accidental human exposure or environmental contamination is low. However, paraldehyde decomposes to acetaldehyde and acetic acid (Gosselin, et al. 1976); these compounds have been found to be toxic. In this sense, occupational exposure or environmental contamination is possible. Since paraldehyde is prepared from acetaldehyde by polymerization in the presence of an acid catalyst, there exists a potential for adverse effects, although none have been reported in the available literature.

II. EXPOSURE

No monitoring data are available to indicate ambient air or water levels of the compound. Human exposure to paraldehyde from ingestion cannot be assessed, due to a lack of monitoring data. No data on dermal exposure of humans were found in the available literature.

III. PHARMACOKINETICS

Paraldehyde is rapidly absorbed from the gastrointestinal tract and parenteral sites. Following oral administration to rats, the maximum concentration in the brain is reached within 30 minutes (Figot, et al. 1953). A significant percentage is excreted unchanged through the lungs. Lang, et al. (1969) reported that human-subjects given unspecified oral doses exhaled 7 percent of the administered dose within 4 hours. Only traces are observed in the urine; the rest is metabolized by the liver. There is indirect evidence that paraldehyde is depolymerized to acetaldehyde in the liver, then oxidized by aldehyde dehydrogenase to acetic acid which, in turn, is ultimately metabolized to carbon dioxide and water in mice (Hitchcock and Nelson, 1943).

No data on bioaccumulation of paraldehyde were found in the available literature. Based on the evidence of metabolism above, however, significant bioaccumulation would appear unlikely.

IV. EFFECTS

A. Carcinogenicity

Paraldehyde has been designated a "suspect carcinogen" (NIOSH, 1978), although no increase in neoplasms was observed in the mouse-skin painting study (Row and Salaman, 1955), which was cited by NIOSH.

B. Mutagenicity, Teratogenicity and Other Reproductive Effects.

Pertinent data could not be located in the available literature.

C. Chronic Toxicity

In low doses (4-8 ml), paraldehyde has found use as a therapeutic agent. However, if used for a prolonged period of time, intoxication results in tolerance and dependence. Paraldehyde addiction resembles alcoholism; withdrawal may result in delirium tremens and vivid hallucinations (Goodman and Gilman, 1970).

Acidosis, bleeding gastritis, muscular irritability, azotemia, oliguria, albuminuria, leukocytosis, fatty changes in the liver and kidney with toxic hepatitis and nephrosis, pulmonary hemorrhages, edema, and dilation of the right heart have all been observed in cases of chronic paraldehyde poisoning. Metabolic acidosis is a manifestation of paraldehyde intoxication in the paraldehyde addict. The etiology of the acidosis is uncertain (Beier, et al. 1963).

D. Acute Toxicity

Figot, et al. (1953) reported an oral LD_{50} of 1.65 g/kg for paraldehyde in rats. These investigators reported that the level of paraldehyde in the brain was predictive of the degree of toxicity. The median brain concentration lethal to rats was 47 mg percent.

In humans, therapeutic oral doses of 4-8 ml induce sleep. At this dose, little effect on respiration or blood pressure is seen. There appears to be little margin of safety, and slight increases in dosage may result in poisoning. The poisoned patient commonly exhibits very rapid, labored respiratory movements (Goodman and Gilman, 1970). Accompanying the rapid respiration is a marked depression of blood pressure which persists for several hours. Degenerative changes in the kidney and liver have also been observed (Kirk and Othmer, 1979). Unfortunately, it is not absolutely certain whether these effects are due to paraldehyde or to its decomposition products, acetaldehyde and acetic acid.

Toxic doses of unspecified amounts, given intravenously, cause diffuse, massive pulmonary hemorrhages and edema, as well as dilation of the right heart. Adverse effects, as seen in cases of severe acute paraldehyde intoxication, resemble those seen in chronically exposed individuals, e.g., addicts.

Metabolic acidosis is also found in the severe acute cases. Hayward and Boshell (1957) produced metabolic acidosis and other toxic effects, including pulmonary edema in dogs, by administering unspecified amounts of deteriorated paraldehyde through gastric tubes over a period of 18 hours. In this case it is uncertain whether the paraldehyde or the deteriorated product was the cause of the observed effects. The same is true in another study where a deteriorated product (40 percent acetic acid) produced sudden death with intense corrosion of buccal mucosa and upper air passages. Rectal administration (a common route in therapeutic settings) in another poisoning victim caused great pain and sloughing of rectal mucosa (Gosselin, et al. 1976).

High concentrations (unspecified) depressed cholinergic junctions in frogs, apparently by reducing the amount of acetylcholine liberated from nerve endings (Nicholls and Quillam, 1956; Quillam, 1959).

The lethal dose in humans is disputable. Less than one ounce by mouth has been shown to be lethal in some cases, while others have tolerated four ounces. Death results from respiratory failure preceded by prolonged and profound coma (Goodman and Gilman, 1970).

Paraldehyde has been used in obstetrics; however, it readily crosses the placental barrier and appears in the fetal circulation. Undesirable effects, including delay in respiratory movements, have been

observed in neonates following administration to the mother during labor (Goodman and Gilman, 1970). Consequently, paraldehyde finds little or no use in obstetrics today.

The lowest dose of paraldehyde reported to produce any toxic effect (unspecified) in humans is 121 mg/kg. Oral LD_{50} values have been reported for the following species: rats, 1530 mg/kg; rabbits, 3304 mg/kg; and dogs, 3500 mg/kg. NIOSH (1978) has reported the lowest lethal inhalation concentration to be 2000 ppm.

V.   AQUATIC TOXICITY

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

VI.   EXISTING GUIDELINES AND STANDARDS

No exposure limits or standards were found in the available literature to exist for air or water.

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Pentachlorobenzene

Health and Environmental Effects

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APRIL 30, 1980

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141-1

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This report represents a survey of the potential health
and environmental hazards from exposure to the subject chemi-
cal. 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.

PENTACHLOROBENZENE

Summary

Oral feeding of pentachlorobenzene to pregnant rats has produced developmental effects and decreased body weights in fetuses. No adverse reproductive or developmental effects were seen in mice following maternal administration of the compound orally.

There is no information available on the mutagenic effects of pentachlorobenzene.

A single study has alluded to carcinogenic effects of pentachlorobenzene in mice and lack of carcinogenic effects in dogs and rats. The details of this study were not available for evaluation.

Reported 96-hour LC_{50} values for the bluegill, mysid shrimp, and sheepshead minnow range from 250 to 830 μg/l. Daphnia is considerably less sensitive. Studies with algae, with 96-hour EC_{50} values based on chlorophyll a concentration, have reported values ranging from 2,000 to 7,000 μg/l. The steady-state bioconcentration factor for the bluegill is 1,800.

I. INTRODUCTION

Pentachlorobenzene, CAS registry number 608-93-5, is a colorless crystalline solid with a pleasant aroma. It is produced mainly as a byproduct of other chlorobenzenes and has the following physical and chemical properties (Windholz, 1976; Weast, 1972; Hawley, 1971):

Formula:	C_6HCl_5
Molecular Weight:	250.34
Melting Point:	86^oC
Boiling Point:	277^oC
Density:	$1.8342^{16.5}$
Solubility:	Soluble in carbon disulfide, chloroform, and hot alcohol, insoluble in water

Pentachlorobenzene is used primarily as a precursor in the synthesis of the fungicide pentachloronitrobenzene, and as a flame retardant.

II. EXPOSURE

A. Water

Burlingame (1977) has identified pentachlorobenzene in the effluent from a wastewater treatment plant in southern California. Access to water can occur by industrial discharge or from the degradation of other organochlorine compounds.

B. Food

Pentachlorobenzene has been detected in plants (Balba and Saha, 1974; Kohli, et al. 1976a) and in animal fat (Stijve, 1971; Saha and Burrage, 1976; Greve, 1973), and was shown to arise from the metabolic breakdown of lindane or other organochlorine compounds. The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for pentachlorobenzene to be 7,800 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on steady-state bioconcentration studies in bluegills.

C. Inhalation

The primary site for inhalation exposure could be the workplace in industries utilizing or producing pentachlorobenzene.

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

From studies with rabbits it would appear that pentachlorobenzene is very poorly absorbed from the gastrointestinal tract (Parke and Williams, 1960).

B. Distribution

The distribution of pentachlorobenzene favors retention in the fat (Parke and Williams, 1960). Khera and Villeneuve (1975) have found widespread tissue distribution of the compound following oral administration to pregnant rats and accumulation in fetal tissues.

C. Metabolism

There appear to be some qualitative and quantitative differences between species in the metabolism of pentachlorobenzene. In the rat and rabbit, pentachlorobenzene was shown to be metabolized to a variety of isomers of tetrachlorophenol, with the amount of unchanged pentachlorobenzene excreted in the urine of the rabbit being one percent (Kohli, et al. 1976b), and in the rat being nine percent (Koss and Koransky, 1977). Kohli and co-workers (1976b) suggest that the dechlorination hydroxylation step to the tetrachlorophenol derivative proceeds through an arene oxide intermediate.

D. Excretion

In rats and rabbits urinary excretion of metabolites or unchanged pentachlorobenzene predominated. Rozman, et al. (1978) found the biological half-life of pentachlorobenzene to be two to three months in rhesus monkeys.

After 40 days, ten percent of the total dose was secreted in the urine; of this, 58 percent was pentachlorophenol. After the same period, about 40 percent of the dose was excreted in the feces, 99 percent as pentachloroben-zene. The authors suggest that biliary excretion was occurring.

IV. EFFECTS

A. Carcinogenicity

There is one report, which could not be critically evaluated, which alludes to pentachlorobenzene being carcinogenic in mice but not in rats or dogs (Preussman, 1975).

B. Mutagenicity

Pertinent data could not be located in the available literature.

C. Teratogenicity

Rats receiving 50, 100, and 200 mg/kg pentachlorobenzene on days 6 to 15 of gestation had pups with increased suprauni ribs at all doses (Khera and Villeneuve, 1975). The high dose also produced sternal defects consist-ing of unossified or nonaligned sternabrae with cartilagenous precursors present. The authors did not consider these defects to be teratogenic.

D. Other Reproductive Effects

Oral administration of pentachlorobenzene (50 or 100 mg/kg) to pregnant mice on days 6 to 15 of gestation produced no teratogenic or ad-verse reproductive effects (Courtney, et al. 1977).

E. Chronic Toxicity

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

V. AQUATIC TOXICITY

A. Acute

The U.S. EPA (1978) reported 96-hour LC_{50} values for the blue-gill (Lepomis macrochirus) exposed to pentachlorobenzene to be 250 µg/1.

The 48-hour EC_{50} value reported for <u>Daphnia</u> <u>magna</u> is 5,280 µg/l (U.S. EPA, 1978). For the saltwater species, sheepshead minnow (<u>Cyprinodon</u> <u>variegatus</u>) and mysid shrimp (<u>Mysidopsis</u> <u>bahia</u>), the determined 96-hour LC_{50} values are 830 and 160 µg/l, respectively.

B.   Chronic

Pertinent data could not be located in the available literature.

C.   Plant Effects

The reported 96-hour EC_{50} value for <u>Selenastrum</u> <u>capricornatum</u> based on chlorophyll <u>a</u> concentration is 6,780 µg/l (U.S. EPA, 1978). For the marine alga <u>Skeletonema</u> <u>costatum</u>, a 96-hour EC_{50} value on the same basis is 1,980 ug/l (U.S. EPA, 1978).

D.   Residue

After a 28-day exposure, the steady-state bioconcentration factor for the bluegill for pentachlorobenzene is 1,800. The half-life is greater than seven days (U.S. EPA, 1978).

VI.   EXISTING GUIDELINES AND STANDARDS

A.   Human

The U.S. EPA (1979) has drafted a criterion of 0.5 µg/l for the protection of human health.

B.   Aquatic

No criteria have been developed or proposed to protect aquatic organisms from pentachlorobenzene toxicity due to the lack of pertinent data.

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Pentachloronitrobenzene

Health and Environmental Effects

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142-1

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142-2

SPECIAL NOTATION

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

DISCLAIMER

The mention of company trade names or products does not constitute endorsement by the U.S. EPA or the Federal government.

142-4

PENTACHLORONITROBENZENE

Summary

Increased incidence of hepatoma formation was reported in hybrid mice treated with pentachlorobenzene (PCNB). PCNB was found to be mutagenic in the hcr-strain of *Escherichia coli* ochre, but not in another *E. coli* strain.

PCNB containing a number of contaminants produced renal agenesis and cleft palate in C57Bl/6 mice, cleft palate in CD-1 mice, but was not teratogenic in CD rats. Purified PCNB (less than 20 ppm hexachlorobenzene) resulted in fewer cleft palates in the fetuses. No significant teratogenic effects in rats were detected at dosages as high as 1,563 ppm. In a three generation study using doses as high as 500 ppm, PCNB had no significant effects on the reproduction of rats.

Acute toxicity data for fish were: a 96-hour LC_{50} in bluegill from 0.29 to 0.38 ppm and a 96-hour LC_{50} of 0.31 ppm in rainbow trout.

I. INTRODUCTION

This profile is based on the Initial Scientific Review of Pentachloro-nitrobenzene, PCNB, plus relevant scientific research articles published subsequent to that document (U.S. EPA, 1976).

Pentachloronitrobenzene (molecular weight, 295.34) is a pale yellow-to-white solid, depending on purity, that melts between 142° and 146°C, has a boiling point of 328°C at 760 mm Hg, and a density of 1.718 g/cm^3 at 25°C. Reported vapor pressure values for PCNB are: 1.16 x 10^{-5} mm Hg at 10°C, 5.0 x 10^{-5} mm Hg at 20°C, and 11.3 x 10^{-5} mm Hg at 25°C (U.S. EPA, 1976). PCNB has a relative vapor density (air = 1) of 10.2 (Verschueren, 1977). Water solubility of PCNB is 0.44 mg/l at 20°C and 2 mg PCNB will dissolve in one liter ethanol at 25°C. PCNB is freely sol-uble in carbon disulfide, benzene, chloroform, ketones, and aromatic and chlorinated hydrocarbons, and slightly soluble in alkanols (U.S. EPA, 1976).

PNCB is primarily registered as a soil fungicide for a wide variety of crops and is also used as a seed-treatment fungicide. It is effective against bunt of wheat, <u>Botrytis</u>, <u>Rhizoctonia</u>, and <u>Sclerotinia</u> spp. There are no current nonagricultural uses of PCNB (U.S. EPA, 1976). PCNB is manu-factured domestically under the trade name Terraclor® with an estimated annual production in 1971 of 3 million pounds (U.S. EPA, 1972). According to the Olin Corporation (1974), 60 to 70 percent of the PCNB produced will be used in the United States. The United States has imported from 20,000 to 132,000 lbs. between 1966 and 1969 (U.S. EPA, 1976). PCNB manufactured in Europe is marketed under the common name Quintozene (Dejonckheere, et al.

1976). It may be worth noting that commercial PCNB fungicides contain impurities such as hexachlorobenzene, pentachlorobenzene and tetrachloronitrobenzene, which may be more hazardous than PCNB itself (Dunn, et al. 1978; Simon, et al. 1979).

No data are available for the disassociation of PCNB in aqueous systems. Crosby and Hamadmad (1971) studied the photoreduction of PCNB. The compound remained unchanged in sunlight, probably excluding photolysis as a major route of environmental degradation. At temperatures above 328°C, some decomposition of PCNB has been noted (U.S. EPA, 1976).

PCNB can be biodegraded by pure cultures of actinomycetes and filamentous fungi during their active growth phase (Chacko, et al. 1966).

II. EXPOSURE

PCNB is prepared by either chlorination or nitration reactions. The reaction temperature for the chlorination process is 60 to 70°C. Although this reaction is well below the boiling point of PCNB, atmospheric emissions are possible because of PCNB's relatively high vapor pressure. Furthermore, there exists a potential for environmental release via wastewater effluents at the manufacturing sites. No monitoring data are available for ambient air or water levels of the compound. The major source of environmental contamination is through its application as a fungicide. In the United States, PCNB is used primarily on cotton and peanut crops. Geographic use distribution is mainly concentrated west of the Mississippi River (U.S. EPA, 1976). Carey, et al. (1979) in their study of pesticide residues in the soil detected PCNB in only three of the 1,483 sample sites. The detected residue concentration was from 0.22 to 2.61 ppm. It should be noted, however, that their study was primarily confined to the eastern United States.

Routes of human exposure to PCNB include water, air, contaminated foods, and fish. Casanova and Dubroca (1973) studied the residues of PCNB found in lettuce grown in soil treated with the fungicide. Residue values were 0.73 ppm (15 kg PCNB/ha) and 1.56 ppm (45 kg PCNB/ha). Goursaud, et al. (1972) detected PCNB contamination in endive roots. Since the main objective of their study was the uptake of hexachlorobenzene, actual PCNB concentrations were not noted. However, in a subsequent experiment Goursaud, et al. (1972) fed cows endive roots containing 2.16 ppm PCNB. PCNB residues found in the cows' milk were negligible. Bioaccumulation of PCNB in White Leghorn cockerels (Dunn, et al. 1978) was also found to be negligible (accumulation ratio 0.001 = tissue concentration/dietary concentration). Broiler chickens (Reed, et al. 1977) did not accumulate PCNB or its metabolites to any appreciable extent (0.002 ppm). No additional information on the levels of PCNB in foods is available.

Bioaccumulation data on PCNB were not found in the literature for aquatic organisms. Ko and Lockwood (1968) reported that the mycelium of fungi had accumulated a concentration of PCNB seven times that of the surrounding soil.

III. PHARMACOKINETICS

A. Absorption

Absorption data on PCNB were restricted to oral administration involving three test species. Betts, et al. (1955) reported that 60 percent of the oral dosage was not absorbed from the gastrointestinal tract in rabbits. Two subsequent studies, however, report that PCNB is readily absorbed from the gastrointestinal tract and/or metabolized by gut flora to another compound and then almost fully absorbed. Kögel, et al. (1979) found that PCNB was readily and almost completely absorbed from the gastrointestinal

tract of Rhesus monkeys. After a single dose of 2 mg/kg given in methyl cellulose suspension, only 7.4 percent of the administered amount was ex-creted as unmetabolized PCNB in the feces. When 91 mg/kg PCNB was given in sesame oil, only 4.3 percent of the dose was excreted unmetabolized. Uptake occurs mainly by the portal venous route, with little involvement of the lymphatic system, bringing the absorbed PCNB directly to the liver where biotransformation can begin. Studies of Comet Red and White Leghorn chick-ens yielded similar results. Chickens fed 300 ppm PCNB in laying mash for sixteen weeks excreted only 1.1 ppm PCNB (Simon, et al. 1979).

B. Distribution

Several studies have been conducted on the distribution and stor-age of ingested PCNB. Due to rapid metabolism and elimination, this com-pound shows very little accumulation in body tissues. Betts, et al. (1955) used rabbits and Borzelleca, et al. (1971) employed beagles and rats. In neither experiment was PCNB detected in liver, kidney, muscle, or adipose tissue. Other studies have indicated very low concentrations of PCNB in various tissues. Simon, et al. (1979) found PCNB at concentrations of 0.85 ppm in fat and 0.005 ppm in egg whites of chickens fed 300 ppm PCNB for six-teen weeks. Other tissues examined contained no detectable levels of PCNB. Dunn, et al. (1978) found the highest tissue residues of PCNB in adipose tissue (1.14 and 1.87 ppm) and the gizzard (1.60 and 0.84 ppm) in chickens given 100 ppm and 1,000 ppm PCNB in feed, respectively. Leg and breast mus-cles and heart, kidney, and liver contained very low (0.16 to 0.07 ppm) or trace amounts of PCNB.

Concentrations of PCNB in various organs of Rhesus monkeys after chronic feeding of 2 ppm PCNB in the daily diet were (in ppm): blood, 0.07; muscle, 0.01; brain, 0.03; liver, 0.19; kidney, 0.14; adrenal cortex, 0.08;

thymus, 0.20; lymph nodes (large intestine), 0.12; bone marrow, 0.13; and omental fat, 0.21 (Mueller, et al. 1978). Kögel, et al. (1979) found the highest concentration of PCNB and/or its metabolites occurring in bile (7.73 ± 0.2 ppm in males and 3.72 ± 0.05 in females) after feeding of 2 ppm PCNB for 70 days.

C. Metabolism

PCNB metabolism has been studied in rats, dogs, cows, and rabbits. Pentachloroaniline and methyl pentachlorophenyl sulfide are the major metabolites. Tissue retention of these compounds is found primarily in body fat with minimal concentrations found in muscle (U.S. EPA, 1976). Two major pathways for the biotransformation of PCNB in Rhesus monkeys are: 1) the reduction of the nitro-moeity to the corresponding aniline, and 2) the cleavage of the C-N bond, presumably via conjugation with sulfur-containing amino acids (Kögel, et al. 1979).

D. Excretion

PCNB and its metabolites are excreted mainly in the urine and feces. Mueller, et al. (1978) reported that Rhesus monkeys excreted almost 80 percent of the ingested PCNB within 5 days; of the excreted radioactivity, 91.2 percent was in the form of metabolites.

IV. EFFECTS

A. Carcinogenicity

Very little information on possible carcinogenic effects of PCNB was found in the available literature. Courtney, et al. (1976) cite one study which found PCNB to be carcinogenic in a hybrid mouse with an increased incidence of hepatoma formation. Levels of exposure were not given.

B. Mutagenicity

PCNB was found to be mutagenic in the hcr-strain of _Escherichia coli_ B/r ochre, but not in another _E. coli_ strain. In the host-mediated assay in mice, no significant increase in mutation rates in _Salmonella typhimurium_ and _Serratia morcescens_ was observed after subcutaneous injection of PCNB. The compound also gave negative results in spot tests (U.S. EPA, 1976).

C. Teratogenicity and Other Reproductive Effects

PCNB was administered to pregnant rats by intubation on days 6 and 15 of gestation at dosages from 100 to 1,563 ppm. Fetuses were examined for gross malformations. No significant effects on the number of corpora lutae, the position and numbers of dead or resorbed fetuses, or the fetal weights and sex ratios were observed at any dose level. No significant skeletal or soft tissue anomalies were reported in the fetuses (U.S. EPA, 1976).

A three-generation study with groups of rats fed diets containing 0, 5, 50 or 500 ppm (Olin technical PCNB) showed no significant effects on fertility, gestation, viability, lactation, rats born per litter, or rats weaned per litter or their average weaning weights (U.S. EPA, 1976).

PCNB containing a number of contaminants, however, produced renal agenesis and cleft palate in C56B1/6 mice and cleft palate in CD-1 mice, but was not teratogenic in CD rats. Purified PCNB (less than 20 ppm hexachlorobenzene) resulted in few cleft palates in fetuses (Courtney, et al. 1976).

D. Chronic Toxicity

PCNB does not appear to be chronically toxic when administered in feeding studies. Rhesus monkeys given 2 ppm or 91 ppm PCNB in their diet for 70 days were monitored for clinical chemistry and hematology parameters throughout the study. These parameters remained unchanged, indicating that

organ function and hematopoiesis was not affected by PCNB or its metabolites (Kögel, et al. 1979).

White Leghorn chickens fed PCNB at concentrations up to 1,000 ppm for the first 8 weeks of life did not develop tissue lesions and hens fed up to 1,000 ppm for 35 weeks failed to develop histopathological changes (Dunn, et al. 1978).

Kögel, et al. (1979) cite studies which report that the toxic effect of Terraclor[R] in rats and dogs is limited to liver enlargement due to hepatocellular hypertrophy. Also, cats had increased methemoglobin levels after moderate and high doses of Terraclor[R] and dogs fed a very high dose (5,000 ppm) of PCNB of undetermined purity for two years were found to have reduced hematopoiesis. These effects, however, may be due to the presence of hexachlorobenzene as a contaminant (Kögel, et al. 1979).

E.   Acute Toxicity

Cholakis, under contract with the U.S. EPA, administered single doses of pentachloronitrobenzene by gavage to several species of microtine rodents (voles) (U.S. EPA, 1978). The acute oral LD_{50} values in male and female M. montanus were 4,194 mg/kg and 3,717 mg/kg, respectively. In M. ochrogaster, M. canicaudus, and M. pennsylvanicus, values were greater than 5,000 mg/kg for both sexes. Toxicologic signs observed were some piloerection, loss of righting reflex and lachrymation. Most signs disappeared after 24 hours. Most deaths occurred within two to six days of dosing.

V.   AQUATIC TOXICITY

A.   Acute Toxicity

In static, acute toxicity bioassays using various PCNB formulations, bluegill (Lepomis macrochirus) had 96-hour median lethal concentration (LC_{50}) values ranging from 0.29 to 0.38 ppm. Rainbow trout (Salmo

<u>gairdneri</u>) had a 96-hour LC_{50} value of 0.31 ppm (U.S. EPA, 1976).

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

No guidelines or standards were located in the available literature for humans or aquatic life.

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No. 143

Pentachlorophenol

Health and Environmental Effects

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

APRIL 30, 1980

143-1

DISCLAIMER

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

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143-2

PENTACHLOROPHENOL

SUMMARY

Pentachlorophenol has shown no evidence of carcinogenicity. Evidence for mutagenicity is equivocal. Pentachlorophenol is teratogenic in experimental animals at levels which produce maternal or fetal toxicity. Adverse health effects have been minimal in workers chronically exposed to pentachlorophenol. Relatively high levels of continous exposure produce muscle weakness, headache, anorexia, abdominal pain, weight loss, and irritation of skin, eyes, and respiratory tract. Pentachlorophenol is a strong uncoupler of oxidative phosphorylation.

Pentachlorophenol has been demonstrated to be acutely toxic to freshwater salmonids at levels as low as 37 µg/l. Comparable levels of toxicity were observed for marine fish. Freshwater plants were also highly susceptible to the action of this chemical with effective concentrations as low as 7.5 µg/l.

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PENTACHLOROPHENOL

I.   INTRODUCTION

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

Pentachlorophenol. (PCP; C_6Cl_5OH; molecular weight 266.35) has the following physical and chemical properties (Stecher, 1968; Natl. Fire Prot. Assoc., 1973; Sax, 1975; Spector, 1956; Weast, 1975-76):

Melting Point Range	$190 - 191^{\circ}$ C
Boiling Point Range	$309 - 310^{\circ}$ (decomposes)
Vapor Pressure	0.12 mm Hg at 100° C
Solubility	Water: 14 mg/l at 20° C

Commercial preparations of pentachlorophenol contain "caustic insolubles" or "nonphenolic. neutral impurities" such as octachlorodibenzofurans and tetra-, penta-, hexa-, hepta-, and octachlorodibenzo-p-dioxins (Johnson, et al. 1973; Schwetz, et al. 1974). In addition, commercial pentachlorophenol contains three to ten percent tetrachlorophenol (Goldstein, et al. 1977; Schwetz, et al. 1978).

Pentachlorophenol is a commercially produced bactericide, fungicide, and slimicide used primarily for the preservation of wood, wood products, and other materials. As a chlorinated hydrocarbon, PCP is also used as a herbicide, insecticide, and molluscicide (U.S. EPA, 1979).

Pentachlorophenol and its sodium salt are widely disseminated in the environment (U.S. EPA, 1979). Pentachlorophenol undergoes photochemical degradation in solution in the presence of sunlight (Mitchell, 1961; Hanadmad, 1967; Wong and Crosby, 1977) and is reported to persist in warm moist soils for a period

of 12 months (Harvey and Crafts, 1952). In laboratory experiments, some microorganisms have been reported to metabolize pentachloro-phenol and its sodium salt (Watanabe, 1973; Suzuki and Nose, 1971; Cserjesi, 1967; Reiner, et al. 1977).

II. EXPOSURE

Residues of pentachlorophenol have been found in food, water and human tissues. Pentachlorophenol levels of 0.06 µg/l in finished drinking water prepared from untreated water contain-ing 0.17 µg/l have been reported (Buhler, et al. 1973). Penta-chlorophenol has been detected in 13 of 240 food composites at levels of 0.01 to 0.04 mg/kg (Johnson and Manske, 1977). The calculated daily dietary exposure is one to six µg/person/day (Duggan and Corneliusen, 1972).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of pentachlorophenol at 58 for the edible portion of fish and shellfish consumed by Americans. This esti-mate is based on measured steady-state bioconcentration studies in goldfish (Carassius auratus), bluegill (Lepomis macrochirus), eastern oyster (Crassostrea virginica), and sheepshead minnow (Cyprinodon variegatus).

Inhalation and dermal exposure data for the general popula-tion are not available (U.S. EPA, 1979). These routes of expo-sure are more likely to occur occupationally.

Total body exposures, based on reported urine levels of pentachlorophenol, appear to be in the range of 10-17 µg/person/ day for the general population and 1500-4400 µg/person/day for occupational exposures (U.S. EPA, 1979). These values may be

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due not only to direct exposure to pentachlorophenol, but also to exposure to hexachlorobenzene (pesticide, fungicide) and lindane (pesticide), which are degraded in part to pentachlorophenol (Yang, et al. 1975; Lui and Sweeney, 1975; Mehendale, et al. 1975; Koss and Koransky, 1978; Karapally, et al. 1973; Engst, et al. 1976).

III. PHARMACOKINETICS

A. Absorption

The half-life for absorption in humans after oral ingestion of pentachlorophenol is 1.3 $\pm$ 0.4 hr. In humans, a peak plasma concentration of 0.248 mg/l was observed four hours after ingestion of a 0.1 mg/kg dose (Braun, et al. 1978). Absorption in rats is similar to that found in humans (Braun, et al. 1977).

Pentachlorophenol is readily absorbed through the skin as indicated by its lethality after dermal exposure (Deichmann, et al. 1942; Armstrong, et al. 1969).

B. Distribution

In humans (fatal pentachlorophenol intoxication) and in rats (non-lethal exposure), the highest levels of pentachlorophenol are found in liver, kidney, and blood, with the lowest levels in brain, spleen, and fat (Cretney, 1976; Armstrong, et al. 1969; Braun, et al. 1977; Larsen, et al. 1975).

C. Metabolism

In four male volunteers ingesting 0.1 mg pentachlorophenol/kg, approximately 74 percent of the dose was eliminated in the urine as pentachlorophenol (PCP) and 12 percent as PCP glucuronide; four percent was eliminated in feces as pentachloro-

phenol and PCP glucuronide (Braun, et al. 1978). Rats excrete 75 percent of administered pentachlorophenol as the unchanged PCP, 16 percent as tetrachlorohydroquinone, and nine percent as PCP glucuronide (Braun, et al. 1977). In another study (Ahlborg, 1978), trichloro-p-hydroquinone was found as an additional metabolite of pentachlorophenol in rats. Mice also metabolize pentachlorophenol to tetrachlorohydroquinone (Jakobson and Yllner, 1971).

D.   Excretion

In humans and in experimental animals, the primary mode of excretion for pentachlorophenol is in the urine (Diechmann, et al. 1942; Braun, et al. 1977, 1978; Larsen, et al. 1975; Jakobson and Yllner, 1971).

In humans, the plasma pentachlorophenol half-life is 30.2 $\pm$ 4.0 hours. The half-lives for elimination of pentachlorophenol and PCP glucuronide from urine are 33.1 $\pm$ 4.5 and 12.7 $\pm$ 5.4 hours, respectively (Braun, et al. 1978). Elimination of pentachlorophenol by the rat is similar to elimination by humans (Braun, et al. 1977).

The available literature indicates that pentachlorophenol does not accumulate in body tissues to any significant extent (U.S. EPA, 1979). Long term, low level tissue binding has not been adequately studied.

IV. EFFECTS

A.   Carcinogenicity

Pentachlorophenol has not shown evidence of carcinogenicity. Pentachlorophenol did not promote papillomas or carcinomas when applied repeatedly to the skin at high concentra-

tions after initiation with dimethylbenzanthracene (Boutwell and Bosch, 1959). Mice receiving commercial pentachlorophenol in the diet throughout their lifespans (about 18 months) did not have a significant incidence of tumors (Innes, et al. 1969). Pentachlorophenol, with low levels of nonphenolic contaminants, was non-carcinogenic when fed to rats for 22 to 24 months (Schwetz, et al. 1978).

B.   Mutagenicity

Pentachlorophenol has been shown to be mutagenic in a few test systems. Recrystallized pentachlorophenol increased the frequency of mutations and mitotic gene conversion in Sac-charomyces cerevisiae when used at a level (400 mg/l) which re-sulted in a 59 percent survival rate of test organisms (Fahrig, et al. 1978). Four of the 473 offspring of female mice injected with a single high dose of pure pentachlorophenol during gesta-tion were reported to have changes in hair coat color (spots) of genetic significance (Fahrig, et al. 1978).

No mutagenic activity was detected in male germ cells of Drosophila (Vogel and Chandler, 1974), in the mouse host-mediated assay, in in vitro spot tests (Buselmaier, et al. 1973), or in histidine-required mutants of Salmonella typhimurium (Anderson, et al. 1972).

C.   Teratogenicity

Information suggesting pentachlorophenol is a human teratogen was not encountered. Pentachlorophenol of both com-mercial and purified grades produced fetal anomalies in rats at levels considered to be toxic either to the maternal rat or

to the fetus (Larsen, et al. 1975; Schwetz, et al. 1974; 1978).
Abnormalities included subcutaneous edema, dilated ureters, de-
layed ossification of the skull, skeletal anomalies, dwarfism,
exencephaly, macropthalmia, and taillessness.

    D.   Other Reproductive Effects

    In a study in which male and female rats were fed
3 or 30 mg/kg pentachlorophenol continuously starting 62 days
before mating, no adverse effects were observed at the 3 mg/kg
level. At 30 mg/kg, the following indices were decreased: maternal
body weight; percent liveborn pups; 7, 14, 21 day survival; 1,
7, 14, 21 day body weight-pups; 7, 14, 21 day litter size. Selected
abnormalities were also seen at this dose.(Schwetz, et al. 1978).

    E. Chronic Toxicity

    Adverse health effects have been minimal in workers
chronically exposed to pentachlorophenol (Klemmer, 1972; Takahashi,
et al. 1976). Increased levels of serum enzymes SGOT, SGPT,
and LDH, and elevated levels of total bilirubin and creatine
phosphokinase were noted, but all levels were still within normal
limits. A significantly higher prevalence of gamma mobility
C-reactive protein (CRP) was detected in the sera of chronically
exposed workers. CRP levels are often elevated in acute states
of various inflammatory disorders or tissue damage (Takahashi,
et al. 1976). A chronic health effect which has been associated
with human exposure to certain types of commercial PCP is chlor-
acne (Baader and Bauer, 1951; Nomura, 1953). Chloracne could
have resulted from impurities in the pentachlorophenol; commercial
PCP containing high levels of chlorodioxins produced chloracne
in the rabbit ear test, while pure pentachlorophenol or penta-

chlorophenol with reduced dioxin content did not (Johnson, et al. 1973).

Chronic intoxication in humans results from relatively high levels of continuous exposure. Symptoms include muscle weakness, headache, anorexia, abdominal pain, and weight loss in addition to skin, eye, and respiratory tract irritation (U.S. EPA, 1979).

Rats fed pentachlorophenol containing low levels of nonphenolic contaminants at daily levels of 1 to 30 mg/kg for eight months (Goldstein, et al. 1977) and 22 to 24 months (Schwetz, et al. 1978) had decreased body weight gains at dosage levels of 30 and 10 mg/kg, respectively. In the 22 to 24 month study, the 30 mg/kg dose resulted in increased serum enzyme SGPT levels and increased specific gravity of the urine.

F.   Other Relevant Information

Pentachlorophenol is a strong uncoupler of oxidative phosphorylation (Weinbach and Garbus, 1965; Mitsuda, et al. 1963).

V.   AQUATIC TOXICITY

A.   Acute Toxicity

The results of 38 freshwater flow-through bioassays reveal a range of 96-hour LC_{50} values of from 63 µg/l for the sockeye salmon (Oncorhynchus nerka) (Webb and Brett, 1973) to 340 µg/l for the fathead minnow (Pimephales promelas) (Ruesink and Smith, 1975). In 19 static assays, LC_{50} values ranged from 37 µg/l for the coho salmon (O. kisutch) to 600 µg/l for the fathead minnow. Five species of salmonids were more sensitive than 4 other species of minnows or centrachids. Freshwater invertebrates displayed LC_{50} values ranging from 310 µg/l to 1,400

µg/l for the tubificid worm (<u>Tubifex tubifex</u>) and were affected by increasing the PH from 7.5 to 9.5. The acute toxicity of pentachlorophenol to saltwater fish ranged from 38 µg/l in a 96-hour static pinfish (prolarvae) (<u>Lagodon rhomboides</u>) assay (Borthwick and Schimmel, 1978) to 442 µg/l for juvenile sheepshead minnows (<u>Cyprinodon variegatus</u>) (Parrish, et al. 1978). For three marine invertebrate species tested, LC_{50} values ranged from 40 to 5,600 µg/l, with the eastern oyster (<u>Crassostrea virginica</u>) being the most sensitive marine invertebrate.

B.   Chronic Toxicity

Freshwater chronic studies for fish or invertebrates were not available. A life-cycle chronic test of 151 days in the marine sheepshead minnow produced a chronic value of 64 µg/l (Parrish, et al. 1978). Data for marine invertebrates was not available (U.S. EPA, 1979).

C.   Plant Effects

For freshwater plants, the lowest effective concentration was 7.5 µg/l, which resulted in the total destruction of chlorophyll in the alga <u>Chlorella pyrenoidosa</u> after 72 hours. A drastic decrease in cell numbers of the marine alga <u>Monochrysis lutheri</u> was observed after 12 days of exposure to 293 µg/l (Woelke, 1965), and 50 percent inactivation of photosynthesis was seen in kelp (<u>Macrocystis pyrifera</u>) exposed for 4 days to 300 µg/l (Clendenning and North, 1960).

D.   Residues

Equilibrium levels of PCP in water and tissues of aquatic organisms are attainable within four days; and when previously exposed marine eastern oysters (<u>Crassostrea virginica</u>)

or freshwater bluegills (<u>Lepomis</u> <u>macrochirus</u>) were held in PCP-free water, a rapid loss of PCP from the organism occurred (Schimmel, et al. 1978; Pruitt, et al. 1977). Bioconcentration factors in marine organisms ranged from 0.26 for the juvenile brown shrimp (<u>Penaeus</u> <u>aztecus</u>) to 78 for the eastern oyster. In freshwater fish, bioconcentration factors of 1,000 for the whole body of the goldfish (<u>Carassius</u> <u>auratus</u>) and of 13 for the muscle tissue of the bluegill have been reported (Kobayashi and Akitake, 1975; Pruitt, et al. 1977).

VI.   EXISTING GUIDELINES AND STANDARDS

    A.   Human.

        The U.S. EPA (1979) draft criterion for pentachlorophenol in ambient water is 680 ug/l.

        The maximum air concentration established by the American Industrial Hygiene Association (1970) is 0.5 mg pentachlorophenol or 0.5 mg sodium pentachlorophenate/m^3 for an 8-hour exposure (TLV). The code of Federal Regulations 21, part 121, paragraph 121:2556 allows up to 50 ppm pentachlorophenol in treated wood which will come in contact with food.

        A NOEL in drinking water of 0.021 mg pentachlorophenol/l is suggested by the National Research Council (1977), based on a NOEL of 3 mg/kg in 90 day and 8 month rat studies and an uncertainty factor of 1,000.

    B.   Aquatic

        The draft criterion to protect marine life is 6.2 µg/l as a 24-hour average, not to exceed 14 µg/l at any time. The draft criterion to protect marine life is 3.7 µg/l for a 24-hour average, not to exceed 8.5 µg/l at any time (U.S. EPA, 1979).

PENTACHLOROPHENOL

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Phenol

Health and Environmental Effects

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DISCLAIMER

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

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PHENOL

SUMMARY

Insufficient data exist to indicate that phenol is a
carcinogenic agent. In skin painting studies, phenol appears
to function primarily as a nonspecific irritant. Information
on the mutagenicity of phenol is equivocal. Phenol does not
appear to be teratogenic. Chronic exposure to phenol at rel-
atively high levels causes liver damage in humans and ani-
mals, and kidney damage in animals. Exposure to acutely tox-
ic levels of phenol causes CNS depression.

The toxic effects of phenol have been extensively exam-
ined in freshwater organisms by acute studies in 13 fish and -
13 invertebrate species. Considerable interspecies and intra
species variation were described, with acute values ranging
from 5,020 to 780,000 ug/l. Only three marine species were
examined in acute tests, and LC_{50} values ranged from
5,200 to 58,250 ug/l.

PHENOL

I. INTRODUCTION

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

Phenol (C_6H_5OH; molecular weight 94.11) is a clear, colorless (light pink when impurities are present) hygroscopic, crystalline solid at 25° C with the following physical and chemical properties (Manufacturing Chemist Assoc., 1974; Kirk and Othmer, 1963; Weast, 1974).

Melting Point	43° C
Boiling Point	182° C at 760 mm Hg
Flash Point	open cup 85° C
	closed cup 79° C
Vapor Pressure	0.35 mm Hg at 25° C
Solubility	Water: 6.7 g/100 ml at 16° C and is soluble at all proportions at 66° C. Also soluble in ether, alcohol, acetic acid, glycerol, liquid sulfur dioxide, benzene, and oils.

Industrial capacity for production is 1.44 to 10^6 tons per year (Chem. Eng. News, 1975). About 90 percent of the phenol produced is used in the production of phenolic resins, caprolactam, bisphenol-A, alkylphenols, and adipic acid (Chemical Profiles, 1972).

Phenol may be biochemically hydroxylated to ortho- and para-dihydroxybenzenes and readily oxidized to the corresponding benzoquinones. These may in turn react with numerous components of industrial waters or sewage such as mercaptans, amines, or the -SH or -NH groups of proteins (Stom, 1975). When ambient water containing phenols is chlorinated, various chlorinated phenols may be produced in sufficient

quantities to produce an objectionable taste and odor (Aly, 1968; Barnhart and Campbell, 1972; Jolley, 1973; Jolley, et al. 1975).

II. EXPOSURE

A. Water

There have been no market basket surveys of free and conjugated phenols with which to estimate the average daily dietary intake of phenols. The National Organic Monitoring Survey (U.S. EPA, 1977) reported finding unspecified concentrations of phenol in 2 out of 110 raw water supplies. The Survey found no phenol in any finished water supplies. The National Commission on Water Quality (1975) reported an annual mean concentration of 1.5 µg phenol/1 in raw water from the lower Mississippi River.

B. Food

Phenol is produced endogenously in the mammalian intestinal tract through microbial metabolism (Harborne, 1964) and free and conjugated phenol is a normal constituent of animal matter (U.S. EPA, 1979). Phenol concentrations of 7 mg/kg in smoked summer sausage and 28.6 mg/kg in smoked pork belly have been reported (Lustre and Issenberg, 1970). Several mouthwashes and lozenges contain phenol in amounts of up to 32.5 mg total phenol/lozenge.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for phenol to be 2.3 in the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of phenol.

C.   Inhalation

The inhalation of phenol vapor appears to be large-
ly restricted to the occupational environment (U.S. EPA,
1979). Dermal exposures can be from a number of medicinal
preparations for skin application (lotions, powders, oint-
ments) containing up to 4.75 percent phenol, or from certain
feminine hygiene products, and hemorrhoidal products (U.S.
EPA, 1979).

III. PHARMACOKINETICS

A.   Absorption

Phenol is readily absorbed by all routes. This is
illustrated by the fact that acutely toxic doses of phenol
can produce symptoms within minutes of administration regard-
less of the route of entry (U.S. EPA, 1979). Sixty to 80
percent of inhaled phenol is retained in the lungs. Piotrow-
ski (1971) found that phenol vapor could be readily absorbed
by intact human skin. The rate of dermal absorption for
phenol vapor can be represented by the formula $A=(0.35)C$,
when A is the amount of phenol absorbed in mg/hour and C is
the phenol concentration in mg/m^3 (Piotrowski, 1971; recal-
culation of data of Ohtsuji and Ikeda, 1972 by U.S. EPA,
1979).

B.   Distribution

Free and conjugated phenol appear to be normal
trace constituents in humans and other mammals (Harborne,
1964). Values reported for free and conjugated phenol in
normal human blood vary greatly due in part to the specifi-
city of the analytical methods used in and in part to the

amount of the dietary protein which increases urinary phenol excretion. Recent values in normal human blood are between 0.04 to 0.56 mg/l for the free phenol and 1.06 to 5.18 mg/l for conjugated phenols (Dirmikis and Darbre, 1974). For the total phenol (free and conjugated) a range between 2 and 18 mg/l has been reported (Van Haaften and Sie, 1965).

Upon absorption, phenol is rapidly distributed to all organ systems, followed by relatively rapid metabolism and excretion. Within 15 minutes of an oral dose, the highest concentrations are found in the liver, followed by heart, kidneys, lungs, brain and blood (Deichmann, 1944).

C.   Metabolism

The major metabolites of phenol are sulfate and glucuronic acid conjugates of phenol and 1,4-dihydroxyben-zene. There are, however, species differences in the excretion pattern of these metabolites (Capel, et al. 1972). The cat, which is sensitive to phenol, in addition to sulfate conjugated phenols, excretes also, as a major metabolite, 1,4-dihydroxybenzene (Miller, et al. 1976). The metabolic pattern is also dose dependent. Other agents, which are normally metabolized to phenol, such as benzene or phenylsalicylate, produce increased urinary excretion of phenol metabolites (Kociba, et al. 1976).

D.   Excretion

In humans and in all mammals that have been tested, nearly all of the phenol and its metabolites are excreted in the urine within 24 hours (U.S. EPA, 1979; Piotrowski, 1971; Deichmann and Keplinger, 1963). Reported normal background

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values for human urinary phenol range from 1.5 to 5 mg/l
(Fishbeck, et al. 1975; U.S. EPA, 1979). Urinary excretion
levels of phenol metabolites in workers exposed to phenylsal-
icylate ranged from 150 to 1,371 mg/l. Upon ingestion of
eight chloraseptic lozenges at the recommended dosing sched-
ule, the total phenol and the free phenol concentrations in
the urine peaked at 270 and 10 mg/l, respectively. When dogs
were fed 125 mg phenylsalicylate/kg/day for 41 days, the peak
urinary phenol concentration was 6,144 mg/l and the treatment
was not associated with ill effects (Kociba, et al. 1976).
The half-life of phenol in man is approximately 3.5 hours
(U.S. EPA, 1979).

IV. EFFECTS

   A. Carcinogenicity

       There is no convincing evidence that phenol acts as
a carcinogen, particularly at concentrations within normal
physiologic limits. Phenol appears to function primarily as
a nonspecific irritant (NIOSH, 1976). Only one case of human
cancer associated with exposure to phenol was found in the
literature. A 72-year old man who had applied a salve of
phenol and ergot to his back daily for 20 years developed an
invasive squammous cell epithelioma (Stevens and Callaway,
1940).

       Phenol produced papillomas but not carcinomas when ap-
plied to the skin of some strains of mice. Phenol has car-
cinogenic activity when applied repeatedly to the skin of a
specially bred strain of Sutter mice at concentrations which
produce repeated skin damage (Boutwell and Bosch, 1959; Sala-

man and Glendenning, 1956). Phenol promotes skin cancer in mice when repeatedly applied after initiation with known carcinogens (Boutwell and Bosch, 1959; Salaman and Glendenning, 1956; Van Duuren, et al. 1971). Tumorigenesis is highest at dose levels of phenol which have some sclerosing activity. Phenol has no cocarcinogenic activity when applied simultaneously and repeatedly with benzo(a)pyrene to mouse skin (Van Duuren, et al. 1973).

B. Mutagenicity

Phenol was found to be mutagenic in Drosphila (Hadorn and Niggli, 1946) and also reported to be nonmutagenic for Neurospora (Dickey, et al. 1949). Phenol produced back mutations in E. coli from streptomycin dependence to non-dependence at phenol concentrations high enough that the survival of bacteria was only 0.5 to 1.7 percent (Demerec, et al. 1951).

C. Teratogenicity

Studies dealing directly with teratogenicity were not reported in the U.S. EPA (1979) or NIOSH (1976) documents. In a study, not designed specifically as a teratogenicity study, rats were given phenol at concentrations of 100 to 12,000 mg/l in their drinking water over three to five generations. Specific teratogenic effects were not noted (Heller and Pursell, 1938).

D. Other Reproductive Effects

In the study mentioned under teratogenicity, higher concentrations of phenol in the drinking water (7,000 mg/l) produced stunted growth in the young, death of the offspring

at birth (10,000 mg/l), and failure to reproduce (12,000 mg/l) (Heller and Pursell, 1938).

E.   Chronic Toxicity

Repeated exposures to phenol at high concentrations have resulted in chronic liver damage in humans (Merliss, 1972). In unpublished studies by Dow Chemical Company (1976), rats received 135 doses of 100 mg phenol/kg or 50 mg phenol/kg by gavage over a six month period. The growth of the rats was comparable to that of controls. Very slight liver changes and slight to moderate kidney damage were seen at the higher dose of phenol. The lower dose of phenol produced only slight kidney damage.

Rats given phenol in their drinking water at 800, 1,200, 1,600, 2,000, and 2,400 mg/l had corresponding average intakes of 21, 30, 49, 56, and 55 mg phenol per rat per day based on actual water consumption data. The rats at the three lower dosage levels showed no overt symptoms of toxicity. The weight gain of the rats at the two highest dose levels was depressed (Deichmann and Oesper, 1940).

F.   Other Relevant Information

The primary effect of exposure to acutely toxic levels of phenol is CNS depression. Significant evidence could not be found to support the occurrence of synergistic or antagonistic actions of phenol with other compounds in mammals (U.S. EPA, 1979).

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V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity data for phenol display a wide range of interspecific variability and intraspecific sensitivity. The range of LC_{50} values for 13 species of freshwater fish is 5,020 µg/l for the rainbow trout (<u>Salmo gairdneri</u>) to 200,000 µg/l for the goldfish (<u>Carassius auratus</u>) (Cairns, et al. 1978). Several studies have indicated an inverse relationship between survival time and temperature for rainbow trout, golden shiner (<u>Notemigonius crysoleueus</u>) (U.S. EPA, 1979). Similar intraspecific sensitivity and interspecific variability was demonstrated by bioassays with freshwater invertebrates as test organisms. The cladocerans, <u>Daphnia</u> <u>magna</u> and <u>D</u>. <u>longispina</u>, displayed the greatest sensitivity to phenol with LC_{50} values as low as 7,000 ug/l reported. The freshwater clam, <u>Sphaerium corneum</u>, was the most resistant species with an LC_{50} value of 780,000 µg/l (U.S. EPA, 1979).

Data for the acute toxicity of phenol to marine organisms is not nearly as extensive as that for freshwater species. For marine fish, LC_{50} values of 5,200 and 6,014 ug/l were obtained for rainbow trout in saline waters and mountain bass (<u>Kuhlia sandvicensis</u>), respectively (U.S. EPA, 1979). Eastern oyster embryos (<u>Crassostrea virginica</u>) and hardclam embryos (<u>Mercenaria mercenaria</u>) were much more resistant with LC_{50} values of 58,250 and 52,630 µg/l, respectively (Davis and Hidu, 1969).

B.   Chronic

Data for the chronic effects of phenol on fresh-
water fish are not available. In a life cycle chronic test,
a chronic value of 3,074 µg/l was obtained for the freshwater
cladoceran, Daphnia magna (U.S. EPA, 1978). Chronic data
for marine organisms were not available.

C.   Plant Effects

Plants are relatively insensitive to phenol expo-
sure with effective concentrations ranging from 20,000 to
1,504,000 µg/l for three species of algae, one species of
diatom, and duckweed. Marine plants species have not been
examined for toxic effects of phenol.

D.   Residues

Measured bioconcentration factors of 1.2 to 2.3
have been determined for goldfish (Kobayashi, et al. 1976;
Kobayashi and Akitake, 1975). Bioconcentration factors have
not been determined for freshwater invertebrates or plants,
or for any marine species.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria de-
rived 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

On the basis of chronic toxicity data for rats and
an uncertainity factor of 500, the U.S. EPA (1979) has de-
rived a draft criterion of 3.4 mg/l for phenol in ambient
water corresponding to the calculated acceptable daily intake

of 0.7 mg. The draft criterion for phenol is 1.0 μg/l in those instances where chlorination of phenol may take place during water purification processes.

The 1974 Federal standard and the ACGIH (1977) recommendation for phenol in air in the workplace is 19 mg/m^3 (5 ppm) as a time-weighted average.

The NIOSH (1976) criterion for a recommended standard for occupational exposure to phenol is 20 mg/m^3 in air as a time weighted average for up to a 10-hour work day and a 40-hour work week, with a ceiling concentration of 60 mg/m^3 for any 15-minute sampling period.

The U.S. EPA interim drinking water limit for phenol is 1 μg/l, which is largely an organoleptic standard based on the objectionable taste and odor produced by chlorinated phenols. In response to a phenol spill in southern Wisconsin, the U.S. EPA proposed on November 26, 1974 an emergency standard of 0.1 mg phenol/l as being temporarily acceptable for human consumption.

B.   Aquatic

The draft criterion for protecting freshwater organisms is 600 μg/l, not to exceed 3,400 μg/l. No criterion for marine organisms was derived (U.S. EPA, 1979).

PHENOL

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No. 145

Phorate

Health and Environmental Effects

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

APRIL 30, 1980

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DISCLAIMER

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

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PHORATE

Summary

Phorate is an organophosphorous insecticide used on a variety of crops, mainly in south-central states. Phorate is readily absorbed through inhalation and skin contact and is highly toxic to humans and other animals. Primarily, it affects the central and peripheral nervous systems by inhibiting cholinesterase activity. Information concerning carcinogenic and mutagenic effects was not located in the available literature. The threshold limit value for phorate is 50 μg/m³, based on dermal contact. Additionally, phorate has been classified for restrictive use by the U.S. EPA.

Although phorate is highly toxic to certain aquatic organisms, no apparent adverse effects have been observed in the aquatic environment.

I. INTRODUCTION

Phorate is a highly toxic organophosphorous insecticide used on a variety of agricultural crops. It was introduced in 1954 by the American Cyanamid Co. under the trade name Thimet® (Martin and Worthing, 1974). Phorate is prepared by the reaction of phosphorous pentasulfide with ethanol, formaldehyde, and ethyl mercapton. Production in the U.S. totaled 3400 tonnes in 1977 (NAS, 1977). Virtually all of the phorate is used on root and field cropsoils to control sucking insects and nematodes (NAS, 1975). Phorate is slightly soluble in water and hydrolyzes in moisture. It has an overall degradation rate constant of 0.02/day and a bioconcentration factor of 5.2. Other properties are listed in Table 1.

II. EXPOSURE

A. Water

Phorate is produced in the United States by the American Cyanamid Co. at Hannibal, Mo. (SRI, 1977). Available information on an annual U.S. production shows that 1900 tonnes were produced in 1971, 3600 tonnes in 1974, and 3400 tonnes in 1977 (NAS, 1975, 1977). Berg, et al. (1972) noted an application rate of 1 pound of actual material per acre (1.1 kg/ha; in this case, to control corn borers). Application rates vary according to use.

Phorate has found increasing use on croplands in the south-central states to protect cotton, hops, alfalfa, barley, sorghum, peanuts, sugar beets, sugar cane, potatoes, rice, and tomatoes. Only small amounts are used in the southeastern and northeastern U.S. American Cyanamid Co. reported that phorate may fill the void left by the removal from the market of chlorinated hydrocarbons and projected a strong demand for phorate in the corn rootworm market (Berg, et al. 1977).

TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF PHORATE

Synonyms: 0,0-diethyl-S-(ethylthiomethyl)phosphorodithioate;
0,0-diethyl-S-ethylmercaptomethyl dithiophosphate;
THIMET American Cyanamid (3911): timet (USSR);
CAS Registry No. (298-02-2); Dranutox; Rampart; Vergfru

Structural Formula: $(C_2H_5O)_2(P=S)SCH_2SC_2H_5$

Molecular Weight: 260.4

Description: Clear liquid
Miscible with: CCl_4, dioxan, vegetable oils, xylene, alcohols, ethers, esters

Soil Attenuation: K_d approx. 5×10^2; $K_{oc} = 3199$

Specific Gravity and/or Density: $d^{25} = 1.167$

Melting and/or Boiling Points: bp 118 to 120°C at 0.8 mm
mp less than -15°C

Stability: Stable at room temperature
Hydrolyzed in the presence of moisture
Overall degradation rate constant (0.02/day)

Soil half-life: 1-4 weeks
Bacterial/Hydrolysis: constant = $8 \times 10^{-4} hr^{-1}$

Solubility (water): 50 ppm at room temp.
$$\frac{sediment}{H_2O} : \frac{4.5}{1}$$

Vapor Pressure: 8.4×10^{-4} mm Hg at 20°C

Bioconcentration Factor (BCF) and/or
Octanol/water partition coefficient (K_{ow}): $K_{ow} = 18$
$BCF = 5.2$

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

Little information was found on phorate production processes. Lawless, et al. (1977) noted that in the production, crude phorate was washed and filtered. No information was given on the treatment of the waste water or filter cake associated with this process. No information on waste sludge or landfill disposal was found in the available literature.

Phorate can enter water by runoff or by ground water drainage after application. Phorate is relatively stable in ground water. Only 10 percent decomposition was estimated in a river environment in 5 days (50 to 250 mile transport; 80-400 km). Also, estimates show that less than 90 percent decomposition per year occurs in a lake environment (U.S. EPA, 1980). There are no estimates on the amount of phorate entering the environment or on the levels of phorate in ambient water. Menzie (1974) noted that phorate decomposes to phorate sulfoxide and phorate sulfone and the sulfoxide and sulfone of the oxygen analog.

Walter-Echols and Lichtenstein (1977) showed that some oxidation products of phorate (phorate sulfoxide) reduce to phorate in lake mud under certain conditions. Using a flooded phorate sulfoxide-treated loam soil, they noticed the production of only small amounts of phorate. After lake mud was added, the reduction of phorate sulfoxide to phorate increased dramatically and, after two weeks' incubation, accounted for 44 percent of the recovered residues. They related the reduction process to the activity of microorganisms in an environment of organic nutrients.

B.   Food

Information available in the open literature does not quantify the amount of phorate detected on foods. In a study reported by Menzie (1974), phorate was applied to bermuda grass and corn at the rate of 2 pounds per

acre (2.2 kg/ha). Fourteen days after treatment, less than 1 ppm phorate residue was noted on the corn; after 21 days less than 1 ppm was found on bermuda grass.

C. Inhalation and Dermal

Data are not available indicating the number of people subject to inhalation or dermal exposure to phorate. The primary human exposure would appear to occur during production and application. The U.S. EPA (1976) listed by occupational group the frequency of illness caused by exposure to organophosphorous pesticides. Of 1157 reported cases, most illnesses occurred among ground applicators (229) and mixer/loaders (142); the lack of, or refusal to use, safety equipment was a major factor of this contamination. Other groups affected were gardeners (101), field workers exposed to pesticide residues (117), nursery and greenhouse workers (75), soil fumigators in agriculture (29), equipment cleaners and mechanics (28), tractor drivers and irrigators (23), workers exposed to pesticide drift (22), pilots (crop dusters) (17), and flaggers for aerial application (6). Most illnesses 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 workers.

III. PHARMACOKINETICS

A. Absorption

Newell and Dilley (1978) exposed four different groups of rats to phorate via four routes of administration. They compared LD_{50} and LC_{50} values and found that inhalation was the most toxic route, followed, in decreasing order, by intravenous, oral, and dermal routes. The phorate aero-

sol generated in the laboratory had a particle size range of 0.3-3.0 μm diameter, a size small enough to enter the gas exchange regions of the lung.

Young, et al. (1979) reported on two occupational exposure incidents that suggested absorption in the lungs was the most effective route of entry. In both cases, the individuals wore protective clothing, goggles, and respirators while working in the dust house where technical grade phorate was produced. Gas chromatographic analyses of air samples from the dust house showed phorate levels ranging from 0.7 to 14.6 mg/m^3. No estimate of particle size was reported by the authors.

B. Distribution

Phorate would be expected to distribute in the body like organophosphorous pesticides of similar solubility. A report by Pugh and Forest (1975) described the distribution in calves exposed to phorate in a manger containing 1200 ppm. Phorate concentrations in the liver ranged from 0.004-0.26 ppm; in the kidney, 0.002-0.021 ppm; and in the brain, 0.025-0.19 ppm.

C. Metabolism

The major phorate metabolites found in blood after oral administration to rats are phorate sulfoxide, phorate sulfone, and phoratoxon sulfone (NAS, 1977). Bowman and Casida (1958) showed that phorate hydrolyzes in rats to produce urinary diethylphosphorodithioic acid, diethylphosphorothioic acid, and diethylphosphoric acid. Oxidative metabolites are not found as components of excretory products of animals treated with phorate (NAS, 1977). However, DuBois, et al. (1950) showed that in rat liver slices, phorate was converted to its oxidative products.

D. Excretion

The previous section notes that phorate is eliminated primarily through the urinary system.

IV. EFFECTS

A. Carcinogenicity and Mutagenicity

Pertinent data could not be located in the available literature on the carcinogenicity or mutagenicity of phorate. Formaldehyde, a suspected carcinogen, and other contaminants may be present in technical grade phorate.

B. Teratogenicity

In a study described in the absorption section of this report, Newell and Dilley (1978) did not find dose-related teratogenesis in rats exposed to phorate via inhalation, intravenous, dermal, or oral routes. In the chick embryo test, Richert and Prahlad (1972) injected 1.5 or 2.0 ppm in a peanut oil medium into eggs on the tenth day of incubation. Controls received only peanut oil. Hatchability of the eggs decreased in a dose-dependent manner. Malformations were produced, but these did not seem to be dose-related. The relevance of these studies to mammalian teratology is unclear (NAS, 1977).

C. Other Reproductive Effects

In a study in which CFI mice were fed diets containing 98.7 percent phorate at 0.6, 1.5, and 3.0 ppm, the no-adverse-effect level for reproductive performance was 1.5 ppm (NAS, 1977).

D. Chronic Toxicity and Other Relevant Information

Pertinent data on chronic toxicity could not be located in the available literature. Several subchronic studies have been reported. In subchronic feeding studies of 1, 5, and 25 ppm phorate for 28 days, cholinesterase in the 1 ppm group was not decreased (Tusing, 1955). In a second rat study, Tusing (1956) fed groups of 50 males and females 92 percent phorate for 13 weeks at 0.22, 0.66, 2.0, 6.0, 12.0, and 18.0 ppm. He noted a no-adverse-effect dosage at 0.66 ppm.

Tusing (1956) fed three dogs 92 percent phorate at 0.01, 0.05, 0.25 and 1.24 mg/kg 6 days per week for 13-15 weeks. The no-adverse-effect dosage was judged to be 0.01 mg/kg; even at this level, a very slight decrease in plasma cholinesterase resulted. Higher dosages caused significant depression of cholinesterase, culminating in death at the two highest dosages.

Rat feeding studies showed higher subchronic toxicities on phorate oxidative metabolites than on phorate, according to Rombunski, et al. (1958). Others have also noted that phorate metabolites are more potent cholinesterase inhibitors than phorate (Curry, et al. 1961).

Young, et al. (1979) reported on acute exposures to high levels of phorate (up to 14.6 mg/m^3) in a production facility (see absorption section). The symptoms accompanying the exposures were confusion, dizziness, nausea, vomiting, pupil constriction, respiratory distress, cardiac arrhythmia, and unconsciousness. Treatment involved a regime of PAM and atropine. According to Gleason (1969), the symptoms produced by a sublethal dose are typical of central and peripheral nervous system toxicity. EPA's accident files contain reports of 21 episodes of poisoning involving phorate for 1971-1973. Eleven were agriculturally related. There are no controlled studies in humans from which no-adverse-effect dosages could be derived.

For humans, the lowest published lethal (LD$_{LO}$) value is estimated to be 5 mg/kg. The following studies list acute phorate toxicity levels for human and nonhuman species, reported by Fairchild (1977):

Species	Exposure	LD_{50} (mg/kg)
Rat	Oral	1.1
Rat	Skin	2.5
Rat	Intravenous	1.2
Mouse	Oral	11
Guinea pig	Oral	20
Guinea pig	Skin	20
Duck	Oral	2.55
Duck	Skin	203
Wild Bird	Oral	1

V.   AQUATIC TOXICITY

A.   Acute and Chronic Toxicity

Phorate is highly toxic to certain species of fish, crustaceans, and terrestrial wildlife (NAS, 1977). NAS noted that there were no reported killings of these species in the environment.

B.   Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES

A.   Human

The threshold limit value for phorate is 50 μg/m^3, based on skin contact (Fairchild, 1977). An 8-hour time-weighted average of 50 mg/m^3 was adapted for phorate by the Tennessee Department of Health (Young, et al. 1979). In addition, phorate is classified for restrictive use by the U.S. EPA for liquid formulations containing 65 percent and greater active ingredients. The restriction was influenced by the acute dermal toxicity of phorate and by residue effects on avian species (applicable to foliar applications only).

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8. Aquatic

Pertinent data could not be located in the available literature.

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Phthalate Esters

Health and Environmental Effects

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

APRIL 30, 1980

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DISCLAIMER

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

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PHTHALATE ESTERS

Summary

Certain phthalates (dimethyl phthalate, diethyl phthalate, mono-2-ethyl-hexyl phthalate and dimethoxyethyl phthalate), have shown mutagenic effects in both bacterial systems and the dominant lethal assay.

All eight phthalates tested by injection in pregnant rats produced teratogenic effects. These effects were not noted when DEHP or dibutyl phthalate were administered orally to pregnant rats. Additional reproductive effects produced include impaired implantation, parturition and decreased fertility in rats. Testicular damage has been reported following intraperitoneal (i.p.) or oral administration of DEHP, or oral administration of dibutyl phthalate. No evidence of carcinogenic effects produced by phthalates is available.

Chronic toxicity includes toxic polyneuritis in workers exposed primarily to dibutyl phthalate. DEHP animal studies show induced liver and kidney changes while dimethyl phthalate induced only kidney effects. Following injection dibutoxyethyl phthalate, di-(2-methoxyethyl) phthalate, and octylisodecyl phthalate have caused damage to the developing chick embryo nervous system.

Toxicity of the phthalate esters to aquatic organisms varies within this group of chemicals. Freshwater organisms have appeared somewhat more sensitive than marine species. The data is insufficient to allow for the drafting of criteria to protect aquatic life for any of the phthalates.

PHTHALATE ESTERS

I. INTRODUCTION

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

The phthalate esters are esters of the benzenedicarboxylic acid ortho form. Esters of the parent compound meta and para forms will not be reviewed in this profile. The phthalate esters are colorless liquids of low volatility, poorly soluble in water and soluble in organic solvents and oils. Some physical and chemical properties of the phthalate esters are indicated in Table 1 on the following page (U.S. EPA, 1979).

The phthalate esters are widely used as placticizers, and through this application are incorporated into wire and cable covering, floor tiles, swimming pool liners, upholstery and seat covers, footwear, and in food and medical packaging materials. Non-plasticizer uses include incorporation into pesticide carriers, cosmetics, fragrances, munitions, industrial oils, and insect repellants (U.S. Int. Trade Commission, 1978). The most current production figure is 6×10^5 tons/year in 1977 (U.S. EPA, 1979).

Phthalate esters are ubiquitous. Monitoring surveys have detected phthalates in soil, air, water, animal and human tissues, and certain vegetation. Some plants and animal tissues may synthesize phthalic acid esters (Peakall, 1975). From in vitro studies indications, certain bacterial flora may be capable of metabolizing phthalates to the monoester form (Englehardt, et al. 1975).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of the phthalates may occur through leaching of plasticizers 'from polyvinyl chloride (PVC) materials, volatilization of phthalates from PVC

materials, and the incineration of PVC items. Human exposure to phthalates includes contaminated foods and fish, dermal application of phthalates in cosmetics and insect repellants, and parenteral administration by use of PVC blood bags, tubings, and infusion devices (U.S. EPA, 1979).

TABLE 1

PHYSICAL AND CHEMICAL PROPERTIES OF PHTHALATE ESTERS

Phthalate Compounds	Molecular Weight	Specific Gravity	Bp, °C	Percent Solubility in H_2O, g/100 ml
Dimethyl	194.18	1.189 (25/25)	282	0.5
Diethyl	222.23	1.123 (25/4)	296.1	Insoluble
Diallyl	246.27	1.120 (20/20)	290	0.01
Diisobutyl	278.30	1.040	327	Insoluble
Dibutyl	278.34	1.047 (21)	340	0.45 (25°C)
Dimethoxyethyl	282.00	1.171 (20)	190-210	0.85
Dicyclohexyl	330.00	1.200 (25/25)	220-228	Insoluble
Butyl octyl	334.00	—	340	—
Dihexyl	334.00	0.990	—	Insoluble
Butylphthayl butyl glycolate	336.37	1.097 (25/25)	219/5 mm	0.012
Dibutoxyethyl ethyl	366.00	1.063	210	0.03
Di-2-ethylhexyl	391.00	0.985 (20/20)	386.9/5 mm	Insoluble
Diisooctyl	391.00	0.981	239/5 mm	Insoluble
Di-n-octyl	391.00	0.978	220/5 mm	Insoluble
Dinonyl	419.00	0.965	413	Insoluble

Source: U.S. EPA, 1979

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Monitoring studies have indicated that most water phthalate concentrations are in the ppm range, approximately 1-2 ug/1 (U.S. EPA, 1979). Air levels of phthalates in closed PVC tiled rooms have been reported to be from 0.15 to 0.26 mg/m^3 (Peakall, 1975), while industrial monitoring has measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1973). Phthalate levels in various foods have ranged from non-detectable to 82 ppm (Tomita, et al. 1977). Cheeses, milk, fish and shellfish present potential sources of high phthalate intake (U.S. EPA, 1979). Estimates of patient parenteral exposure to di-2-ethylhexyl phthalate (DEHP) during use of PVC medical appliances have indicated approximately 150 mg DEHP exposure from a single hemodialysis course. Through application of certain cosmetics and insect repellants dermal exposure to phthalates is possible (U.S. EPA, 1979).

Using average human fish and shellfish consumption data, the U.S. EPA (1979) has derived the following bioconcentration factors for the edible portions of fish and shellfish consumed by Americans - diethyl phthalate, 270; dibutylphthalate, 1500; DEHP, 95; dimethyl phthalate, 130. DMP, DEP and BBP are based on the steady-state bioconcentrations in bluegills and in fathead minnows for DEHP. A weighted average bioconcentration factor of 26 was calculated for dibutyl phthalate utilizing the octanol water partition coefficient (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

The phthalic acid esters and/or their metabolites are readily absorbed from the intestinal tract, the peritoneal cavity, and the lungs (U.S. EPA, 1979). Daniel and Bratt (1974) found that seven days following administration of radiolabelled-DEHP, 42 percent of the dose is recovered in the urine and 57 percent recovered in the feces of rats. Biliary excretion of

orally administered DEHP has been noted by Wallin, et al. (1974). Limited human studies indicate that 2 to 4.5 percent of orally administered DEHP is recovered in the urine within 24 hours (Shaffer, et al. 1945). Lake, et al. (1975) suggest orally administered phthalates are absorbed after metabolic conversion to the monoester form in the gut.

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

B. Distribution

Studies in rats injected with radiolabelled-DEHP have shown that from 60 to 70 percent of the administered dose was detected in the liver and lungs within 2 hours after injection (Daniel and Bratt, 1974). Wadell, et al. (1977) have reported rapid accumulation of radiolabelled-DEHP in the kidney and liver of rats after intravenous (i.v.) injection, followed by rapid excretion into the urine, bile, and intestine. Seven days after i.v. administration of radiolabelled-DEHP to mice, levels of the compound were found preferentially in the lungs and to a lesser extent in the brain, fat, heart, and blood (Autian, 1973).

An examination of tissue samples from two deceased patients, recipients of large volumes of transfused blood, detected DEHP in the spleen, liver, lungs, and abdominal fat (Jaeger and Rubin, 1970). Daniel and Bratt (1974) have suggested phthalates achieve a steady-state concentration, after which the compounds or metabolites are rapidly eliminated by various routes.

Injection of radiolabelled-DEHP and diethyl phthalate in pregnant rats has shown the phthalates may cross the placental barrier (Singh, et al. 1975).

C. Metabolism

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

D. Excretion

Elimination of orally administratered DEHP is virtually completed within four days in the rat (Lake, et al. 1975). Major excretion is through the urine and feces, with biliary excretion increasing the content of DEHP (or metabolites) in the intestine (U.S. EPA, 1979). Schulz and Rubin (1973) have noted a progressive increase in total water soluble metabolites in the first 24 hours following injection of radiolabelled DEHP to rats. Within one hour, eight percent of the DEHP was found in the liver, intestine and urine. After 24 hours, 54.6 percent DEHP was recovered in the intestinal tract, excreted feces and urine, and only 20.5 percent DEHP was recovered in organic extractable form.

The half-life of phthalate elimination from the tissues and total body is short (U.S. EPA, 1979). Biphasic elimination of DEHP from the blood of rats showed half-life values of 9 minutes and 22 minutes, respectively (Schulz and Rubin, 1973).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be found in the available literature.

B. Mutagenicity

Testing of several phthalates in the Ames *Salmonella* assay has shown that diethyl phthalate has some mutagenic activity (Rubin, et al. 1979). Dibutyl, mono-2-ethylhexyl, di-(2-ethylhexyl) and butylbenzyl phthalate all produced negative effects in this test system. Yagi, et al. (1978) have reported mutagenic effects of mono-2-ethylhexyl phthalate in a *Bacillus* *subtillus* recombinant assay system.

Results of a dominant lethal assay in mice have indicated DEHP and dimethoxyethyl phthalate showed some mutagenic activity (Singh, et al. 1974).

C. Teratogenicity

The teratogenic effects of a number of phthalate esters (DEHP, dimethyl, dimethoxyethyl, diethyl, diisobutyl, butylcarbobutoxymethyl, and dioctyl phthalates) have been reported in rats (Singh, et al. 1972). Teratogenic effects were not seen following oral administration of DEHP and dibutyl phthalate to rats (Nikonorow, et al. 1973). Damage to the nervous system or developing chick embryos has been produced by injection of dibutoxyethyl phthalate, di-(2-methoxy-ethyl) phthalate, and octyl-isodecyl phthalate (Bower, et al. 1970).

D. Other Reproductive Effects

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

Testicular damage has been reported in rats administered DEHP intraparenteneally or orally. Seth, et al. (1976) found degeneration of the seminiferous tubules and changes in spermatagonia; testicular atrophy and morphological damage was noted in rats fed DEHP or dibutyl phthalate (Carter, et al. 1977).

E. Chronic Toxicity

An increase in toxic polyneuritis has been reported by Milkov, et al. (1973) in workers exposed primarily to dibutyl phthalate. Lesser levels of exposure to dioctyl, diisooctyl, benzylbutyl phthalates, and tricresyl phosphate were also noted. Neurological symptoms have been observed in several phthalate plasticizer workers (Gilioli, 1978). Animal studies have shown central nervous system degeneration and encephalopathy in rats administered large oral or intraperitoneal doses of butylbenzyl phthalate (Mallette and Von Hamm, 1952).

Oral DEHP feeding has produced liver and kidney weight increases in several animal studies (U.S. EPA, 1979). Chronic exposure to transfused blood containing DEHP has produced liver damage in monkeys (Kevy, et al. 1978). Lake, et al. (1975) have produced liver damage in rats by administration of mono-2-ethylhexyl phthalate.

Two-year feeding studies with female rats have shown some kidney effects produced by dimethyl phthalate (Draize, et al. 1948).

F. Other Relevant Information

Several animal studies have demonstrated that DEHP pretreatment of rats resulted in increased hexobarbital sleeping times (Daniel and Bratt, 1974; Rubin and Jaeger, 1973; Swinyard, et al. 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute values for freshwater fish were derived from eight 96-hour bioassays for four phthalate esters. LC_{50} values ranged from 730 µg/l for di-n-butyl phthalate in the bluegill sunfish (Lepomis macrochirus) (Mayer and Sanders, 1973) to 98,200 µg/l in diethyl phthalate for the bluegill, Lepomis macrochirus. Butylbenzyl and dimethyl phthalates were intermediate in their toxicity in bluegill assays with LC_{50} values of 43,300 to 49,500 µg/l respectively (U.S. EPA, 1978). The scud, Gammarus pseudolimnaeus, was the most sensitive of freshwater species tested, producing a static 48-hour adjusted LC_{50} value of 765 µg/l (Mayer and Sanders, 1973). In 48-hour static Daphnia magna assays, the adjusted LC_{50} values for butylbenzyl, di-ethyl dimethyl, and di-n-ethylhexyl phthalates were 92,300, 52,100, 33,000, and 11,100 µg/l, respectively. Among marine fish, juvenile sheepshead min-nows, Cyprinodon variegatus, were most susceptible to diethyl phthalate, producing a static 96-hour LC_{50} value of 29,600 µg/l. In similar assays, the LC_{50} values for butylbenzyl and dimethyl phthalate were 445,000 µg/l and 58,000 µg/l respectively. The marine mysid shrimp, Mysidopsis bahia, was tested with diethyl phthalate, and produced a 96-hour LC_{50} value of 7,590 µg/l. LC_{50} values of 9,630 and 73,700 µg/l were reported for butyl-benzyl and dimethyl phthalates, respectively, in mysid shrimp assays.

B. Chronic Toxicity

The only chronic studies available are for one species of fresh-water fish and one species of freshwater invertebrate (Mehrle and Mayer, 1976; Mayer and Sanders, 1973). A chronic value of 4.2 µg/l was obtained in a rainbow trout, Salmo gairdneri, embryo-larval study of di-(2-ethylhexyl)

phthalate. In _Daohnia_ _magna_ significant reproductive impairment was observ-
ed for di-2(-ethylhexyl) phthalate at 3.0 µg/l, the lowest concentration
tested. Chronic marine data was not available.

    C. Plant Effects

    In the freshwater algae, _Selenastrum_ _capricornutum_, effective con-
centration ranges of 110 to 130 µg/l; 85,600 to 90,300 µg/l and 39,800 to
42,700 µg/l were obtained for butylbenzyl, diethyl and dimethyl phthalates
respectively. Effective concentrations were based on chlorophyll _a_ content
and cell number.

    D. Residues

    Bioconcentration factors have been obtained for five of the phtha-
lates. In the scud, bioconcentration factors of 1400 were reported for di-
n-butyl phthalate, and 54,2680 for di-(2-ethylhexyl) phthalate. In the
bluegill, bioconcentration factors of 57, 117, and 663 were obtained for di-
methyl, diethyl, and butylbenzyl phthalates, respectively. For di-(2-ethyl-
hexyl) phthalate bioconcentration factors were reported from 24 to 150 for
the sowbug, _Ascellus_ _brevicaudus_, 42 to 113 for the rainbow trout, and 155
to 886 for the fathead minnow.

VI. EXISTING GUIDELINES AND STANDARDS

    Neither the human health nor the aquatic criteria derived by U.S. EPA
(1979), which are summarized below, have gone through the process of public
review; therefore, there is a possibility that these criteria will be
changed.

    A. Human

    Based on "no effect" levels observed in chronic feeding studies of
rats or dogs, the U.S. EPA calculated acceptable daily intake (ADI) levels
for several phthalates, and established recommended water quality criteria

levels to protect human health for dimethyl phthalate, diethyl phthalate, dibutyl phthalate, and DEHP. These levels are listed in Table 2 (U.S. EPA, 1979)

B. Aquatic

Data are insufficient to derive draft criteria for any of the phthalate esters in either freshwater or marine environments (U.S. EPA, 1979).

TABLE 2

CALCULATED ALLOWABLE DAILY INTAKE IN WATER AND
FISH FOR VARIOUS PHTHALATE ESTERS (U.S. EPA, 1979)

Ester	No Effect Dose (mg/kg/day)	Species	Days	ADI** (mg/day)	F***	Recommended Criteria (mg/1)
Dimethyl	1000	Rat	104	700	130	160
Diethyl	625	Dog	52	438	270	60
Dibutyl	18	Dog	52	12.6	26	5
Dicyclohexyl	14	Dog	52	9.8	Not Established	
Methyl phthayl ethyl glycolate	750	Rat	104	525	Not Established	
Ethyl phthayl ethyl glycolate	250	Rat	104	175	Not Established	
Butyl phthayl ethyl glycolate	140	Dog	104	98	Not Established	
Di-2-ethyhexyl	60	Dog	52	42	95	10

**Allowable Daily Intake for 70 kg person (100 safety factor)
***F = Biomagnification factor

PHTHALATE ESTERS

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Phthalic Anhydride

Health and Environmental Effects

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APRIL 30, 1980

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147-1

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PHTHALIC ANHYDRIDE

Summary

Phthalic anhydride failed to produce carcinogenic effects in rats or mice in a long term National Cancer Institute (NCI) feeding study (7,500 ppm; 15,000 ppm).

Information on the mutagenic effects of phthalic anhydride was not found in the available literature.

The hydrolysis product of phthalic anhydride, phthalic acid, has shown teratogenic effects in the developing chick embryo, but not in any mammalian tests. Phthalic anhydride inhalation at high levels may produce reproductive impairment in male rats.

Chronic occupational exposure to phthalic anhydride has been reported to produce progressive respiratory damage in workers, including marked fibrosis of the lungs.

Data concerning the effects of phthalic anhydride to aquatic organisms was not found in the available literature.

PHTHALIC ANHYDRIDE

I. INTRODUCTION

This profile is based on the Preliminary Environmental Hazard Assessment of Chlorinated Naphthalenes, Silicones, Fluorocarbons, Benzene-polycarboxylates, and Chlorophenols (U.S. EPA, 1973).

Phthalic anhydride (molecular weight - 148.1) is a white, crystalline solid that melts (sublimes) at 131^0C, has a boiling point of 284.5^{0}C, a density of 1.527, and a solubility of 0.62 gms/100 gms water at 25^{0}C (Towle, et al. 1968). This compound is soluble in alcohol and sparingly soluble in ether.

The major uses of phthalic anhydride are in the synthesis of plasticizers, alkyd resins, unsaturated polyester resins, and in the preparation of various classes of chemical dyes (U.S. EPA, 1973).

Production of phthalic anhydride in 1971 was 4×10^5 tons (Blackford, 1970).

Phthalic anhydride is in equilibrium with phthalic acid in aqueous systems. Under dry conditions, phthalic anhydride is relatively stable at ambient temperature (U.S. EPA, 1973). Elevated temperatures will produce oxidative degradation of phthalic anhydride.

Phthalic anhydride is biodegraded by microorganisms (Ribbons and Evans, 1960; Saegar and Tucker, 1973).

II. EXPOSURE

Phthalic anhydride is used in large quantities and therefore has potential for industrial release and environmental contamination. No monitoring data are available to indicate ambient air or water levels of the compound. Fawcett (1970) has determined 40-200 ppm by volume in phthalic anhydride

off-gas process. Phthalic acid wastes have been noted in waste waters from paint and varnish industries (Mirland and Sporykhina, 1968) and alkyd resin plants (Minkovich, 1960).

Human exposure to phthalic anhydride from foods cannot be assessed, due to a lack of monitoring data.

Release of phthalic acid from parenterally-used plastic medical devices (blood bags, plastic tubings, catheters, etc.) may occur since these materials have been treated with phthalate plasticizers; however, no data on this type of release are available (U.S. EPA, 1973).

Bioaccumulation data on phthalic anhydride were not found in the available literature.

III. PHARMACOKINETICS

Specific information on the metabolism, distribution, absorption, or elimination of phthalic anhydride was not found in the available literature.

IV. EFFECTS

A. Carcinogenicity

A long-term carcinogenesis bioassay in rats and mice fed phthalic anhydride (7,500 ppm; 15,000 ppm) has been conducted by the NCI (1979). The results indicate that oral administration of these levels of the compound produced no carcinogenic effects in either of the species used.

B. Mutagenicity

Information on the mutagenic effects of phthalic anhydride was not found in the available literature.

C. Teratogenicity

Phthalic acid was shown to produce an increase in teratogenic effects in the developing chick embryo following injection (Verrett, 'et al.

1969). Mammalian testing of phthalic acid for teratogenicity failed to show effects in mice (Koehler, et al. 1971).

D. Reproductive Effects

Inhalation exposure of rats to phthalic anhydride at high levels (100-200 mg/1) has been reported to cause testicular changes and impaired reproductive capability (Protsenko, 1970).

E. Chronic Toxicity

Markman and Savinkina (1964) have reported progressive respiratory damage in workers exposed to phthalic anhydride for two years or more. Workers exposed for six years evidenced marked fibrosis of the lungs.

F. Other Relevant Information

Phthalic anhydride has been implicated as a skin sensitizing agent in some individuals exposed for prolonged periods of time (Amer. Ind. Hyg; Assoc., 1967).

V. AQUATIC TOXICITY

Data concerning the effects of phthalic anhydride to aquatic organisms were not found in the available literature.

VI. EXISTING GUIDELINES

The 8-hour, TWA occupational exposure limit established for phthalic anhydride is 1 ppm (ACGIH, 1977).

PHTHALIC ANHYDRIDE

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No. 148

2-Picoline

Health and Environmental Effects

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APRIL 30, 1980

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and environmental hazards from exposure to the subject chemi-
cal. The information contained in the report is drawn chiefly
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adverse health and environmental impacts presented by the
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ensure its technical accuracy.

2-PICOLINE

Summary

Pertinent data could not be found that defined 2-picoline as a carcinogen or a mutagen. Studies on rats indicated that the structure and composition of the liver and the structure and growth pattern of the skin were disrupted in the offspring of tested rats who were given 157 mg per kg body weight daily during their pregnancy.

2-picoline has been shown to produce biochemical and physical changes in the liver, spleen, bone marrow, and lymph nodes.

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I.   INTRODUCTION

2-picoline (alpha-picoline, 2-methylpyridine; CAS No. 109-06-8) is a colorless liquid possessing a strong unpleasant odor. It has the following physical properties:

Formula: C_6H_7N

Molecular Weight: 93.12

Melting Point: -70°C

Boiling Point: 129°C

Vapor Pressure: 8 mm Hg at 20°C

Vapor Density: 3.21

2-picoline is freely soluble in water and miscible with alcohol and ether (Windholz, 1976). 2-picoline is used as an organic solvent and intermediate in the dye and resins industries.

II. EXPOSURE

A.   Water

Pertinent data could not be located in the available literature.

B.   Food

Pertinent data could not be located in the available literature.

C.   Inhalation

2-picoline occurs in the working environment of coke oven workers (Naizer and Mashek, 1974) and is present in cigarette smoke (Brennemann et. al., 1979).

D.   Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

    A.   Absorption

        In rats, 2-picoline is rapidly absorbed and taken up by the liver, heart, spleen, lungs, brain, and muscles during the first 10 to 20 minutes after oral administration (Kupor, 1972).

    B.   Distribution

        Pertinent data could not be located in the available literature.

    C.   Metabolism and Excretion

        Most of an administered dose in an acute toxicity study was excreted in the urine within 48 hours (Kuper, 1972).

IV   EFFECTS

    A.   Carcinogenicity

        Pertinent data could not be found in the available literature.

    B.   Mutagenicity

        Pertinent data could not be found in the available literature.

    C.   Teratogenicity

        The structure and composition of the liver and the structure and growth pattern of the skin were disrupted in the offspring of treated rats who were administered 157 mg per kg body weight of 2-picoline throughout their pregnancy (Nikiforova and Taskaev, 1974).

    D.   Other Reproductive Effects

        Glycolytic processes and protein formation in the liver was disturbed during the pregnancy of rats inhaling 2-picoline at

the maximum permissable concentration for 4 months. The pregnancy complicated toxicosis which without pregnancy was successfully compensated by the liver (Taskaev, 1979).

     E.   Chronic Toxicity

     The following biochemical and physical changes have been observed in rats after the administration of 2-picoline; changes occurred in the liver carbohydrate metabolism (Taskaev, 1979; Kuper and Gruzdeva, 1974) and changes occurred in protein synthesis of the liver noted after chronic oral (Kuper and Gruzdeva, 1974) and inhalation (Taskaev, 1979) exposure. Administration of low doses results in changes in LDH isoenzyme distribution and activity (Gruzdeva, 1976). The major chronic effects of 2-picoline are injury to the liver (Ovchinnikova, 1978; Taskaev, 1979; Ovchinnikova, 1977) and spleen, bone marrow, and lymph nodes (Semchenko, 1973 and 1972).

     F.   Other Relevant Information

     Pertinent data could not be found in the available literature.

V.   AQUATIC TOXICITY

     A.   Acute Toxicity

     Pertinent information could not be found in the available literature.

     B.   Chronic Toxicity, Plant Effects and Residues

     Pertinent information could not be found in the available literature.

     C.   Other Relevant Information

     Pertinent information could not be found in the available literature.

VI.   EXISTING GUIDELINES AND STANDARDS

   A.   Human

   The 8-hour, time-weighted average occupational exposure
limit for alpha-picoline has been set in Russia at 5 mg/m^3
(Verschueren, 1977). Maximum allowable concentration in Class I
waters for the production of drinking waters has been set in the
Netherlands at 0.05 mg/l (Verschueren, 1977).

   B.   Aquatic

   Pertinent information could not be found in the available
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Polynuclear Aromatic Hydrocarbons (PAH)

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated
polynuclear aromatic hydrocarbons and has found sufficient
evidence to indicate that this compound is carcinogenic.

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POLYNUCLEAR AROMATIC HYDROCARBONS (PAH)

SUMMARY

The first chemicals ever shown to be involved in the development of cancer belong to the polycyclic aromatic hydrocarbon (PAH) class. Several PAH are well-known as animal carcinogens by all routes of administration. Others are not carcinogenic alone, but in certain cases can enhance or inhibit the tumorigenic response of carcinogenic PAH. Numerous studies of workers exposed to coal gas, coal tars, and coke oven emissions, all of which have large amounts of PAH, have demonstrated a positive association between their exposures and lung cancer development. The carcinogenic risk of ingested PAH in humans, however, has not been extensively studied.

No standard toxicity data for aquatic organisms are available for freshwater or marine life. Limited information concerning toxic responses of freshwater fish reveals that concentrations of 1,000 $\mu g/l$ for six months produced an 87% mortality in one warm water species.

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I. INTRODUCTION

This profile is based primarily upon the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multi-media Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Polycyclic aromatic hydrocarbons (PAH) are a diverse class of compounds consisting of substituted and unsubstituted polycyclic and heterocyclic aromatic rings. PAH are formed as a result of incomplete combustion of organic material (e.g., fossil fuels, wood, etc.). This leads to formation of C-H free radicals which can polymerize to form various PAH. Among these PAH are compounds such as benzo(a)pyrene (BaP) and benz(a)anthracene (BaA), which are ubiquitous in the environment and well-known for their carcinogenic activity. The presence in ambient air of over one hundred individual PAH has been reported, but quantitative data on only 26 PAH are available thus far.

Most of the PAH are high melting-point, high boiling-point solids that are very insoluble in water. As the ring size increases, the volatility decreases significantly. The PAH are strong absorbers of ultraviolet light, and PAH fluoresce strongly; both of these properties lead to analytical methods for detection of trace quantities. Because of their high melting points and low water solubilities and vapor pressures, most PAH are generally associated with particulate matter. In air, they are adsorbed on small diameter particles that can be easily inhaled. In water, PAH appear to also be primarily associated with particulate matter. Based upon water treatability of PAH, the compounds appear to exist in equal proportions in three forms; bound to large suspended particles; bound to finely dispersed particles, and as the dissolved form (U.S. EPA, 1979a).

PAH adsorbed to airborne particulate matter appear to be fairly stable in the environment. Nevertheless, some photooxidation occurs with atmospheric PAH since quinone derivatives have been detected in the atmosphere, and their concentrations increase during the summer when the light intensity is greatest.

Considerable study on the microbial and chemical stability and degradation of PAH in the aquatic environment has been conducted. In general, the low molecular weight molecules appear to biodegrade relatively rapidly while PAH containing more than three rings appear to be extremely stable. The first step in the microbial degradation process appears to be the formation of ortho-dihydrodiols which rapidly react to open the ring. PAH also appear to be light sensitive in aquatic systems, but the rate of degradation is difficult to determine experimentally since the vast majority of the compounds are adsorbed to particulate matter. Recent studies have shown that adsorption of many PAH compounds to sediments is a major transport process in aqueous systems. Studies in water treatment of municipal and industrial sewage indicate that about two-thirds of the PAH can be eliminated by sedimentation and biodegradation. If this secondary effluent is subjected to chemical treatment (chlorination or ozonation) the remaining PAH can be degraded.

II. EXPOSURE

A. Water

Based upon work by Basu and Saxena (1978) the average concentrations of BaP, carcinogenic PAH (BaP, benzo(j)fluoranthene, indeno(1,2,3-cd)-pyrene), and total PAH (above 3 compounds plus benzo(g,h,i)perylene, benzo-(b)fluoranthene, and fluoranthene) in U.S. drinking water are 0.55 ng/l, 2.1 ng/l, and 13.5 ng/l, respectively. No drinking water monitoring data on

other PAH compounds are available. The low con- centrations are somewhat a
reflection of the extremely low water solu- bilities of PAH compounds.
Slightly higher drinking water values have been reported in Europe (e.g. 3-5
ng/l carcinogenic PAH and 40-60 ng/l total PAH), but these differences will
have relatively negligible effects on the calculated daily intake values
through drinking water compared to other sources (U.S. EPA, 1979a).
Assuming that a human consumes approximately 2 liters of water per day, the
daily intake of PAH via drinking water would be:

0.55 ng/l x 2 liters/day = 0.0011 µg/day (BaP)
2.1 ng/l x 2 liters/day = 0.0042 µg/day (carcinogenic PAH)
13.5 ng/l x 2 liters/day = 0.0270 µg/day (total PAH)

B. Food

It is difficult to evaluate the human dietary intake of PAH through
foods since the amount not only depends on the food habits of the individual
and the style of cooking, but it also depends upon the origin of the foods.
In order to provide a reasonably accurate estimate of the PAH dietary in-
take, average concentrations of PAH in representative food items would have
to be available. Unfortunately, as of this date, these data have not been
generated. However, examination of the available food monitoring data does
suggest that a typical range of concentrations for PAH and BaP are 1.0-10.0
ppb and 0.1-1.0 ppb, respectively (U.S. EPA, 1979a). Combining these ranges
with average total daily food consumption by man from all types of foods of
1600 g/day, the following estimates of dietary PAH and BaP intake are poss-
ible:

0.1 - 1.0 ppb x 1600 g/day = 0.16 - 1.6 µg/day (BaP)
1.0 - 10 ppb x 1600 g/day = 1.6 - 16 µg/day (PAH)

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factors for the edible portion of all aquatic organisms consumed by Americans. These range from 120 to 24,000, and are based on the octanol-/water partition coefficients for each compound.

C. Ambient Air

It is not possible to determine the average intake of PAH from inhalation of ambient air in the United States because the monitoring data have focused mostly on BaP concentrations. However, by making some assumptions, it is possible to provide estimates that are reasonably close to probable actual values. Using the 1974-1975 Los Angeles monitoring data from Gordon (1976), the relative amounts to carcinogenic PAH and total PAH compared to the average BaP concentration are presented below.

	BaP	Carcinogenic PAH	Total PAH
Ambient conc. ng/m^3	0.5-2.9	2.0	10.9
Inhalation intake, micrograms/day[a]	0.0095-0.0435	0.038	0.207

[a]Assumed average air breathed per day was 19 m^3

III. PHARMACOKINETICS

There are no data available concerning the pharmacokinetics of PAH in humans. Nevertheless, it is possible to make limited assumptions based on the results of animal studies conducted with several PAH, particularly BaP. The metabolism of PAH in human and animal tissues has been especially well-studied, and has contributed significantly to an understanding of the mechanisms of PAH-induced cancer.

A. Absorption

Regardless of the route of exposure, it can be demonstrated in laboratory animals that PAH are readily absorbed across all epithelia which are in contact with the external environment (Rees, et al. 1971; Kotin, et al. 1969; Vainio, et al. 1976). The fact that PAH are generallly high lipid-soluble neutral molecules greatly facilitates their passage through the predominantly lipid-like cell membranes of animals, including man.

B. Distribution

Upon reaching the bloodstream, PAH are rapidly distributed to most internal body organs (Kotin, et al. 1969; Bock and Dao, 1961; Dao, et al. 1959; Flesher, 1967). Under experimental conditions with laboratory animals, the route of exposure has little apparent influence on the tissue localization of PAH. Extensive localization in the fat and fatty tissues (e.g., breast) is observed (Bock and Dao, 1961; Schlede, et al. 1970 a,b) and suggests that these tissues may act as a chemical trap, creating a situation for sustained release of the unchanged substance. In pregnant rats, it is apparent that BaP and 7,12-dimethylbenz(a)anthracene, but probably not 3-methylcholanthrene, are capable of transplacental passage and localization in the fetus (Shendrikova and Aleksandrov, 1974).

C. Metabolism

PAH are metabolized by the microsomal mixed-function oxidase system, also known as aryl hydrocarbon hydroxylase. This enzyme system is readily inducible and is found in most mammalian tissues, although predominantly in the liver. In conjunction with various P-450 type cytochromes, this enzyme complex is involved in detoxification of many xeno-

biotics, but may also catalyze the formation of reactive epoxide metabolites, themselves leading to carcinogenesis. A second microsomal enzyme, epoxide hydrase, converts epoxide metabolites of PAH to vicinal glycols, a process which may also be of critical importance in the process of carcinogenesis.

Because of the importance of metabolic activation for the expression of carcinogenic effects by PAH, the chemical fate of many representative compounds in mammalian cells has been extensively explored (U.S. EPA, 1979a). By far the most widely studied of the PAH has been BaP, one of the principal carcinogenic products from the combustion of organic material. The metabolites of BaP (and all PAH) can be divided into a water-soluble and an organic solvent-soluble fraction. Components of the latter fraction are primarily ring-hydroxylated products, quinones, and labile epoxide intermediates. For BaP there are at least three dihydrodiols, three quinones, and four phenols which can be detected as positional isomers. The K-region (4,5-) and non-K-region (7,8-; 9,10-) epoxides are precursors of the corresponding vicinal diols, which are formed by the action of the epoxide hydrase enzyme. A subsequent oxidative attack by aryl hydrocarbon hydroxylase may convert the non-K-region diols to vicinal diol epoxides, one of which (7,8-diol-9,10-epoxide) is an ultimate carcinogenic form of BaP.

In the water-soluble fraction containing BaP metabolites are mainly conjugates of hydroxylated products with glutathione, glucuronic acid, and sulfate. This group of metabolies is tentatively regarded to be composed of non-toxic excretion products.

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The general scheme of metabolism for unsubstituted PAH closely parallels that for BaP, although several other major environmental PAH have not been studied. It is also evident that K-region derivatives of PAH may be preferred targets for conjugation and excretion, whereas non-K-region epoxides undergo further reductions and oxidative attack to form toxicologically important molecules. For PAH bearing alkyl substituents (e.g., DMBA, MCA), the primary metabolites formed are hydroxymethyl derivatives. Nevertheless, epoxidation reactions at K-region and non-K-region aromatic double bonds occur which are catalyzed by aryl hydrocarbon hydroxylase. Removal of activated intermediates occurs by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols.

D. Excretion

Over forty years ago, researchers recognized that various PAH were excreted primarily through the hepatobiliary system and the feces (Peacock, 1936; Chalmers and Kirby, 1940). However, the rate of disappearance of various PAH from the body, and the principal routes of excretion are influenced both by structure of the parent compound and the route of administration (Heidelberger and Weiss, 1959; Aitio, 1974a,b). Moreover, the rate of disappearance of a PAH (i.e., benzo(a)pyrene) from body tissues can be stimulated markedly by prior treatment with inducers of microsomal enzymes (e.g., benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene, 3-methylcholanthrene, chrysene) (Schlede, et al. 1970a,b). Likewise, it has been shown that inhibitors of microsomal enzyme activity, such as parathion and paraoxon, can decrease the rate of BaP metabolism in certain animal tissues (Weber, et al. 1976). From the available data concerning excretion of PAH in animals, it is apparent extensive bioaccumulation is not likely to occur.

IV. EFFECTS

A. Carcinogenicity

PAH were the first compounds ever shown to be associated with carcinogenesis. As of this date, carcinogenic PAH are still distinguished by several unique features: (1) several of the PAH are among the most potent carcinogens known to exist, producing tumors by single exposures to microgram quantities; (2) they act both at the site of application and at organs distant to the site of absorption; and (3) their effects have been demonstrated in nearly every tissue and species tested, regardless of the route of administration (U.S. EPA, 1979a). Among the more common PAH, at least one, BaP, is ubiquitous in the environment. In animals, PAH produce tumors which resemble human carcinomas. The demonstration that organic extracts of particulate air pollutants are carcinogenic to animals has raised concern over the involvement of PAH in human cancer formation (Hoffmann and Wynder, 1976).

Oral administration of PAH to rodents can result in tumors of the fore-stomach, mammary gland, ovary, lung, liver, and lymphoid and hematopoietic tissues (U.S. EPA, 1979a). Exposure to very small doses of PAH by inhalation or intratracheal instillation can also be an effective means of producing tumors of the respiratory tract. However, for both oral and intratracheal routes of administration, BaP is less effective than other PAH (e.g., DMBA, MCA) in producing carcinomas. However, BaP has a remarkable potency for the induction of skin tumors in mice that cannot be matched by any other environmental PAH. Therefore, caution must be exercised in considering the carcinogenicity of PAH as a class, or in using BaP as a representative example in evaluating the carcinogenic risk of PAH.

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The presence of PAH in the air, or as components of soot, tars, and oils, have long been associated with an excess incidence of cancer in human populations (U.S. EPA, 1979a,b). However, it has never been possible to study a population having exposure to PAH in the absence of other potential carcinogens, cocarcinogens, tumor initiators, or tumor promoters.

Convincing evidence from air pollution studies indicates an excess of lung cancer mortality among workers exposed to large amounts of PAH-containing materials such as coal gas, tars, soot, and coke-oven emissions (Kennaway, 1925; Kennaway and Kennaway, 1936, 1947; Henry, et al. 1931; Kuroda, 1937; Reid and Buck, 1956; Doll, 1952; Doll, et al. 1965, 1972; Redmond, et al. 1972, 1976; Mazumdar, et al. 1975; Hammond, et al. 1976; Kawai, et al. 1967). However, no definite proof exists that the PAH present in these materials are responsible for the cancers observed. Nevertheless, our understanding of the characteristics of PAH-induced tumors in animals, and their close resemblance to human carcinomas of the same target organs, suggests PAH pose a carcinogenic threat to man, regardless of the route of exposure.

B. Mutagenicity

The demonstration of mutagenicity in bacterial and mammalian cells by exposure to PAH is generally equated with the capability to induce tumor formation. This assumption is based on the participation of a common electrophilic metabolite in producing the carcinogenic/mutagenic event, and the common target site in the cell (i.e., DNA or other components of the genome) for the effect to be produced.

In recent years, considerable research effort has been directed at determining the mutagenicity of various PAH derivatives as a means of identifying structural features associated with the biological effect produced.

Working with bacterial mutants which can be reverted to histidine independence by a chemically-induced mutation, epoxides of carcinogenic PAH were shown to possess significant mutagenicity (U.S. EPA, 1979a). Further work with cultured mammalian cells established that carcinogenic PAH can produce forward mutations when a drug metabolizing enzyme system is available (Huberman and Sachs, 1974, 1976).

Numerous attempts have been made to correlate exposure to PAH with the induction of chromosomal aberrations. Although variations in chromosome number and structure accompany PAH-induced tumors in rodents, it is not clear whether these changes are consistently observable (U.S. EPA, 1979a,b). No evidence in the published literature has been found to indicate that PAH may produce somatic mutations in the absence of neoplastic transformation.

C. Teratogenicity

PAH are not generally regarded to have significant teratogenic activity. BaP showed no effect on the developing embryo in several mammalian and non-mammalian species (Rigdon and Rennels, 1964; Rigdon and Neal, 1965). In contrast, DMBA and its hydroxymethyl derivatives apparently are teratogenic in the rat, but only at high doses (Currie, et al. 1970; Bird, et al. 1970).

D. Other Reproductive Effects

Little additional information is presently available to indicate whether PAH present a significant hazard to reproductive success. Furthermore, effects on the fetus which may be due to maternal toxicity or experimental conditions (e.g., injection vehicle, stress) have not been adequately dissociated from true embryotoxicity or teratogenesis.

E.   Chronic Toxicity

Little attention has been paid to the non-carcinogenic effects of exposure to PAH. Nevertheless, it is known that tissues of the rapidly proliferating type (e.g., intestinal epithelium, bone marrow, lymphoid organs, testis) seem to be the preferred targets for PAH-induced cytotoxicity (U.S. EPA, 1979). This action is probably due to a specific attack on DNA of cells in the S phase of the mitotic cycle (Philips, et al. 1972).

Acute and chronic exposure to various carcinogenic PAH has resulted in selective destruction of hematopoietic and lymphoid elements, ovotoxicity and anti-spermatogenic effects, adrenal necrosis, and changes in the intestinal and respiratory epithelia (U.S. EPA, 1979a). For the most part, however, tissue damage occurs at dose levels that would also be expected to induce carcinomas, and thus the threat of malignancy predominates in evaluating PAH toxicity. For the non-carcinogenic PAH, there is a shortage of available data concerning their involvement in toxic responses.

V.   AQUATIC TOXICITY

A. Acute Toxicity

Standard toxicity determinations for freshwater or marine organisms have not been conducted for any PAH. The marine worm, Neanther arenaceodenta, was exposed to crude oil extracts, and LC_{50} values for various PAH ranged from 300 to 1,000 µg/l (Neff, et al. 1976a,b). A 90 percent lethality, determined from photodynamic response, was obtained for the protozoa, Paramecium caudatum at an for anthracene concentration of 0-1 µg/l in one-hour exposures (Epstein, 1963). Bluegill sunfish (Lepomis macrochirus) displayed an 87% mortality at concentration of 1,000 µg/l benzo-a-anthracene.

B. Chronic

Standard toxicity studies using either freshwater or marine organisms have not been conducted on any PAH. A six-month study of benzo-(a)pyrene on the bluegill sunfish (Lepomis macrochirus) produced 87 percent mortality at a concentration of 1,000 ug/l (Brown, et al. 1975).

C. Plants

Studies of the effects of PAH on freshwater or marine plants could not be located in the available literature.

D. Residues

In short-term modeling of freshwater ecosystem studies, three-day bioconcentration factors for benzo(a)pyrene of 930, 5,258, 11,536, 82,231, and 134,248 were obtained for the mosquito-fish (Gambusia affinis), the algae Oedogonium cardiacum, the mosquito Culex pipiens quinquefasciatus, the snail Physa sp., and cladoceran Daphnia pulex, respectively (Lu, et al. 1977). For anthracene, a 1-hour bioconcentration factor of 200 was obtained for Daphnia magna (Herbes, 1976). For marine molluscs, bioconcentration factor values ranged from 8.2 for the clam (Rangia cuneata) (Neff, et al. 1976a) to 242 for the eastern oyster (Crassostrea virginica) (Couch, et al., in press).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health and aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have not gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

To date, one recommended standard for PAH as a class has been developed. The World Health Organization (1970) recommends a concentration of PAH in water not to exceed 0.2 µg/l. This recommended standard is based on the composite analysis of six PAH in drinking water: (1) fluoranthene, (2) benzo(a)pyrene, (3) benzo(g,h,i)perylene, (4) benzo(b)-fluoranthene, (5) benzo(k)fluoranthene, and (6) indeno(1,2,3-cd)pyrene.

In the occupational environment, a Federal standard has been promulgated for coke oven emissions, based primarily on the presumed effects of the carcinogenic PAH contained in the mixture as measured by the benzene soluble fraction of total particulate matter. Similarly, the American Conference of Governmental Industrial Hygiensists recommends a workplace exposure limit for coal tar pitch volatiles, based on the benzene-soluble fraction containing carcinogenic PAH. The National Institute for Occupational Safety and Health has also recommended a workplace criterion for coal tar products (coal tar, creosote, and coal tar pitch), based on measurements of the cyclohexane extractable fraction. These criteria are summarized below:

Substance	Exposure Limit	Agency
Coke Oven Emissions	0.150 mg/m^3, 8-hr. time-weighted average	U.S. Occupational Safety and Health Administration
Coal Tar Products	0.1 mg/m^3, 10-hr. time-weighted average	U.S. National Institute for Occupational Safety and Health
Coal Tar Pitch Volatiles	0.2 mg/m^3, (benzene soluble fraction) 8-hr. time-weighted average	American Conference of Governmental Industrial Hygienists

Based on animal bioassay data, and using the "one-hit" model, the U.S. EPA (1979a) has set draft ambient water quality criteria for BaP and dibenz(a,h)anthracene (DBA) which will result in specified risk levels of human cancer as shown in the table below.

BaP

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria ng/l		
	$\underline{0}$ $\quad\underline{10}^{-7}$	$\underline{10}^{-6}$	$\underline{10}^{-5}$
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0 $\quad$ 0.275	2.75	27.5
Consumption of fish and shellfish only.	0 $\quad$ 1.25	12.5	125

DBA

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria ng/l		
	$\underline{0}$ $\quad\underline{10}^{-7}$	$\underline{10}^{-6}$	$\underline{10}^{-5}$
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0 $\quad$ 0.43	4.3	43
Consumption of fish and shellfish only.	1.96	19.6	196

B. Aquatic

Criteria have not been proposed for the protection of aquatic organisms (U.S. EPA, 1979a).

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Pyridine

Health and Environmental Effects

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DISCLAIMER

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PYRIDINE

Summary

Pyridine has not shown carcinogenic effects following repeated subcutaneous administration to rats; the compound did not show mutagenic activity in the Ames _Salmonella_ assay.

A single study has indicated that pyridine produced developmental abnormalities when administered to chicken embryos.

Chronic exposure to pyridine produces CNS disturbances and may produce adverse hepatic and renal effects.

Pyridine has been shown to be toxic to freshwater fish at concentrations ranging from 100,000 to 1,580,000 $\mu g/l$. For freshwater invertebrates, toxic concentrations of pyridine range from 575,000 to 2,470,000 $\mu g/l$.

I. INTRODUCTION

Pyridine (CAS number 110-86-1) is a colorless liquid possessing a sharp, penetrating odor. It has the following physical properties:

Formula:	C_5H_5N
Molecular Weight:	79.1
Melting Point:	$-42^{\circ}C$
Boiling Point:	$115.3^{\circ}C$
Density:	0.982
Vapor Pressure:	10 mm Hg at $13.2^{\circ}C$ (Sax, 1975)
Solubility:	miscible with water, alcohol, ether, and other organic solvents (Windholz, 1976)

Pyridine is a weak base and forms salts with strong acids. It is used as a solvent for anhydrous mineral salts, in various organic synthetic preparations, and in analytical chemistry (Windholz, 1976). The estimated annual production of pyridine is in excess of 60 million pounds (Federal Register 43:16688, April 19, 1978).

II. EXPOSURE

A. Water

Pertinent data could not be located in the available literature.

B. Food

Reported levels of pyridine in foods include: from 0.02 to 0.12 ppm, ice cream; 0.4 ppm, baked goods; 1.0 ppm, non-alcoholic beverages; 0.4 ppm, candy. Pyridine has also been found to occur naturally in coffee and tobacco (Furia, 1975).

C. Inhalation

Pyridine may be produced and released during the combustion of coke and as a combustion product in cigarette smoke (Graedel, 1978).

The major release of pyridine is from emissions from manufacturing and chemical processes. Based on total annual production, the U.S. EPA (1976) has estimated a significant potential emission of pyridine during manufacture.

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

Absorption of pyridine occurs through the respiratory and gastro-intestinal tracts, but probably not through the skin (Gosselin, et al. 1976).

B. Distribution

Pertinent data could not be located in the available literature.

C. Metabolism and Excretion

Pyridine may be partly excreted unchanged or may be methylated at the N-position (Patty, 1963) and excreted as N-methyl pyridinium hydroxide, its chief metabolite (Browning, 1965). Methylation occurs in mice but not in rats, and it may occur to some extent in man   The fate of the majority of absorbed pyridine is not known (Browning, 1965).

IV. EFFECTS

A. Carcinogenicity

Subcutaneous injection of pyridine at levels of 3 to 100 mg/kg twice weekly for a year did not produce tumors in rats (Mason, et al. 1971).

B. Mutagenicity

Pyridine did not show mutagenic effects with activation in the Ames Salmonella assay (Commoner, 1976).

C. Teratogenicity

Pyridine caused chick embryo abnormalities in one limited study (Federal Register 43:16688, April 19, 1978).

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D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

Prolonged daily exposure to pyridine at levels from 6 to 12 ppm causes mild central nervous system (CNS) disturbances in workers, while exposure from 15 to 330 ppm causes insomnia, nervousness, and low-back or abdominal pain accompanied by frequent urination (Gosselin, et al. 1976).

In animals, the major effects of repeated feeding of pyridine are hepatic and renal injury (Patty, 1963). Chronic exposure to 10 or 50 ppm pyridine vapors causes increased liver/body weight ratios in rats (ILO, 1971).

F. Other Relevant Information

Symptoms in humans associated with inhalation or ingestion of pyridine are CNS depression, and liver and kidney damage (Federal Register 4:16688, April 19, 1978; Gosselin, et al. 1976; Sax, 1975; ILO, 1971). Vapors are also irritating to eyes, skin, and nasal membranes (ACGIH, 1977; Sax, 1975). Skin eruptions induced by pyridine may be provoked by exposure to light (Arena, 1974). Ingestion of pyridine causes CNS depression, heart and gastrointestinal distress, fever, and, at high doses, death; and may stimulate bone marrow production of platelets in low doses (ACGIH, 1977; Gosselin, et al. 1976). Death may be due to either hepatic or renal damage, or from pulmonary injury (Gosselin, et al. 1976; ACGIH, 1977).

Exposure to vapors of pyridine from 1,250 to 10,000 ppm for 1 to 7 hours did not cause mortality in rats, but a 0.1 percent diet of pyridine induced rapid weight loss and death in two weeks (ILO, 1971).

V. AQUATIC TOXICITY

A. Acute Toxicity

McKee and Wolf (1963) have reviewed the effects of pyridine on several aquatic organisms. The freshwater minnow, bleak (Alburnus lucidus), was the most sensitive species tested with threshold toxicities ranging from 100,000 to 160,000 µg/l. Tests with the freshwater mosquitofish (Gambusia affinis) revealed a 96-hour LC_{50} value of 1,300,000 µg of pyridine per liter of turbid water. Orange-spotted sunfish (Lepomis humilis) were killed in one hour from exposure to pyridine at concentrations ranging from 1,480,000 to 1,580,000 µg/l, while goldfish (Carassius auratus) were killed after 10 to 30 hours' exposure to pyridine. Verschueren (1979) has reported a 24-hour LC_{50} value of 1,350,000 µg/l for mosquitofish exposed to pyridine.

Dowden and Bennett (1965) demonstrated a 48-hour LC_{50} value of 2,114,000 µg/l for Daphnia magna exposed to pyridine. McKee and Wolf (1963) reported a threshold effect of 40,000 µg/l for Daphnia sp. Canton and Adema (1978) determined 48-hour LC_{50} values ranging from 1,130,000 to 1,755,000 µg/l for Daphnia magna, and 48-hour LC_{50} values of 575,000 and 2,470,000 µg/l for Daphnia pulex and Daphnia cucullata, respectively.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

C. Other Relevant Information

Thomas (1973) reports that pyridine exposure levels of 5,000 µg/l impart an off-flavor to fish flesh.

VI. EXISTING GUIDELINES AND STANDARDS

A.   Human

The 8-hour, time-weighted-average occupational exposure limit for pyridine recommended by the American Conference of Governmental Industrial Hygienists is 5 ppm (ACGIH, 1977).

B.   Aquatic

Based on 96-hour LC_{50} data, Hahn and Jensen (1974) have assigned pyridine an aquatic toxicity rating of from 100,000 to 1,000,000 µg/l.

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Quinones

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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QUINONE

Summary

Quinone has been reported to produce neoplasms, but insufficient data are available to assess its carcenogenic potential. Quinone was not mutagenic to <u>Orosophila</u> <u>melanogaster</u>, human leukocytes, nor <u>Neurospora</u>.

Quinone is very toxic to fish and plants. Exposure to humans causes conjunctival irritation and, in some cases, corneal edema, ulceration, and scarring; transient eye irritation was noted above 0.1 ppm. Quinone is highly toxic to mammals via the oral and inhalation route.

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I. INTRODUCTION

Quinone (p-Benzoquinone; Cas No. 106-51-4) is a yellow, crystalline solid with chlorine-like irritating odor. It has the following physical properties:

Formula:	$C_6H_4O_2$
Physical State:	large, yellow, monoclinic prisms
Molecular Weight:	108.09
Specific Gravity:	1.318 (20°C)
Melting Point:	112.9°C
Boiling Point:	sublimes
Vapor Pressure:	considerable; sublimes readily upon gentle heating (Patty,1967)

Quinone is soluble in alcohol, ether, and alkali; and slightly soluble in hot water. Quinone can be prepared by oxidation starting with aniline or by the reduction of hydroquinone with bromic acid. The compound has found wide application in the dye, textile, chemical, tanning, photography, and cosmetic industries primarily because of its ability to transform certin nitrogen-containing compounds into a variety of colored substances (Patty, 1967).

II. EXPOSURE

A. Water

Pertinent data could not be located in the availabe literature.

B. Food

Pertinent data could not be located in the available literature.

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C.   Inhalation

Because of its ability to sublime, quinone becomes an air
contaminant problem at the production site.

D.   Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A.   Absorption

Quinone is readily absorbed from the gastroenteric tract
and subcutaneous tissues (Patty, 1967). Sax, 1979, reports quinine
as capable of causing death or permanent injury due to the exposures
of normal use via absorption through oral and inhalation routes.
Quinone affects the eyes (Procter, 1978).

B.   Distribution

Pertinent data could not be located in the available literature.

C.   Mebalolism and Excretion

Quinone is partially excreted unchanged; but the bulk is
eliminated in conjugation with hexuronic, sulfuric, and other acids
(Patty, 1967).

IV. EFFECTS

A.   Carcinogenicity

Quinone has been reported to produce neoplasms but upon
review by the International Agency for Research on Cancer, it was
determined that there was insufficient data to conclude that it was
a carcinogen (IARC, 1977)

B.   Mutagenicity

Quinone did not produce mutagenic effects in studies with

Orosophila melanogaster and human leukocytes (Lueers and Obe, 1972).

Another study reported quinone as nonmutagenic to Neurospora

(Reissig, 1963).

C. Teratogenicity

Pertinent data could not be located in the available

literature.

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

Quinone has been reported to oxidize with the lens protein

SH groups in rabbits (Ikemota and Augusteyn, 1976). Chronic exposure

causes the gradual development of changes characterized as follows:

brownish discoloration of the conjunctiva and cornea confined to

the intrapalpebral fissure; small opacities of the cornea; and

structural corneal changes which result in loss of visual acuity

(Sterner, et al., 1947; Anderson and Oglesby, 1958).

F. Other Relevant Information

Acute exposure causes conjunctival irritation and, in

some cases, corneal edema, ulceration, and scarring; transient eye

irritation may be noted above 0.1 ppm and becomes marked at 1 to 2

ppm (AIHA, 1963). Ulceration of the cornea has resulted from one

brief exposure to a high concentration of the vapor of quinone, as

well as from repeated exposures to moderately high concentrations

(Patty, 1967). Absorption of large doses of quinone from the gas

troenteric tract or from subcutaneous tissues of animals induces

chronic convulsions, respiratory difficulties, drop in blood pres-

sure, and death by paralysis of the medullary centers (Patty, 1967).

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Oral rat LD50s have been reported for quinone ranging from 130 to 296 mg per kg body weight (Verschueren, 1977). Inhalation of quinone at concentrations ranging from 230 to 270 mg per cu.m. for 2 hrs was lethal to 100 percent of the test population of rats.

IV. AQUATIC TOXICITY

A. Acute Toxicity

Quinone has been reported to be toxic to invertebrate Daphnia at 0.4 ppm (Verschueren, 1977). Also, quinone has an LD50 for perch ranging from 5 to 10 mg/l (Verschueren, 1977).

B. Chronic Toxicity, Plant Effects, and Residues

Quinone inhibits photosynthesis in the fresh water algae S. capricornutum (Gidding, 1979), decreases chlorophyll flourescence and cyclosis (protoplasmic streaming) of Nitella cells (Apartsin, et al, 1979; Stom, 1977; Stom and Kuzevania, 1976; Stom and Rogozina, 1976), and inhibits carbon metabolism in Ghlorella pyrenoidosa (Printavu, 1975).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The 8-hour, time-weighted average occupational exposure limit for quinone has been set in the United States at a concentration of 0.1 ppm and in the U.S.S.R. at a concentration of 0.01 ppm (Verschueren, 1977).

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No. 152

Resorcinol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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RESORCINOL

Summary

Resorcinol, 1,3-dihydroxybenzene, is a phenolic compound. Resorcinol is weakly antiseptic and resorcinol compounds are used in pharmaceuticals and hair dyes for human use. Major industrial uses are as adhesives in rubber products and tires, wood adhesive resins, and as ultraviolet absorbers in polyolefin plastics. Resorcinol is also a byproduct of coal conversion and is a component of cigarette smoke. Thus, substantial opportunity exists for human exposure.

Many phenolic compounds, including resorcinol, are strong mitotic spindle poisons in plants. This evidence of mutagenic activity and the strong oncogenic activity in plants have not been adequately tested in animals to provide an understanding of the processes. In animals the only cocarcinogenic activity (in cigarette smoke condensate) demonstrated has been as a protective agent against benzo(a)pyrene carcinogenicity.

Resorcinol has been demonstrated to result in chronic toxicity: reducing growth rate in an insect species and causing chronic health complaints from workers in a tire manufacturing plant.

Acute toxicity through oral, eye, skin penetration, and skin irritation has been demonstrated by all tests. Values vary in the literature and are inadequate to draw a quantitative conclusion. Resorcinol has also been shown to be acutely toxic to both freshwater and marine aquatic organisms in 96-hour LC_{50} tests.

No standards or guidelines exist for resorcinol. ACGIH's Committee on Threshold Limits has proposed a TLV of 5 ppm but has not finalized that recommendation. Industry has suggested this value is lower than is required for safety, citing existing workplace levels of 9.6 ppm without worker complaint or evidence of acute or chronic toxicity.

I. INTRODUCTION

Resorcinol is a phenolic compound (molecular weight, 110.1; boiling point, 276°C; melting point, 110.0°C). Synonyms are m-dihydroxybenzene, 1,3-benzenediol, 3-hydroxyphenol, and resorcin. Resorcinol occurs as white or nearly white needle-shaped crystals or powder. It has a faint, characteristic odor and a sweetish taste with a bitter aftertaste. One gram is soluble in 1 ml of water and in 0.1 ml of alcohol.

Resorcinol is a weak antiseptic and is used in antiseptics, keratolytic disease treatments and fungicides (Wilson, et al. 1977). Major uses of resorcinol are: in tires and other rubber products; wood adhesive resins; as an ultraviolet absorber in polyolefin plastics; as an intermediate in dye manufacture (especially hair dyes); and in the production of synthetic tanning agents, explosives, and specialty adhesives. The tire and rubber industries accounted for 43 percent of the use of resorcinol in 1974, primarily as adhesives in fabricating belting, rubberized hose, and rubberized textile sheets (Stanford Research Institute, 1975).

Resorcinol is expected to be a component of various waste streams from coal conversion facilities. The potential for removal through existing waste treatment processes is currently under assessment (Herbes and Beauchamp, 1977).

II. EXPOSURE

Resorcinol is used in substantial quantities in industry and frequently in small quantities in the home. Although the potential for human exposure exists, very little exposure information is available. The Koppers Company, Inc., Monroeville, Pennsylvania, is the major supplier of resorcinol in the United States. They report substantial testing of the plant environment indicating resorcinol concentration up to 9.6 ppm in ambient air (Flickinger, 1976).

Resorcinol is currently sold and transported as a solid, although the Koppers Company reports increasing inquiries regarding bulk shipments of molten resorcinol. They indicate that this would increase the opportunity for industrial and public exposure to the compound (Flickinger, 1976).

In an epidemiological study of rubber workers at a hexamethylenetetramine-resorcinol (HR) resin system tire manufacturing plant, all environmental samples in the study were less than 1 mg/m^3 (Gamble, et al. 1976).

Resorcinol has been shown to be present in cigarette smoke and is a component of the weakly acidic fraction of cigarette smoke condensate which has been shown to have tumor-promoting capability (Schlotzhauer, et al. 1978).

III. PHARMACOKINETICS

_ Despite the presence of resorcinol and resorcinol compounds in numerous pharmaceutical preparations, no specific information on the metabolism, distribution, absorption, or excretion of resorcinol was found in the available literature.

IV. EFFECTS

A. Carcinogenicity

The available data dealing with the potential carcinogenicity of resorcinol are at this time inadequate to formulate a clear understanding of resorcinol's oncogenic potential. In a study of commonly used cutaneous agents, Stenbäck (1977) showed no tumor induction in rabbits and mice from topically applied resorcinol. Resorcinol was selected because of its presence in hair dyes.

Van Duuren and Goldschmidt (1976), in a study of 21 tobacco smoke components, found that resorcinol reduced the carcinogenic potential of benzo(a)pyrene (BaP) in dermal application to mice. Thus, fewer tumors were

induced by BaP in the presence of resorcinol, indicating possible inhibition of carcinogenic activity.

Substantial evidence appears to exist for the oncogenic activity of resorcinol in plants. Anderson (1973) reports that the "strong carcinogenicity" of resorcinol tested in Nicotiana hybrids suggests that "an oncogenic reactivity of phenols is common to plant and animal tissues but with differences in strength of reaction to a derivative in a given system".

B. Mutagenicity

Dean (1978) reports that most phenolic compounds including resorcinol are mitotic spindle poisons in plant tissues. He further reports that considering the severity of effects on plant chromosomes that it is surprising that in vivo plant and animal tests have not been done to determine their clastogenic properties.

By micronucleus test, Hossack and Richardson (1977) were unable to find evidence of mutagenicity in resorcinol or a number of other hair dye constituents tested.

The Ames assay for resorcinol was negative in a test of commonly used cutaneous agents (Stenbäck, 1977).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

In a study of chronic toxicity effects on the black cutworm, Agrotis epsilon, Reese and Beck (1976) found no significant correlation between resorcinol concentration and pupation or survival but found correlation with body weight at various stages of development. They report that resorcinol is the only compound among those tested which had "no adverse effect on any of the nutritional indices and yet reduced growth. It is also the only com-

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pound which inhibited growth but did not inhibit pupation." They hypothesized that resorcinol may act through a temporary inhibition of ingestion but that the insects continued to eat regularly, allowing pupation on a normal schedule (Reese and Beck, 1976).

In the epidemiological study of the HR resin system tire manufacturing plant, Gamble, et al. (1976) reported that HR exposed workers consistently showed an excess of respiratory symptoms and that there was a consistent association of alcohol consumption with increased incidence of symptoms. The reported symptoms included rash, itch, difficult breathing at work, cough, chest tightness, burning eyes, running nose, and burning sensation in the heart region.

E. Acute Toxicity

With one exception, all acute toxicity data in the readily available literature are supplied by Flickinger (1976) for the Koppers Company, the primary manufacturer and supplier of resorcinol in the United States. Lloyd, et al. (1977) independently reported the LD_{50} for acute oral toxicity to be 370 mg/kg for resorcinol.

In a review of the industrial toxicology of the benzenediols, Flickinger (1976) reports various acute toxicity data for resorcinol. A summary of relevant results follows:

An acute oral LD_{50} for resorcinol was reported by Flickinger (1976) as 0.98 gm/kg in the rat. Rats dying during the period showed hyperemia and distension of the stomach and intestines. Surviving rats showed normal weight and no gross lesions at necropsy.

The LD_{50} for dermal application in the rat was 3.36 gm/kg. At higher levels, resorcinol produced skin necrosis. At 1.0 gm/kg levels,

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moderate to severe irritation was followed in 24 hours by slight hyperkera-
tosis. Surviving rats showed reduced weight but no internal gross lesions
upon necropsy.

Flickinger (1976) reported that resorcinol is a severe eye irri-
tant (0.1 gm in eye of male, albino rabbits). No recovery was seen in the
14-day follow-up period with all exposed individuals exhibiting keratoconus
and pannus formation.

Resorcinol is a primary skin irritant. Contact with 0.5 gm of re-
sorcinol on intact and abraided skin produced moderate irritation on intact
skin and varying reactions including necrosis on abraided skin.

Inhalation of up to 2,800 mg/m^3 of resorcinol aerosol for 8
hours resulted in no observable toxic effects to the rats (Flickinger, 1976).

V. AQUATIC TOXICITY

The possibility that resorcinol may be present in some quantity in coal
conversion process effluents requires further investigation as to the feasi-
bility of control technology. Herbes and Beauchamp (1977) compared toxic
interactions of two coal conversion effluents, resorcinol and 6-methylquina-
line. With Daphnia magna as a test species, they found mixtures of the two
compounds to be less toxic than either pure compound tested alone. They re-
port a 48-hour LC_{50} for resorcinol alone to be 1.28 mg/l.

Curtis, et al. (1979) reported the acute toxicity of resorcinol to
freshwater and saltwater organisms. In freshwater, the LC_{50} values for
fathead minnow are as follows: 24 hours, 88.6 mg/l; 48 hours, 72.6 mg/l;
and 96 hours, 53.4 mg/l. In saltwater, the LC_{50} values for Palaemonetes
pugio or Penaeus setiferus are: 24 hours, 169.5 mg/l; 48 hours, 78.0 mg/l;
and 96 hours, 42.4 mg/l. Thus, resorcinol was found to be toxic to aquatic
life in both freshwater and saltwater.

VI. EXISTING GUIDELINES AND STANDARDS

There are no OSHA regulations, NIOSH recommendations, or other guidelines concerning resorcinol. In 1974, ACGIH's Committee on Threshold Limits proposed a TLV for resorcinol of 5 ppm. Flickinger (1976) reports of current industrial 8-hour workday exposures at 9.6 ppm "without signs of intoxication or skin or respiratory irritation" and recommends TLV industrial exposures of "at least 10 ppm, perhaps even 20 ppm or higher". ACGIH has not issued a formal TLV for resorcinol.

Information regarding existing guidelines and standards to protect aquatic life from the effects of resorcinol was not found in the available literature.

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Selenium

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.   20460

APRIL 30, 1980

153-1

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SELENIUM

SUMMARY

Human daily intake of selenium has been estimated at 50 to 150 µg/day. While selenium is an essential nutrient for humans and other species, it is toxic in excessive amounts. Selenium poisoning produces symptoms in man similar to those produced by arsenic. Although it has been shown to produce tumors in animals, the Food and Drug Administration, the International Agency for Research on Cancer and the National Academy of Science have concluded that the available animal data are insufficient to allow an evaluation of the carcinogenicity of selenium compounds.

The data base for selenium for aquatic life is quite limited. No chronic data are available for marine fish. Selenium does not bioconcentrate to a great extent in freshwater species, indicating that tissue residues should not be a hazard to freshwater organisms. This information is not available for marine organisms.

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SELENIUM

I.   INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Selenium (U.S. EPA, 1979).

Selenium (Se; atomic weight 78.96) is a naturally occurring element which reacts with metals to form ionic selenides with a valence of minus 2, and with most other chemials to form covalent compounds.   It may assume any of several valence states ranging from minus 2 to plus 6. Selenium is used in photocopying, the manufacture of glass, electronic devices, pigments, dyes and insecticides (Dept. Interior, 1974).   It is also used in veterinary medicine (U.S. EPA, 1979) and in antidandruff shampoos (Cummings and Kimura, 1971).   The major source of selenium in the environment is the weathering of rocks and soils (Rosenfeld and Beath, 1964) but human activities contribute about 3,500 metric tons per year (U.S. EPA, 1975a). Selenium is an essential nutrient for humans and other species (Schroeder, 1970).

II.   EXPOSURE

Selenium is not present in measurable quantities in most U.S. drinking water supplies.   Of 3,676 residences located in 35 geographically dispersed areas, only 9.96 percent of the samples had selenium levels above the detection limits of 1 μg/l (Craun, et al. 1977).   However, in seleniferous areas of South Dakota, levels of 50 to 330 μg/l were measured in drinking waters (Smith and Westfall, 1937). Sewage plant effluents may contribute to the selenium content of water; as much as 280 μg/l have been reported in raw sewage, 45 μg/l in primary effluent, and 50 μg/l

in secondary effluent (Baird, et al. 1972). Selenium concentrations in plants depend largely on the concentration in the soil where the plants are grown. High selenium concentration in vegetation is transmitted to other food sources, e.g., meats and eggs. The EPA (1979) has estimated the weighted average bioconcentration factor for selenium to be 18 for consumed fish and shellfish. Zoller and Reamer (1976) reported that most urban regions have concentrations of particulate selenium ranging from 0.1 to 10 ng/m^3.

III. PHARMACOKINETICS

A. Absorption

Selenium appears to be effectively absorbed by the gastrointestinal tract. Thomson and Stewart (1974) reported absorptions of 70, 64, and 44 percent for sodium selenite in three young women. Data from rats are similar with absorptions ranging from 81 to 97 percent for a number of organic selenium compounds and sodium selenite (Thomson and Stewart, 1973; Thomson, et al. 1975). The literature contains no information on absorption by inhalation or dermal exposures (National Research Council, 1976).

B. Distribution

The primary disposition sites for selenium in the body are the liver, kidney, spleen, and middle and lower sections of the small intestine (U.S. EPA, 1979). Based on the work of Kincaid, et al. (1977) it is apparent that tissue concentration levels of selenium can be affected both by dose and normal dietary intake, although the primary deposition sites remain the same.

C. Metabolism

Selenium is an essential element and at nutritional levels it is incorporated into specific functional proteins; at higher concentrations, it is substituted for sulfur in sulfur-containing compounds. Selenium analogs are often less stable than sulfur compounds, and this lability may be the basis of toxicity (Stadtman, 1974). Selenite and selenate are methylated by mammalian tissues in an apparent detoxification process. Mouse liver, lung and kidney (Ganther, 1966) are active in methylation, but muscle, spleen, and heart have little activity.

D. Excretion

Thomson and Stewart (1974) studied selenium excretion by feeding three women selenite. It was apparent that the primary routes of excretion were in the feces and urine, with little loss through the skin or lungs.

IV. EFFECTS

A. Carcinogenicity

Only six studies have been performed to specifically investigate whether selenium is carcinogenic. From these studies there is no conclusive evidence that selenium has induced tumors in the test animals. The Food and Drug Administration has declared that selenium poses no carcinogenic risk (Food and Drug Administration, 1973).

B. Mutagenicity

Selenium has been shown to affect the genetic process in barley (Walker and Ting, 1967) and in <u>Drosophila</u> <u>melanogaster</u> (Ting and Walker, 1969; Walker and Bradley, 1969). However, these

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ana other genotoxic effects are not true mutagenic effects. There is no study in which a true mutagenic activity for selenium has been demonstrated.

C. Teratogenicity

The consumption of seleniferous diets interfered with the normal development of the embryo in many mammalian species, including rats, pigs, sheep and cattle (U.S. EPA, 1979). Robertson (1970) suggested that selenium may be a teratogen in man from the examination of the older literature which correlated malformed babies and the consumption of toxic grains by people in Columbia.

D. Other Reproductive Effects

Vesce (1947) noted changes in endocrine glands, especially the ovaries, following oral administration of 5 to 12.5 mg sodium selenide to guinea pigs over two periods of 20 days.

E. Chronic Toxicity

Chronic effects from prolonged feeding of diets containing added selenium in amounts of 5 to 15 µg/g include liver damage in the form of atrophy, necrosis, cirrhosis, and hemorrhage, and marked and progressive anemia in some species (Fishbein, 1977). In man hepatic necrosis has not been observed following chronic exposure; however, lassitude, loss of hair, discoloration and loss of fingernails were symptoms (Beath, 1962).

F. Other Relevant Information

The essentiality of selenium for several animals has been known since the 1950's (Ganther, 1970; Schwarz, 1961) with selenium deficiency resulting in white muscle disease in ruminants, hepatic degeneration and peridontal disease in other mammals.

Synergism/antagonism exists between the actions of selenium and other metals such as arsenic, mercury, cadmium, silver and thallium (Diplock, 1976).

V.   AQUATIC TOXICITY

A.   Acute Toxicity

Cardwell, et al. (1976) exposed 6 species of freshwater fish to selenium dioxide and observed the 96-hour LC_{50} values to range from 2,060 to 28,500 μg/l.   The 96-hour LC_{50} values for fathead minnow fry and juveniles are 2,060 and 5,200 μg/l, respectively, indicating an apparent decrease in toxicity with age.   With the invertebrates Daphnia magna and scud, the LC_{50} values are 430 and 318 μg/l respectively (U.S. EPA, 1978; Adams, 1976).

The 96-hour LC_{50} values for marine species are 6,710 μg/l for the sheephead minnow (U.S. EPA, 1978) and 600 μg/l for mysid shrimp (U.S. EPA, 1978).

B.   Chronic Toxicity

No pertinent data are available on the chronic toxicity of selenium to freshwater organisms (U.S. EPA, 1979).   The only data available in marine species is that of the mysid shrimp (Mysidopsis bahia).   It has been exposed to selenium for its life cycle and the chronic value is 135 μg/l.

C.   Plant Effects

Selenium is toxic to two freshwater algal species, Chlorella vulgaris and Haematoccus cupensis, with growth being retarded at 50 μg/l (Hutchinson and Stokes, 1975).   For the saltwater alga, Skeltonema costatum, the 96-hour EC_{50} values for

chlorophyll a and cell numbers are 7,930 and 8,240 µg/l, respectively (U.S. EPA, 1978).

D. Residues

Bioconcentration factors have been determined for the rainbow trout, fathead minnow and bluegill. These factors range from 2 to 20 (Adams, 1976; U.S. EPA, 1978). The tissue half-life for the bluegill is between 1 and 7 days (U.S. EPA, 1978). These results show that tissue accumulation of selenium should not present a hazard to freshwater aquatic organisms.

No residue data are available for marine species (U.S. EPA, 1979).

VI. EXISTING GUIDELINES

A. Human

The U.S. Environmental Protection Agency (1975b) has established the maximum permissible level of selenium at 0.01 mg/l for U.S. drinking waters. A time-weighted average concentration threshold limit value (TLV) of 0.2 mg/m^3 has been established by the American Conference of Government Industrial Hygienists (ACGIH, 1977). The minimum toxic dose for selenium has been calculated to be 16.1 mg/day. The U.S. EPA (1979) draft water criterion for selenium is 10 µg/l. As a result of public comments received, additional review and consideration of the recommended criterion is required.

B. Aquatic

For selenium in freshwater, the draft criterion to protect aquatic life is 9.7 µg/l as a 24-hour average and the concentration should not exceed 22 µg/l at any time (U.S. EPA, 1979). In saltwater the criterion is 4.4 µg/l as a 24-hour average and the concentration should not exceed 10 µg/l at any time.

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SELENIUM

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Silver

Health and Environmental Effects

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APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health
and environmental hazards from exposure to the subject chemi-
cal. The information contained in the report is drawn chiefly
from secondary sources and available reference documents.
Because of the limitations of such sources, this short profile
may not reflect all available information including all the
adverse health and environmental impacts presented by the
subject chemical. This document has undergone scrutiny to
ensure its technical accuracy.

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SILVER

SUMMARY

While metallic silver in the zero valence state is not
considered to be toxic, most of its salts are toxic to a
large number of organisms. Silver salts can combine with
certain biological molecules and subsequently alter their
properties. Upon ingestion, many silver salts are absorbed
in the human circulatory system and deposited in various body
tissues, resulting in generalized or sometimes localized gray
pigmentation of the skin and mucous membranes known as argy-
ria. Silver has not been shown to be a carcinogen (except by
the mechanism of solid state tumorigenisis); however, there
is some evidence that silver salts can effect the growth of
tumors. The acceptable daily intake for silver has been de-
termined to be 1.6 mg per day for a 70 kg man.

Silver is acutely lethal to aquatic species in the µg/l
range. In terms of acute lethality, <u>Daphnia</u> <u>magna</u> appears to
be the most sensitive species, with a 48-hour EC_{50} of 1.5
µg/l. At levels as low as 0.17 µg/l, silver caused premature
egg hatching and reduced fry growth in fathead minnows.

SILVER

I.   INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Silver (U.S. EPA, 1979).

Silver (Ag; atomic weight 107.87) is a white ductile metal occuring naturally in the pure form and in ores. Silver can exist in two valence states, Ag^+ and Ag^{++}. The solubility of common silver salts varies greatly, with silver nitrate having a solubility of 2.5×10^9 µg/l and silver iodide having a solubility of 30 µg/l (Windholz, 1976). Many silver salts are light-sensitive. Water or atmospheric oxygen have no effect on metallic silver; however, ozone, hydrogen sulfide, and sulfur react with it. The principle uses of silver are in photographic materials, electroplating, dental alloys, solder and brazing alloys, paints, jewelry, silverware, coinage, mirror production.

II.   EXPOSURE

Exposure to silver is mainly through food and water intake with only minimal contribution from ambient aerosols. Concentrations of silver in surface waters have been shown to vary from 0 - 38 µg/l with a mean of 2.6 µg/l in samples containing silver. High silver concentrations are obtained in high silver mineralized areas or in waters receiving effluent from industries that use silver.

The average intake of silver from food has been calculated to be 40 µg/day (Tipton, et al. 1966) to 88 µg/day (Kehoe, et al. 1940) in the U.S. Although silver is detected in meats and vegetables, the concentrations in fish, shell-

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fish, and crustacea are greater. Marine animals accumulate silver in concentrations which are higher than their environment. This is particularly significatnt in areas such as sewage-sludge dumping sites, which contain high concentrations of silver in the sediment. The dead bodies of animals in reducing environments will contribute their silver to sediments, a major factor in the geochemical cycle of silver (Boyle, 1968).

Exposure to high levels of silver has also occurred by inhalation in specific industries (e.g., silver smelting and photography) and from mechanical uses of silver compounds. Steel mills do not seem to contribute to ambient air concentrations of silver (Harrison, et al. 1971).

III. PHARMACOKINETICS

A. Absorption

Silver may enter the body via the respiratory tract, the gastrointestinal tract, mucous membranes, or broken skin. The efficiency of absorption by any of these routes is poor. Colloidal silver given orally to rats showed two to five percent absorption by the gastrointestinal tract (U.S. EPA, 1979). Dogs receiving orally a tracer quantity of silver nitrate absorbed ten percent. It was shown in humans who accidently inhaled silver that the biological half-life of silver was about one day, probably due to rapid muco-ciliary clearance, swallowing, and fecal excretion (Newton , and Holmes, 1966). Some absorpotion did take place since there was localization of silver in the liver, but quantification was impossible. In human burn patients treated with

silver nitrate dressing, only 0.008 percent of the silver was absorbed (U.S. EPA, 1979).

B.   Distribution

The amount of silver, its chemical form, and the route by which it is administered affects the tissue content and distribution of silver within the body (Furchner, et al. 1968). Table 1 summarizes data on the distribution of silver in rats.

Table 1:   Distribution of Silver in the Rat and Day 6 Following Intramuscular Injections of Different Doses of Silver (percent of dose per organ) (Scott and Hamilton, 1950).

| | Dose | | |
	Carrier-Free	0.1 mg	1.0 mg
Percent of Dose			
Absorbed	92.1	63.7	53.5
Absorbed			
Heart and Lungs	0.06	0.13	0.59
Spleen	0.01	0.13	2.69
Blood	0.50	0.95	3.03
Liver	0.36	2.24	33.73
Kidney	0.07	0.92	0.63
G.I. tract	1.12	4.22	8.21
Muscle	0.27	0.56	2.39
Bone	0.18	0.35	2.20
Skin	0.24	0.67	7.39
Urine	0.64	0.88	1.82
Feces	96.56	88.95	37.33
Unabsorbed	7.9	36.3	46.5

Silver administered to other species appears to generally follow this distribution pattern.

C. Metabolism

Inhaled silver particles that are not removed from the lungs by the mucociliary reflex and coughing are probably

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phagocytized and transported via the protein fractions of the blood plasma to the liver, from which they are eventually excreted in the bile. Formation of silver selinide deposits in the liver, as well as the formation of metallic silver, silver sulfide, or silver complexes with sulfur amino acids may be a method of detoxifying silver. In the kidney, complexation with metallothionein may be another detoxification pathway (U.S. EPA, 1979).

D.   Excretion

Regardless of route and chemical form of silver administered, fecal excretion always predominates over urinary excretion. Most absorbed silver is excreted into the intestines by the liver via the bile. Phalen and Morrow (1973) exposed beagle dogs to an atmosphere containing silver aerosols and showed the biological half-life to be 8.4 to 12.9 days.

IV.   EFFECTS

A.   Carcinogenicity

Implanted foils and disks and injected colloidal suspensions of metallic silver have been found to produce tumors or hyperplasia in several studies. These tumors may be due to the particular physical form of the metal or to its being an exogenous irritant. There is no evidence that silver or its salts produce tumors by any other mechanisms. In one study, intratumoral injections of colloidal silver appeared to stimulate cancer growth (Guyer and Mohs, 1933), and in another study silver nitrate appeared to act as a promoter with DMBA (7,12-dimethylbenz(a)anthracene) initiated mice

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(Saffrotti and Shubik, 1963). On the other hand, Taylor and Carmichael (1953) showed a tumor growth inhibitor effect of silver chloride. The evidence for any carcinogenic effect of silver is very tenuous (U.S. EPA, 1979).

B. Mutagenicity

Silver nitrate (Demerec, et al. 1951), silver chloride (Nishioka, 1975), and silver sulfadiazine (Fox, et al. 1969) have been examined for mutagenicity in microorganisms and shown to be nonmutagenic in these test systems.

C. Teratogenicity

Few associations between silver and birth defects have appeared in the literature and one is apparently erroneous. Kukizaki (1975) found only weak cytotoxic effects when silver-tin alloy powder was incubated in seawater with fertilized eggs or early embryos of the sea urchin <u>Hemicentrotus</u> <u>pulcherrimus</u>. Silver salts were tested for toxicity to 4- and 8-day-old chick embryos but did not produce abnormalities in development (Ridgway and Karnofsky, 1952).

D. Other Reproductive Effects

Pertinent information could not be located in the available literature concerning any other reproductive effects due to exposure to silver.

E. Chronic Toxicity

In rats, chronic exposure to 0.4 mg/l of silver in drinking water causes hemorrhages in the kidney. Larger doses cause changes in conditioned-reflex activity, lowering of immunological resistance (0.5 mg/l), and growth depression (20 mg/l). In humans, the most common noticeable effect of

chronic exposure to silver or silver compounds is generalized
argyria (generalized gray pigmentation).

F.   Other Relevant Information

Silver exhibits antagonism to selenium, vitamin E,
and copper, inducing deficiency symptoms in animals fed ade-
quate diets or aggravating deficiency symptoms when the ani-
mal's diet lacks one or more of the nutrients. The effects
have been described in dogs, sheep, pigs, rats, chicks, tur-
key, poults, and ducklings (U.S. EPA, 1979).

V.   AQUATIC TOXICITY

A.   Acute Toxicity

Davies, et al. (1978) conducted 96-hour tests with
rainbow trout in both hard (350 mg/l as $CaCO_3$) and soft
water (26 mg/l as $CaCO_3$) water. The LC_{50} values were
6.5 and 13 µg/l for soft and hard water, respectively. There
are too few data to assess the relative importance of hard-
ness and experimental variability on these nonreplicated re-
sults.

The 48-hour static EC_{50} for Daphnia magna in
soft water (40 mg/l as $CaCO_3$) is 1.3 µg/l (U.S. EPA, 1978),
indicating that this species is the most sensitive freshwater
invertebrate species tested.

Acute toxicity data are available only for four
saltwater invertebrate species and range from 5.8 to 262 µg/l.
(Calabrese, et al. 1973; Calabrese and Nelson, 1974; Nelson,
et al. 1976; Sosnowski and Gentile in: U.S. EPA, 1979). The
American oyster is the most sensitive saltwater species test-
ed, and the mysid shrimp is the most resistant.

B. Acute Toxicity

Davies, et al. (1978) conducted an 18-month mortal-
ity test with rainbow trout and found the no-effect concen-
tration of silver to be 0.09 - 0.17 μg/l (17.2% mortality at
0.17 μg/l and no mortality at 0.09 μg/l). There was also
premature hatching of eggs and reduced growth of fry at 0.17
μg/l.

The chronic toxicity of silver to mysid shrimp has
been determined based on a flow-through, life-cycle exposure
(Sosnowski and Gentile in: U.S. EPA, 1979). No spawning
occurred at 103 μg/l. The time of spawning was delayed to
seven days at 33.3 μg/l. Brood size was statistically
smaller at 33.3 μg/l when compared to the controls, although
larval survival was not affected. The highest concentration
of silver tested that had no effect on growth, reproduction,
or survival was 10.2 μg/l, which is approximately 0.04 times
the 96-hour LC_{50} determined for adult shrimp.

C. Plant Effects

Hutchinson and Stokes (1975) observed growth retar-
dation in the freshwater alga, <u>Chlorella</u> <u>vulgaris</u>, at silver
concentrations between 10 and 60 μg/l. A concentration of
2,000 μg/l was determined to be toxic to six additional algal
species (Gratteau, 1970).

The only marine algal species tested, <u>Skeltonema</u>
<u>costatum</u>, showed growth inhibition after a 96-hour exposure
to 130 μg/l (U.S. EPA, 1978).

D. Residues

Bioconcentration factors of 17 to 368 were deter-
mined for three species of insects exposed to silver

(Nehring, 1973). Bluegills showed no bioconcentration of silver at a water concentration of 0.03 μg/l after a 28-day test (U.S. EPA, 1978). Pertinent information on residues in saltwater species could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Humans

Both the U.S. standard for silver in drinking water and in workplace air have been based on a presumed 1 g minimum dose of silver that has caused agryia. The existing standards for silver are:

Existing Standards Regarding Silver

Medium	Silver Concentration	Authority
Drinking water	50 μg/l	U.S. EPA (1976);National Academy of Sciences (1977)
Drinking water	0.5 μg/l	State of Illinois (cited in National Academy of Sciences,1977)
Drinking water	10 μg/l	State of California (cited in National Academy of Sciences, 1977)
Workplace air, threshold limit value time-weighted	0.01 mg/m^3	Occupational Safety and Health Administration (1974) (39 FR 23541)
Short-term exposure limit ($\geq$ 15 minutes) 4 times per day	0.03 mg/m^3	American Conference of Governmental Industrial Hygiensts (1977)

The acceptable daily intake (ADI) for silver is 1.6 mg/day. The U.S. EPA draft water criterion for silver is 10 μg/l for the protection of human health. This criterion is presently

undergoing further evaluation and review before final recom-
mendation.

B.   Aquatic

For silver the draft criterion to protect fresh-
water aquatic life is 0.009 µg/l as a 24-hour average; the
concentration should not exceed 1.9 µg/l at any time (U.S.
EPA, 1979).

To protect saltwater aquatic life, the draft cri-
terion is 0.26 µg/l as a 24-hour average; the concentration
should not exceed 0.58 µg/l at any time (U.S. EPA, 1979).

SILVER

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TCDD

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.   20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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-1849-

2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD)

SUMMARY

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) has been found to induce heptocellular carcinomas and tumors in two rat feeding studies. TCDD has also produced fetotoxic and teratogenic effects in laboratory animals. The positive mutagenicity of TCDD has been demonstrated in three bacterial bioassay systems. TCDD is also a potent inducer of hepatic and renal microsomal drug metabolizing enzymes.

No standard tests for acute or chronic toxicity in aquatic life have been conducted with TCDD. Other studies, however, have shown adverse effects over a period of 96 hours to concentrations as low as 0.000056 µg/l. The weighted average bioconcentration factor for TCDD for edible portion of all aquatic organisms consumed by Americans has been calculated to be 5,800.

2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD)

I.   INTRODUCTION

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a contami-
nant unintentionally formed during the production of 2,4,5-
trichlorophenol (TCP) from 1,2,4,5-tetrachlorobenzene.
TCDD is also found as a contaminant of 2,4,5-trichlorophenoxy-
acetic acid (2,4,5-T) (U.S. EPA, 1979).

Characteristically, TCDD ($C_{12}H_4Cl_4O_2$) is a white crystal-
line solid with the following physical properties: melting
point, 302–305°C; solubility in water, 0.2 to 0.6 µg/l;
lipiphilic, and non-volatile (U.S. EPA, 1979).

TCDD is considered a relatively stable compound which
can be degraded at temperatures in excess of 500°C, or by
irradiation with UV light or sunlight under certain condi-
tions (U.S. EPA, 1979). It has been shown to disappear
slowly from soil with residues persisting for ten years
after application. TCDD bio-accumulates in aquatic organisms.

II.   EXPOSURE

A.   Water

The amount of human exposure that can be directly
attributed to drinking water alone is difficult to determine
(U.S. EPA, 1979). It has been stated that no TCDD has ever
been detected in drinking water, with limits of detection
in the parts per trillion range (National Research Council,
1977). Underground water supplies would probably not be
contaminated with TCDD under most conditions since vertical
movement of TCDD has not been demonstrated in soil (Kearney,
et al., 1972).

B.   Food

The occurence of TCDD in food could result from (1) accidental spraying of plant crops; (2) contaminated forage or (3) food chain magnification (U.S. EPA, 1979).

TCDD is neither absorbed by oat and soybean seeds after spraying, nor taken up from the soil into the mature plants (Isensee and Jones, 1971; Matsumura and Benezet, 1973). Aqueous solutions of pure TCDD exposed to either artificial light or sun light, do not decompose, whereas TCDD photodecomposes rapidly when applied to leaf surfaces as a contaminant of the herbicides Agent Orange and Esteron (Crosby, et al., 1971; Crosby and Wong, 1977).

TCDD has been detected in the adipose tissue of cattle feeding on contaminated forage (Kocher, et al., 1978). Studies conducted for the U.S. EPA also found TCDD in fat of cattle previously exposed to 2,4,5-T (U.S. EPA, 1979). No TCDD, however, was detected in liver samples.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of TCDD at 5,800. This estimate is based on measured steady state bioconcentration studies in channel catfish containing 3.2 percent lipids (Isensee and Jones, 1975).

C.   Inhalation

Pertinent information could not be located in the available literature.

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III. PHARMACOKINETICS

A. Absorption

Approximately 83-86 percent of the TCDD administered in a single oral dose, following activation with multiple oral doses, is absorbed from the intestinal tract (Rose, et al., 1976).

B. Distribution

The excretion of a single oral dose of TCDD in rats occurred via the feces (53 percent), urine (13 percent), and expired air (two percent) (Piper, et al., 1973). Analysis after three days showed the highest percent of the administered dose per gram in the liver (3.18 percent) and adipose (2.60 percent).

Rose, et al. (1976) found that 22 days after a single oral dose of ^{14}C labeled TCDD, 1.26 and 1.25 percent of the ^{14}C was retained per gram of liver and adipose tissue, respectively. After repeated oral doses, however, the liver was found to have five times as much radioactivity as adipose tissue. Single oral doses of TCDD were excreted through the feces, whereas significant amounts of radioactivity were found both in the urine and the feces after repeated oral doses.

C. Metabolism

There is no complete agreement as to whether or not TCDD is actually metabolized (U.S. EPA, 1979). Rose, et al. (1976) found unchanged ^{14}C-labeled TCDD in the liver after oral administration, but noted that most of the radio-

activity in the feces came from compounds other than TCDD. The slow elimination of TCDD from rats and monkeys suggests that it is not readily metabolized (Van Miller, et al., 1976).

   D.   Excretion

        See also section B., Distribution.

        Differences in TCDD elimination have been observed between the sexes and between species. Rose, et al. (1976) found male rats excreted 3.1 percent of the cumulative dose in the urine while females excreted 12.5 percent in the urine.

        The half-life of radioactive TCDD following a single oral dose to rats was $31^{\pm}$ 6 days, while that following repeated oral doses was 23.7 days (Rose, et al., 1976).

IV.   EFFECTS

   A.   Carcinogenicity

        Three studies have reported data concerning the carcinogenicity of TCDD. Van Miller, et al. (1977) fed rats dietary levels of TCDD ranging from 0.001 to 1000 $\mu g/kg$ of diet for up to 78 weeks. In 50 animals receiving diets ranging from 0.005 $\mu g/kg$ to 5 $\mu g/kg$ 13 benign and 15 malignant tumors were observed. No tumors were found in controls or those fed a dietary level of 0.0001 $\mu g/kg$. Animals fed diets of 50 $\mu g/kg$ or more died between the second and fourth week of treatment.

        Toth, et al. (1977) administered TCDD to mice at levels of 0.007, 0.7, and 7 $\mu g/kg$ per week for 12 months. No tumors were noted at any dose.

Kociba, et al. (in press) administered 0.1, 0.01, and 0.001 µg/kg ofTCDD per kg of body weight to male and female rats. Males at the 0.1 µg/kg dose exhibited a statistically significant increased incidence of squamous cell carcinomas of the hard palate (4 out of 50) and of the tongue (3 out of 50). No carcinomas were observed in the male controls (0 out of 85). Females at the 0.1 µg/kg dose had a statistically significant increase in incidence of carcinomas at three sites: squamous cell carcinoma of the hard palate (4 out of 49), squamous cell carcinoma of the lung (7 out of 40), and hepatocellular carcinoma of the liver (11 out of 49). Only one carcinoma of these three sites occurred in the female controls (1 out of 86), and that was hepatocellular carcinoma of the liver. Five sites, pancreas, adrenal gland, pituitary gland, uterus, and mammary gland, had a statistically significant decrease in their tumor incidence at certain dose levels (Kociba, et al., in press).

B.   Mutagenicity

Multiple oral doses of TCDD over 6 weeks resulted in vacuolization of liver cell nuclei, increased mitotic rate, and a polyploid chromosome number (Vos, et al., 1974).

TCDD administered by intubation intraperitonealy, or orally did not cause chromosomal aberrations in bone marrow cells (Green and Moreland 1975). However, repeated dosing of TCDD over 13 weeks produced an increase in chromosomal breaks in rat bone marrow (Green, et al. 1977).

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Some studies have been conducted showing that TCDD might be a dominant lethal inducing agent, while others have found no evidence of this effect (U.S. EPA, 1979).

Bacterial assays with E. coli, and S. typhimurium have found TCDD to be mutagenic via intercalation with DNA (Hussain, et al., 1972). Some strains of Salmonella, however, have yielded negative mutagenic results when tested (Seiler, 1973).

Tenchini, et al. (1977) found no significant differences in chromosome number or chromosomal abnormalities in maternal or abortive fetal samples from pregnant women exposed to TCDD during the explosion of a 2,4,5-T factory in Italy.

C. - Teratogenicity

Teratogenic effects from TCDD have been reported in several studies. Both teratogenic and fetotoxic effects were observed in mice and rats administered 2,4,5-T containing 30 ppm TCDD (Courtney, et al., 1970). Smith, et al. (1976) found the incidence of cleft palate to be significantly higher in mice receiving 1 μg/kg and 3 μg/kg per day of TCDD for 10 days during gestation. At 3 μg/kg, the incidence of bilateral dilated renal pelvis among fetuses was also significantly greater. TCDD levels of 0.125 to 2.0 μg/kg/day given orally to rats on days 6 to 15 of gestation produced dose-related increases in fetal mortality, fetal intestinal hemorrhages, and early and late resorptions (Sparschu, et al., 1971).

D.   Other Reproductive Effects

Pertinent information could not be located in the available literature.

E.   Chronic Toxicity

Chronic studies involving administration of TCDD to rats, guinea pigs and mice, have reported toxic effects to the liver and thymus (U.S. EPA, 1979). Female rhesus monkeys fed a diet containing 500 ppt TCDD for up to nine months, exhibited symptoms of facial hair and eyelash loss, edema, accentuated hair follicles, and dry scaly skin (Allen, et al., 1977).

A large number of studies have reported the incidence of chloracne among workers exposed to TCDD during the production of 2,4,5-trichlorophenol (TCP, 2,4-D or 2,4,5-T) (U.S. EPA, 1979). Other chemical manifestations among exposed workers include muscular weakness, loss of appetite and weight, sleep disturbances, orthostatic hypotension, abdominal pain, liver impairment, hyperpigmentation of the skin, hirsutism, and psychopathological changes (U.S. EPA, 1979).

F.   Other Relevant Information

No synergistic effect was detected when 2,4,5-T and TCDD were administered to mice alone, or in combination with each other (U.S. EPA, 1979). Both compounds are capable of producing cleft palates and kidney anomalies in fetuses.

The International Agency for Research on Cancer (1977) has reviewed the literature and concludes that TCDD is a potent inducer of hepatic and renal microsomal drug

metabolizing enzymes. TCDD intoxication results in a marked increase in the cellular smooth endoplasmic reticulum content of hepatic and renal cells. This compound is also capable of simultaneously activating and suppressing certain microsome associated foreign compound and steroid-hormone-metabolizing enzyme systems. It has been found to increase the activity of renal and hepatic glutathione-S-transferase, and hepatic δ-aminolevulinic acid (ALA) synthetase and arylhydrocarbon hydroxylase (AHH).

V. AQUATIC TOXICITY

A. Acute toxicity

Miller, et al. (1973) exposed coho salmon (Oncorhynchus kisutch) to aqueous concentrations of TCDD at 0.000056, 0.0056, or 0.056 µg/L for 24-96 hours under static conditions, then transferred these fish to control water. After 60 days 12 and 55 percent mortalities were observed in the low and intermediate dose groups, respectively. Coho salmon exposed to the high dose for 24 hr were all dead within 40 days. The corresponding mortality for control fish at 60 days was 2 percent.

B. Chronic Toxicity

Pertinent information could not be located in the available literature.

C. Plant Effects

Pertinent information could not be located in the available literature.

D.   Residues

TCDD has a high affinity for the tissues of aquatic species. Isensee and Jones (1975) conducted a model fresh-water ecosystem study on TCDD and observed bioconcentration factors between 3,600 and 26,000 over a 3 to 31 day period. The highest bioconcentration factors were reported for Dyphnia magna (26,000), the mosquito fish, Gambusia affinis (25,000), and the snail, Physa sp. (20,000).

VI. EXISTING GUIDELINES AND STANDARDS

A.   Human

The calculated acceptable daily intake (ADI) for TCDD is 10^{-4} $\mu g/kg/day$. This ADI does not consider TCDD to be a known or suspected carcinogen (NRC, 1977).

The draft ambient water quality criterion has been set by the U.S. EPA (1979) at levels intended to reduce the human carcinogenic risk to rhe range of 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding draft criteria are 4.55 x 10^{-7} $\mu g/l$, 4.55 x 10^{-8} $\mu g/l$, and 4.55 x 10^{-9} $\mu g/l$, respectively.

B.   Aquatic

No drafted criterion is available to protect fresh and saltwater species from TCDD toxicity.

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155-H

No. 156

1,1,1,2-Tetrachloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

156-1

DISCLAIMER

This report represents a survey of the potential health
and environmental hazards from exposure to the subject chemi-
cal. The information contained in the report is drawn chiefly
from secondary sources and available reference documents.
Because of the limitations of such sources, this short profile
may not reflect all available information including all the
adverse health and environmental impacts presented by the
subject chemical. This document has undergone scrutiny to
ensure its technical accuracy.

SUMMARY

1,1,1,2-Tetrachloroethane is potentially formed during chlorination of drinking water and has been identified at a concentration of 0.11 $\mu g/l$. Although inhalation is the major route of exposure to chlorinated ethanes, specific information on 1,1,1,2-tetrachloroethane inhalation is not available.

Literature reporting adverse occupational exposures to this chloroethane cannot be found. Animal experiments measuring the acute and subacute effects indicate, however, that chronic exposure may produce liver damage. 1,1,1,2-Tetrachloroethane is currently being tested by the National Cancer Institute for possible carcinogenicity. The compound not mutagenic according to one report. Data could not be located in the available literature showing it to be teratogenic.

Pertinent information could not be found in the available literature regarding the adverse effects of this compound on aquatic animals or plants.

1,1,1,2-TETRACHLOROETHANE

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms of ethane are replaced by chlorine atoms. In general, water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. 1,1,1,2-Tetrachloroethane (molecular weight 167.9) is a liquid at room temperature with a boiling point of 129°C, a melting point of -68°C, a specific gravity of 1.553, and a solubility in water of 2.85 mg/l (U.S. EPA, 1979a).

1,1,1,2-Tetrachloroethane is used as a solvent and in the manufacture of a number of widely used products, as are the other chloroethanes (U.S. EPA, 1975). In general, these compounds form azeotropes with water (Kirk and Othmer, 1963) and are very soluble in organic solvents (Lange, 1956). Pearson and McConnell (1975) were unable to demonstrate microbial degradation of these compounds, but did report chemical degradation. For a more general treatment of the chlorinated ethanes as a class, the reader is referred to the EPA/ECAO Hazard Profile on Chlorinated Ethanes (U.S. EPA, 1979b).

II. EXPOSURE

1,1,1,2-Tetrachloroethane is potentially formed during chlorination of drinking water and has been identified at a concentration of 0.11 μg/l (U.S. EPA, 1974). Information on the levels of 1,1,1,2-tetrachloroethane in food are not available although other chloroethanes have been detected (U.S. EPA, 1979a). Inhalation is the major route of exposure to chlorinated ethanes. However, specific information on 1,1,1,2-tetrachloroethane exposure is not

available (U.S. EPA, 1979a). As with most solvents, chloroethanes can be absorbed through the skin. This is not, however, a major route of exposure (U.S. EPA, 1979a).

The U.S. EPA (1979a) has estimated a weighted average bioconcentration factor of 18 for 1,1,1,2-tetrachloroethane for the edible portions of fish and shellfish consumed by Americans. This value was based on an estimated steady-state bioconcentration factor of 62, which was determined from an octanol/water partition coefficient of 457.

III. PHARMACOKINETICS

A. Absorption

Specific information on the absorption of 1,1,1,2-tetrachloro-ethane is not available. In general, the chloroethanes are absorbed rapidly following ingestion or inhalation (U.S. EPA, 1979a).

B. Distribution

Inhalation or ingestion of 1,1,1,2-tetrachloroethane results in the presence of high levels of solvent in the fetuses of the exposed animals (Truhaut, et al. 1974). Other studies indicate a widespread distribution of chloroethanes throughout the body after administration (U.S. EPA, 1979a).

C. Metabolism

After oral administration to rats, guinea pigs, and rabbits, 1,1,1,2-tetrachloroethane underwent hydrolytic dehalogenation resulting in formation of trichloroethanol, which was eliminated primarily in the urine in the form of a conjugated glucuronic derivative, urochloralic acid. Oxidation to trichloroacetic acid was considerable only in rats (Nguyen, et al. 1971; Truhaut and Nguyen, 1973). In the latter study monochloroacetic acid and mercaptan derivatives were not found in the urine. The only halogenated

compound found in the expired air was untransformed 1,1,1,2-tetrachloro-
ethane. Trichloroethanol and trichloroacetic acid have also been identified
in the urine of rats following interperitoneal (i.p.) injection or vapor
inhalation of 1,1,1,2-tetrachloroethane (Ikeda and Ohtsuji, 1972), and have
been identified in the urine of mice following i.p. injection of the parent
compound (Yllner, 1971).

In general, the metabolism of chloroethanes involves both enzy-
matic dechlorination and hydroxylation and non-enzymatic oxidation (U.S.
EPA, 1979a). Oxidation reactions may produce unsaturated metabolites which
are then transformed to the alcohol and ester (Yllner, 1971).

D.   Excretion

Murine studies show that, after i.p. injection of 1,1,1,2-tetra-
chloroethane, approximately 78 percent of the dose is excreted in 72 hours;
from 21 to 62 percent of this dose is excreted in the breath and from 18 to
56 percent as metabolites in the urine (Yllner, 1971). Other studies also
indicate that 1,1,1,2-tetrachloroethane is excreted in the urine as
metabolites and in the expired breath as the parent compound (see above).

IV. EFFECTS

A.   Carcinogenicity

1,1,1,2-Tetrachloroethane is currently being tested by NCI for
possible carcinogenicity; results are not available (NTCTP, 1980). Other
information relative to the potential carcinogenicity of
1,1,1,2-tetrachloroethane was not located in the available literature.

B.   Mutagenicity

Simmon, et al. (1977) tested 71 chemicals identified in the U.S.
drinking water for mutagenesis with an Ames Salmonella/microsome assay.
1,1,1,2-Tetrachloroethane was found not to be mutagenic in this study.

C. Teratogenicity and Other Reproductive Effects

The isomer of 1,1,1,2-tetrachloroethane, syn-tetrachloroethane, is a weak teratogen in two strains of mice (Schmidt and Reiner, 1976). Both tetrachloroethanes are embryotoxic (Schmidt and Reiner, 1976; Truhaut, et al., 1974). Other pertinent data have not been found.

D. Chronic Toxicity

Adverse occupational exposure to 1,1,1,2-tetrachloroethane has not been reported by NIOSH. (U.S. EPA, 1979a). Animal experiments measuring acute and subacute effects indicate that chronic inhalation exposure may produce liver damage (see below).

E. Acute and Subacute Toxicities

At 24 hours after the oral administration of 0.5 g 1,1,1,2-tetra-chloroethane/kg to rabbits, the blood cholesterol and total lipid levels were increased and the glutamic-pyruvic transaminase, glutamic-oxalacetic transaminase, creatine phosphokinase, lactate dehydrogenase, and a-hydroxy-butyrate dehydrogenase activities were enhanced. Except for creatine phos-phokinase, these enzyme levels remain elevated at 72 hours after poisoning (Truhaut, et al. 1973). Subsequent studies by this research group found that in rabbits, 1,1,1,2-tetrachloroethane was only slightly irritating to the skin and ocular mucous membrane, and its cutaneous LD_{50} was 20 g/kg. Its acute toxicity by inhalation, for an exposure of 4 hours, was similar in rats and rabbits, with the LC_{50} being 2500 mg/m^3. The oral LD_{50} values in rats and mice were 800 and 1500 mg/kg, respectively. Histological examination revealed hepatotoxic activity, including formation of micro-vacuolizations and centrolobular necrosis. 1,1,1,2-Tetrachloroethane was from two to three times less toxic than 1,1,2,2-tetrachloroethane (Truhaut, et al. 1974).

Recent studies exploring subacute effects indicate that in female Wistar rats, 1,1,1,2-tetrachloroethane (0.30 g/kg, 5 days/week, for 2 weeks, orally) induced hepatic steatosis by accumulation of triglycerides, accompanied by a decrease in liver lactate dehydrogenase, malate dehydrogenase, and glutamic pyruvic transaminase activities. The tetrachloroethane caused no changes in the liver of male rats (Truhaut, et al. 1975). However, another team of investigators found that 1,1,1,2-tetrachloroethane (from 100 to 800 μmoles/kg/day for 7 days, i.p.) to male rats increased liver succinate dehydrogenase, acid phosphatase and glucose 6-phosphatase activities and decreased liver DNA content. In addition, the white cell count was increased and the red cell count and blood cholesterol content were decreased (Chieruttini, et al. 1976).

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature regarding either the acute and chronic toxicity to aquatic animals, or the aquatic residues of 1,1,1,2-tetrachloroethane.

VI. EXISTING GUIDELINES AND STANDARDS

Guidelines for occupational exposure to 1,1,1,2-tetrachloroethane do not exist (International Labor Office, No. 37, 1977; NIOSH, 1978); however, 1,1,2,2-tetrachloroethane exposure is limited in the workplace to 5 ppm (35 mg/cu m) as an 8-hour time-weighted average (TWA) concentration.

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No. 157

1,1,2,2-Tetrachloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.   20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated

1,1,2,2,-tetrachloroethane and has found sufficient evi-

dence to indicate that this compound is carcinogenic.

157-3

1,1,2,2-TETRACHLOROETHANE

SUMMARY

An increased incidence of hepatocellular carcinomas has been shown in mice following oral administration of 1,1,2,2-tetrachloroethane. Mutagenic effects have been reported in the Ames Salmonella assay and in E. coli. There is no available evidence to indicate that 1,1,2,2-tetrachloroethane produces teratogenic effects. Occupational exposure to 1,1,2,2-tetrachloroethane has produced several toxic effects including neurological symptoms, liver and kidney damage, pulmonary edema, and fatty degeneration of heart muscle.

The toxicity of 1,1,2,2-tetrachloroethane has been examined in one species each of freshwater and marine fish, invertebrates, and plants. Freshwater invertebrates appear to be the most sensitive species examined, with acute toxic concentrations of 9,320 μg/l being reported.

157-4

1,1,2,2-TETRACHLOROETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms of ethane are replaced by chlorine atoms. In general, water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. 1,1,2,2-Tetrachloroethane (molecular weight 167.9) is a liquid at room temperature with a boiling point of 146.3°C, a melting point of -36°C, a specific gravity of 1.596, and a solubility in water of 2.9 gm/l (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds.

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a). For additional information regarding the chlorinated ethanes in general, the reader is referred to the Hazard Profile on Chlorinated Ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes present in raw and finished waters are due primarily to industrial discharges. Small amounts of chloroethanes may be formed by chlorination of drinking water or treatment of sewage. Atmospheric chloroethanes result

from evaporation of volatile chloroethanes during use as degreasing agents or in dry cleaning operations (U.S. EPA, 1979a).

Routes of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976). Information on the levels of 1,1,2,2-tetrachloroethane in foods is not available.

The EPA (1979a) has estimated a weighted average bioconcentration factor for 1,1,2,2-tetrachloroethane to be 18 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on steady-state bioconcentration studies in the bluegill.

III. PHARMACOKINETICS

A. Absorption

The chloroethanes are absorbed rapidly following ingestion or inhalation (U.S. EPA, 1979a). Morgan, et al. (1972) have determined that 1,1,2,2-tetrachloroethane has a high octanol/water partition coefficient, high rate of pulmonary absorption, and low rate of elimination by exhalation.

B. Distribution

Pertinent data could not be located in the available literature on 1,1,2,2-tetrachloroethane. The reader is referred to a more general treatment of chlorinated ethanes (U.S. EPA, 1979b), which indicates widespread distribution of these compounds throughout the body.

C. Metabolism

The metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation and non-enzymatic oxidation (U.S. EPA, 1979a). Oxidation reactions may produce unsaturated metabolites which are then transformed to the alcohol and ester (Yllner, 1971). Trichloroethanol and trichloro acetic acid have been identified in the urine of rats following inhalation of 1,1,2,2-tetrachloroethane vapor (Ikeda and Ohtsuji, 1972). Metabolism of this compound appears to involve the activity of the mixed-function oxidase system (Van Dyke and Wineman, 1971).

D. Excretion

The chloroethanes are excreted primarily in the urine and expired air. Murine studies indicate that, after intraperitoneal (i.p.) injection of 1,1,2,2-tetrachloroethane, approximately 80 percent of the dose is excreted in 72 hours. Half of this dose is excreted as carbon dioxide in the breath and one-fourth as metabolites in the urine (Yllner, 1971). Human studies (Morgan, et al. 1972) indicate that after inhalation exposure of 1,1,2,2-tetrachloroethane the amount expired in the breath is less than that observed in animal studies, although a different radioactive tracer was used.

IV. EFFECTS

A. Carcinogenicity

Results of a National Cancer Institute (NCI) carcinogenesis bioassay for 1,1,2,2-tetrachloroethane show that oral administration produced an increased incidence of hepato-

cellular carcinomas in exposed mice (NCI, 1978). No statistically significant tumor increase was seen in rats.

B.   Mutagenicity

The mutagenic activity of 1,1,2,2-tetrachloroethane has been shown in the Ames Salmonella assay and in a DNA polymerase-deficient strain of E. coli (Brem, et al., 1974).

C.   Teratogenicity and Other Reproductive Effects

Embryo toxicity and weak teratogenicity have been reported in two strains of mice exposed with 1,1,2,2-tetrachloroethane (Schmidt and Reimer, 1976). Other pertinent information could not be located in the available literature.

D.   Chronic Toxicity

Occupational exposure to 1,1,2,2-tetrachloroethane has produced toxic effects including neurological symptoms, liver and kidney damage, pulmonary edema, and fatty degeneration of heart muscle (U.S. EPA, 1979a).

Animal experiments have indicated that chronic inhalation exposure may produce liver and kidney degeneration (U.S. EPA, 1979a).

V.   AQUATIC TOXICITY

A.   Acute Toxicity

Toxicity studies on one species from each category of freshwater and marine fish and invertebrates have been reported (U.S. EPA, 1978). In freshwater fish, the study yielded a 96-hour static LC_{50} value of 21,300 μg/l for the bluegill (Lepomis macrochirus). For freshwater invertebrates, the study yielded a 48-hour static LC_{50} value of

9,320 µg/l for the caldoceran <u>Daphnia</u> <u>magna</u>. In marine fish
and invertebrates, the studies yielded a 96-hour static LC_{50}
value of 12,300 µg/l for the sheepshead minnow (<u>Cyprinodon</u>
<u>variegatus</u>), and of 9,020 µg/l for the mysid shrimp (<u>Mysi-</u>
<u>dopsis</u> <u>bahia</u>).

B. Chronic Toxicity

Pertinent information could not be located in the
available literature.

C. Plant Effects

When the freshwater algae <u>Selenastrum</u> <u>capricornutum</u>
was tested for adverse effects of 1,1,2,2-tetrachloroethane
on chlorophyll and cell numbers EC_{50} values of 136,000
and 146,000 µg/l were obtained. When the marine algae <u>Skele-</u>
<u>tonema</u> <u>costatum</u> was tested for these adverse effects, 96-hour
EC_{50} values were 6,440 and 6,230 ug/l, respectively.

D. Residues

A bioconcentration value of 8 was reported for the
bluegill (U.S. EPA, 1979a).

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 will be changed.

A. Human

Based on the NCI carcinogenic data, and using a
linear, nonthreshold model, the U.S. EPA (1979a) has esti-
mated the level of 1,1,2,2-tetrachloroethane in ambient water

that will result in an additional cancer risk of 10^{-5} to be 1.8 µg/l.

The exposure standard determined by OSHA for 1,1,-2,2-tetrachloroethane is 5 ppm as an eight-hour time-weighted average concentration.

B. Aquatic

The draft criterion for protection of freshwater aquatic life is 170 µg/l as a 24-hour average, not to exceed 380 µg/l. The draft criterion to protect marine life from 1,1,2,2-tetrachloroethane is 70 µg/l as a 24-hour average, not to exceed 160 µg/l (U.S. EPA, 1979a).

1,1,2,2-TETRACHLOROETHANE

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No. 158

Tetrachloroethylene

Health and Environmental Effects

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated tetrachloroethylene and has found sufficient evidence to indicate that this compound is carcinogenic.

TETRACHLOROETHYLENE

SUMMARY

Tetrachloroethylene is widespread in the environment, and is found in trace amounts in water, aquatic organisms, air, foodstuffs, and human tissue. Tetrachloroethylene causes mild intoxication and liver dysfunction following chronic exposure to high levels associated with certain industries. Tetrachloroethylene has not been shown to be teratogenic, but it has been shown to be mutagenic in bacterial assays and carcinogenic in mice.

The bluegill (Lepomis macrochirus) is the most sensitive freshwater species to acute tetrachloroethylene toxicity with a reported 96-hour LC_{50} of 12,900 µg/l. In the only acute toxicity study for saltwater species the mysid shrimp (Mysidopsis bahia) has an observed 96-hour LC_{50} value of 10,200 µg/l. The chronic value for this shrimp is 448 µg/l. A freshwater algae has a reported no-effect concentration of tetrachloroethylene at 816,000 µg/l. A marine alga, however, was adversely affected at the considerably lower level of 10,000 µg/l. Tetrachloroethylene is only slightly bioconcentrated by the bluegill (49 times) after 21 days of exposure, and has an elimination half-life of less than one day.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Tetrachloroethylene (U.S. EPA, 1979).

Tetrachloroethylene (C_2Cl_4, 1,1,2,2-tetrachloroethylene, perchloroethylene, PCE; molecular weight 165.85) is a colorless, nonflammable liquid. It has the following physical/chemical properties (Patty, 1963):

Melting Point:	-23.25°C
Density:	1.623 g/ml
Vapor Pressure:	19 mm Hg
Water Solubility:	150 μg/ml
Octanol/Water Partition Coefficient:	339

Tetrachloroethylene is primarily used as a solvent in the dry cleaning industry and, to a lesser extent, as a degreasing solvent in metal industries (Windholz, 1976).

II. EXPOSURE

The National Organics Monitoring Survey (U.S. EPA, 1978) detected tetrachloroethylene in 9 out of 105 drinking water samples between November 1976 and January 1977 (range, <0.2 to 3.1 μg/l; median <0.2 μg/l). No data exist for ingestion of tetrachloroethylene from food for the United States. However, in England, tetrachloroethylene concentrations in foods ranged from nondetectable amounts in orange juice to 13 μg/kg in butter (McConnel, et al., 1975). The U.S. EPA (1979) has estimated the weighted bioconcentration factor of tetrachloroethylene to be 110 for the edible portion of consumed fish and shellfish. This estimate is based on measured steady-state bioconcentration studies in bluegills. Generally,

environmental tetrachloroethylene concentrations in air tend
to be low. A survey of eight locations in the U.S. indicated
concentrations up to 6.7 µg/m^3 in urban areas and less than
0.013 µg/m^3 in rural areas (Lillian, et al., 1975). By far
the most significant exposure to tetrachloroethylene is in
the industrial environment (Fishbein, 1976). Significant der-
mal exposure would be confined to occupational settings.

III. PHARMACOKINETICS

A.　Absorption

Using inhalation exposure, Stewart, et al. (1961)
found that tetrachloroethylene reached near steady-state
levels in the blood of human volunteers with two hours of
continuous exposure. However, steady-state conditions in
this study were probably obtained by a redistribution phenom-
enon, since the biological half-life of tetrachloroethylene
metabolites in humans has been measured to be 144 hours
(Ikeda and Imamura, 1973).

B.　Distribution

In humans (McConnell, et al., 1975) and rats (Savo-
lainen, et al., 1977), tetrachloroethylene tends to accumu-
late in the body fat, and to a lesser extent in the brain and
liver. Measurements in the rat suggests that the level of
PCE in the liver and blood remains constant after three hours
of exposure.

C.　Metabolism

In a qualitative sense, metabolic products appear
to be similar in humans (Ikeda, et al., 1972; Ikeda, 1977)
and experimental animals (Yllner, 1961; Daniel, 1963; Ikeda

and Ohtsuji, 1972). The metabolism of tetrachloroethylene leads to the production of trichloroacetic acid, and is apparently saturable (Ikeda, 1977). The enzyme systems responsible for this metabolism are inducible with phenobarbital (Ikeda and Imamura, 1973) and polychlorinated biphenyls (Moslen, et al., 1977).

D. Excretion

In humans tetrachloroethylene is primarily eliminated from the body via the lungs with a half-life of elimination estimated to be 65 hours (Stewart, et al., 1961, 1970; Ikeda and Imamura, 1973). Its metabolite, trichloroacetic acid, is eliminated in the urine of humans with a half-life estimated to be 144 hours (Ikeda and Imamura, 1973).

IV. EFFECTS

A. Carcinogenicity

Tetrachloroethylene caused hepatocellular carcinomas in B6C3-F1 mice of both sexes (NCI, 1977). An experiment in Osborne-Mendel rats produced negative results, although early mortality precluded the use of this data in evaluating the carcinogenicity of PCE (NCI, 1977).

Greim, et. al. (1975) could not demonstrate an increase in the mutation rate of $\underline{E}$. $\underline{coli}$ K_{12} with tetrachloroethylene. However, Cerna and Kypenova (1977) tested PCE and found elevated mutagenic activity in $\underline{Salmonella}$ strains sensitive to both base pair substitution and frameshift mutations.

C. Teratogenicity

Only one report has appeared concerning possible

tetrachloroethylene-induced teratogenesis (Schwetz, et al.
1975). Female rats and mice were exposed to 2000 mg/m^3 7
hours daily on days 6 to 15 of gestation. Significant de-
creases in fetal body weight and resorption, subcutaneous
edema and delayed ossification of skull bones and sternabone
in the pups were noted. These effects were mild, however,
and led the authors to conclude that PCE was not teratogenic.
Additional work is necessary to determine whether PCE is ter-
atogenic (U.S. EPA, 1979).

D. Other Reproductive Effects

No information available.

E. Chronic Toxicity

Repeated exposure to tetrachloroethylene has re-
sulted in damge to liver and kidney in dogs (Klaassen and
Plaa, 1967). Toxic nephropathy has also been observed in
mice and rats (NCI, 1977). In humans, chronic exposure to
1,890 to 2,600 mg PCE/m^3 caused three of seven men to have
impaired liver function (Coler and Rossmiller, 1953). Occa-
sional reports have even associated tetrachloroethylene expo-
sure with the symptomatology of more serious chronic diseases
such as Raynaud's disease (Lob, 1957; Sparrow, 1977). Spar-
row (1977) reported a case which involved depressed immune
function, mildly depressed liver function, polymyopathy and
severe acrocyanosis. In a group of workers occupationally
exposed to lower concentrations of tetrachloroethylene at ap-
proximately 400 mg/m^3 (one for 15 years), subjective com-
plaints, such as headache, fatigue, somnolence, dizziness,

and a sensation of intoxication were noted (Medek and Kovarik, 1973).

F. Other Relevant Information

. Intolerance of alcohol has been reported with tetrachloroethylene exposure (Gold, 1969).

V. AQUATIC TOXICITY

A. Acute Toxicity

Ninety-six hour LC_{50} values for flow-through and static tests are 18,400 and 21,400 μg/l, respectively, with the fathead minnow, Pimephales promelas (Alexander, et al. 1978). With the bluegill, Lepomis macrochirus, the 96-hour LC_{50} value is 12,900 μg/l (U.S. EPA, 1978). For Daphnia magna, an observed 48-hour LC_{50} value of 17,700 μg/l has been recorded (U.S. EPA, 1978).

No acute data are available for saltwater fish. The mysid shrimp (Mysidopsis bahia) has an observed 96-hour LC_{50} of 10,200 μg/l (U.S. EPA, 1978).

B. Chronic Toxicity

Chronic test data are not available for freshwater species. A chronic value for the saltwater mysid shrimp in a life cycle test is 448 μg/l (U.S. EPA, 1978).

C. Plant Effects

No adverse effects on chlorophyll a concentration or cell numbers with the alga, Selenastrum capricornutum, were observed at exposure concentrations as high as 816,000 μg/l (U.S. EPA, 1978). Two 96-hour EC_{50} values were re- . ported for the marine micro alga, Skeletonema costatum: 504,000 μg/l based on cell numbers and 509,000 μg/l based on

chlorophyll a concentration (U.S. EPA, 1978). The macroalga, Phaeodectylum tricornutum, was considerably more sensitive to tetrachloroethylene toxicity with a reported EC_{50} of 10,500 ug/l (Pearson and McConnell, 1975).

D.   Residues

The bioconcentration factor for bluegills, Lepomis macrochirus, has been reported to be 49 (U.S. EPA, 1978). Equilibrium was reached within 21 days and the depuration rate was rapid with a half-life of less than one day.

VI.G EXISTING GUIDLINES AND STANDARDS

A.   Human

Based on the NCI mice data, and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of tetrachloroethylene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.020 ug/l	0.20 ug/l	2.0 ug/l
Consumption of fish and shellfish only.	0	0.040 ug/l	0.40 ug/l	4.0 ug/l

The present American Governmental Conference on Industrial Hygiene (AGCIH, 1977) threshold limit value (TLV) is 670 mg/m^3.

B.   Aquatic

For tetrachloroethylene, the draft criterion to protect saltwater aquatic life is 79 µg/l as a 24-hour average; the concentration should never exceed 180 µg/l at any time (U.S. EPA, 1979).

For freshwater aquatic life, the draft criterion is 310 µg/l as a 24-hour average; the concentration should never exceed 700 µg/l at any time (U.S. EPA, 1979).

This draft criteria to protect aquatic life is presently being reviewed before final recommendation.

TETRACHLOROETHYLENE

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No. 159

Thallium

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

THALLIUM

Summary

Thallium is a highly toxic element to many organisms, including humans. Symptoms of acute exposure to thallium include alopecia, ataxia, and tremors, occasionally leading to irreversible coma and death. There is no information available on the mutagenic and carcinogenic properties of thallium. Although thallium has been reported to be terato-genic, the evidence is not convincing. The acceptable daily intake (ADI) of thallium has been determined to be 15.4 mg per day. Thallium can be chronically toxic to fish at con-centrations as low as 20 µg/l. Algae are also sensitive, with effects produced at concentrations as low as 100 µg/l.

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THALLIUM

I. INTRODUCTION

This profile is based on the Ambient Water Quality Document for Thallium (U.S. EPA, 1979).

Thallium (Tl; atomic weight 204.37) is a soft, malleable, heavy metal with a silver-white luster (Lee, 1971). Thallium exists in either the monovalent (thallous) or trivalent (thallic) form, the former being the more common and stable and therefore forming more numerous and stable salts (Hampel, 1968). Thallium reacts chemically with moisture in air to form oxides. Thallous oxide is easily oxidized to thallic oxide, a very hygroscopic compound, or reduced to thallium. While thallium itself is relatively insoluble in water (Windholz, 1976), thallium compounds exhibit a wide range of solubilities.

Current production and use of thallium and its compounds approximated 680 kg in 1976 (U.S. Dept. Interior, 1977). Industrial uses of thallium include the manufacture of alloys, electronic devices, and special glass. Many thallium-containing catalysts have been patented for industrial organic reactions (Zitko, 1975).

II. EXPOSURE

There is little information on the extent of thallium contamination of water. In a single study by Greathouse (1978) evaluating drinking water from 3,834 households randomly selected from 35 geographic areas, thallium was detectable in only 0.68 percent of the samples (detection limit was 0.3 ppb), with the average concentration at detection of 0.89

ppb. Assuming a water consumption of 2 liters per day for the average adult, over 99 percent of adults would consume < 1 μg per day. The only study pertaining to natural water measured the thallium content of run-offs from mining and smelting operations involving copper, gold, zinc, and cadmium with which thallium is associated in trace quantities (U.S. EPA, 1978). The highest concentrations reported were 30 ppb in slag run-off near Kellog, Idaho and 21 ppb in the Colorado River below drainage from a copper mine.

Ingestion of thallium from food is mainly due to the consumption of vegetables. Little data is available, although Geilmann, et al. (1960) found an average of 68.2 ppb dry weight thallium in four vegetables analyzed. This may be high due to the small sample size. Breads contain 0.75 ppb dry weight thallium, and the thallium content of meats has not been adequately determined. The EPA (1979) estimated the weighted average bioconcentration factor for thallium to be 61 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegill. A daily intake from food has been calculated at 3.8 μg/day. However, due to the sparse data, this is probably not an accurate estimate.

The contribution of thallium in air to exposure is, in most instances, small. However, thallium is a contaminant in flyash, and in a worst case situation in the vicinity of a coal-fired plant, daily absorption could be as high as 4.9 μg (Carson and Smith, 1977). Due to possible high concentrations in vegetable matter, cigarette smoke may be a signifi-

cant source of thallium, with urinary excretion of thallium
in smokers being twice that in non-smokers (Weinig and Zink,
1967).

III. PHARMACOKINETICS

    A.   Absorption

        Gastrointestinal absorption of trace quantities of
thallium appears to be almost complete in both man (Barclay,
et al. 1953) and rats (Lie, et al. 1960). No information was
found in the available literature concerning the deposition
and clearance of inhaled thallium aerosols. The skin would
not be expected to be a significant route of absorption of
thallium; however, systemic poisoning has resulted from oint-
ments containing 3-8 percent thallium acetate applied to the
skin (Munch, 1934).

    B.   Distribution

        Thallium is widely distributed in the body in the
intracellular space. Active transport of thallium, mediated
by Na/K ATPase into erythrocytes has been demonstrated
(Gehring and Hammond, 1964; Cavieres and Ellroy, 1974).
Other factors besides active transport into cells must be
operating, since in both conditions of normal thallium expo-
sure and fatal exposure in man, there is a tendency for thal-
lium to concentrate in the kidneys, colon and hair (Weinig
and Zink, 1967; Cavanagh, et al. 1974).

        Thallium crosses the placenta freely from the ma-
ternal circulation to the fetus. In studies using rats and
mice, steady state maternal/fetal ratios of 0.84 and 0.46,

respectively, were obtained (Gibson, et al. 1967); and under non-steady state conditions, wide variations in dosage (0.2-6.4 mg/kg/min) did not alter the distribution from mother to fetus (Gibson and Becker, 1970). Richeson (1958) cites one report in which thallium was found in the tissue of a baby whose mother had taken 1.2 g thallium at term.

C. Metabolism

Pertinent information could not be located in the available literature.

D. Excretion

Human excretion of thallium has been estimated from two studies, one involving a tracer dose of 204 Tl given to a middle-age woman with osteogenic carcinoma metastatic to the lungs (Barclay, et al. 1953) and the other involving a woman suffering from thallium poisoning (Innis and Moses, 1978). From these two less than ideal studies, total excretion of thallium per day in adults not exposed to unusual sources of thallium is probably as follows:

Excretory route	ug Tl/day
Urine	1.20
Feces	0.06
Hair	0.32
Skin and Sweat	0.06
Total	1.64

IV. EFFECTS

A. Carcinogenicity and Mutagenicity

Information regarding the carcinogenic and muta-
genic potential of thallium could not be located in the
available literature.

B. Teratogenicity

There are two reports of the teratogenicity of
thallium, one involving chicken embryos (Karnofsky, et al.
1950) and the other rats (Gibson and Becker, 1970). In both
cases, overt fetal toxicity due to thallium was noted, making
it impossible to distinguish teratogenicity from a more
general toxic effect.

C. Other Reproductive Effects

The only known reproductive effect is fetal toxic-
ity in cases of acute poisoning of the mother.

D. Chronic Toxicity

There are few reports of chronic thallium poisoning
in man. In one brief report concerning 13 men exposed 3 to 4,
months, the signs and symptoms were pains in the legs, weari-
ness, loss of hair, disturbance of sensation, psychic trouble
albuminuria and nephritis (Meyer, 1928).

Rats fed thallous acetate in their diet for 105 days ex-
perienced no reduction in weight gain at concentrations of 5
and 15 ppm; 30 ppm, however, proved fatal to approximately
half the animals (Downs, et al. 1960).

E. Other Relevant Information

Potassium has been shown to markedly enhance the
rate of thallium excretion (primarily urinary) in both rats

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and dogs (Gehring and Hammond, 1967). Potassium also increased somewhat the acute LD_{50} of thallium. In humans, potassium also increases urinary excretion with accompanying temporary accentuation of the neurological signs and symptoms (Innis and Moses, 1978; Papp, et al. 1969).

V. AQUATIC TOXICITY

A. Acute Toxicity

The bluegill appears to be extremely resistant to y thallium under renewal and static test conditions with 96-hour LC_{50} values of 132,000 and 121,000 µg/l, respectivel (U.S. EPA, 1979). The fathead minnow was tested under flow-). through conditions with measured concentrations, and the 96- 0 hour LC_{50} value was found to be 860 µg/l (U.S. EPA, 1978 Atlantic salmon, when exposed to thallium for as long as 2,60 hours, experienced 40 and 70 percent mortality at approxi- z0 mately 20 and 45 µg/l, respectively, with mortality occuring throughout the test (Zitko, et al. 1975). The 48-hour LC_5 for Daphnia magna is 2,180 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

An embryo-larval test with the fathead minnow indi-1-cated adverse effects at the lowest thallium concentration tested of 40 µg/l (U.S. EPA, 1978). No chronic data are avai able for freshwater invertebrate species, and no chronic effects of thallium on saltwater organisms have been reported (U.S. EPA, 1979).

C.   Plant Effects

There is a 40 percent inhibition of oxygen evolution by the alga, _Chlamydomonas reinhardi_, exposed to a concentration of 40,800 μg/l (Overnell, 1975). The 96-hour EC_{50} values for chlorophyll a inhibition and cell number are 110 and 100 μg/l, respectively.

D.   Residues

The bluegill bioconcentrated thallium 34 times (whole body), and the Atlantic salmon bioconcentrated this heavy metal 130 times above that of the ambient water (Zitko, et al. 1975; U.S. EPA, 1978).

VI.   EXISTING GUIDELINES

A.   Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) and the Occupational Safety and Health Administration (OSHA) adopted a threshold limit value of 0.1 mg/m^3 for thallium. The acceptable daily intake (ADI) of thallium has been calculated to be 15.4 mg per day. The U.S. EPA (1979) draft water criterion document for thallium recommends a criterion of 4 ug/l for the protection of human health.

B.   Aquatic

A criterion for the protection of aquatic species from excess thallium exposure has not been derived.

THALLIUM

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Toluene

Health and Environmental Effects

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OCTOBER 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical, The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

TOLUENE

Summary

The available studies that describe the carcinogenic or mutagenic potential of toluene are inadequate for drawing any conclusions about its carcinogenicity. There is suggestive evidence, based on skin painting experiments in mice, that toluene has a weak promoting effect on DMBA-initiated skin carcinogenesis. Three studies in rats indicate that toluene damages chromosomes in bone marrow cells. Toluene-exposed workers showed an increase (not statistically significant) of chromosome breaks in peripheral lymphocytes. Some neuromuscular deficiencies have been reported in women exposed chronically to toluene in the workplace. Subacute and chronic studies on experimental animals have failed to show evidence of severe cumulative toxicity. Acute exposure to high levels of toluene causes CNS depression. The U.S. EPA (1979) has calculated an ADI of 29.5 mg for toluene.

Toluene is acutely toxic to freshwater fish at concentrations of 6,940 to 32,400 ug/l and to marine fish at concentrations from 4,470 to 12,000 ug/l. A single chronic value of 2,166 ug/l has been reported for marine fish. Aquatic plants appear to be resistant to the action ot toluene with effective concentrations ranging from 8,000 to 433,000 ug/l.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Toluene (U.S. EPA, 1979) and to a lesser extent on Criteria for a Recommended Standard: Occupational Exposure to Toluene (NIOSH, 1973) and its update (NIOSH, 1977).

Toluene ($C_6H_5CH_3$; molecular weight 92.13) is a clear, colorless, noncorrosive liquid with a sweet pungent odor. It has the following physical and chemical properties (Kirk and Othmer, 1963; Sutton and Calder, 1975; Shell and Ettre, 1971; Weast, et al. 1971):

Boiling Point	110.6°C
Freezing Point	-94.9°C
Flash Point	6-10°C
Vapor Pressure	28 mm Hg at 25°C
Solubility	Water: 534.8 $\pm$ 4.9 mg/l in fresh water and 379.3 $\pm$ 2.8 mg/l in seawater. Miscible with alcohol, chloroform, ether, acetone, glacial acetic acid, carbon disulfate and other organic solvents.
Production	7.3 x 10^3 tons/year (USITC, 1977)

Approximately 85 percent of the toluene produced is converted into benzene and other chemicals. The remainder is used as a solvent and as a gasoline additive (NIOSH, 1973).

Little is known about the transport and persistence of toluene in the environment. Toluene is volatile and can evaporate into the atmosphere from bodies of water (MacKay and Wolkoff, 1973). In the atmosphere, toluene is photochemically degraded to benzaldehyde and traces of peroxybenzoyl nitrate. Toluene can re-enter the hydrosphere in rain (Walker, 1976).

II. EXPOSURE

A. Water

' No estimates of average daily uptake of toluene from water, food, and air are available. In nationwide surveys of organic chemicals in the drinking water of representative U.S. communities, toluene was found to contaminate 1 raw and 11 finished water supplies out of the 133 water supplies surveyed (U.S. EPA, 1975a; 1975b; 1977). Quantitative analyses of five of the above finished waters revealed levels of toluene ranging from 0.1 ug/l to 19 ug/l. Benzaldehyde and benzoic acid, metabolites of toluene, were also detected. Benzaldehyde was found in the water of five cities, and in two of the cities was measured at levels of 0.1 and 0.5 ug/l. Benzoic acid at 15 ug/l was found in the water of another city.

B. Food

Little data on levels of toluene in food are available. Toluene was detected in sea water and fish obtained near petroleum and petrochemical plants in Japan (Ogata and Miyake, 1973). The muscle of one representative fish contained five ug toluene/g of tissue. Benzaldehyde, a metabolite of toluene, occurs naturally in some foods and is intentionally added to others as a flavoring agent. Benzoic acid, another metabolite of toluene, is added to some foods as a preservative.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for toluene to be 20 for the edible portions of fish and shellfish consumed by Americans. This estimate is based

on the octanol/water partition coefficient of toluene and on estimates of fish and shellfish consumption.

C. Inhalation

Toluene has been detected in urban air at concentrations many times lower than vapor levels considered to be potentially harmful in occupational settings. An average level of 37 ppb and a maximum level of 129 ppb were measured in the air of Los Angeles (Lonneman, et al. 1968). Comparable levels were found in the air of Toronto, Canada (Pilar and Graydon, 1973), and the air of Zurich, Switzerland (Grob and Grob, 1971). In these latter studies, atmospheric toluene in urban areas appeared to arise primarily from motor vehicle emissions.

III. PHARMACOKINETICS

A. Absorption

No reports are available on oral administration of toluene to humans (U.S. EPA, 1979). Toluene concentrations in arterial blood of persons continuously inhaling toluene vapors appeared to approach equilibrium after 20 to 30 minutes, at which time blood levels were about 1 ug/ml in persons inhaling 100 ppm, and 2 ug/ml in persons inhaling 200 ppm toluene (Astrand, et al. 1972). Systemic uptake of toluene was doubled by exercise, due primarily to increased ventilation rate (Astrand, et al. 1972). This increased uptake of toluene upon exercise was also noted by Carlsson and Lindqvist (1977), who in addition noted that obese persons retain more toluene than thin ones. In their study, the average uptake of toluene vapor during exercise was approximately 49 percent for obese subjects

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versus 37 percent for thin subjects. The rate of percutaneous toluene absorption in humans was reported to be 14 to 23 $mg/cm^2/hour$ (Dutkiewicz and Tyras, 1968).

Rats absorbed toluene much more rapidly and developed substantially higher peak blood and tissue toluene concentrations when toluene was administered to the lungs, rather than to the gastrointestinal tract (Pyykko, et al. 1977). Toluene absorption through the skin of experimental animals occurred to a considerably lesser degree than through the lungs or gut (Wahlberg, 1976).

B.   Distribution

Toluene is rapidly taken up from the blood into body tissues according to their lipid content and blood perfusion (U.S. EPA, 1979). Partition coefficients (tissue:blood) for toluene in homogenates of rabbit tissues have been determined. The partition coefficient for adipose tissue was 50 times greater, the coefficient for bone marrow was approximately 15 times greater, and those for brain and liver were roughly 2 times greater than the partition coefficients for lung, kidney, heart, and muscle (Sato, et al. 1974). Saturation of liver and brain tissue of mice was not reached even after 3 hours of inhalation of concentrations as high as 4000 ppm toluene (Bruckner and Peterson, 1976).

C.   Metabolism

In humans and experimental animals, toluene is thought to be enzymatically converted by the mixed function oxidase (MFO) system to benzyl alcohol, which is subsequently oxidized to benzaldehyde and benzoic acid. Benzoic acid is then conjugated with

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glycine to form hippuric acid (U.S. EPA, 1979). There has also been a report, however, of glucuronide conjugation of benzoic acid in rabbits given large doses (Bray, et al. 1951). Toluene toxicity is diminished in rats by MFO inducers (Ikeda and Ohtsuji, 1971) and enhanced by MFO inhibitors (Koga and Ohmiya, 1978), suggesting that metabolism of toluene results in detoxication.

D.   Excretion

Toluene is rapidly excreted from the body following inhalation exposure. Most of the estimated absorbed dose of toluene can be accounted for within the first 12 hours as the parent compound in expired air and as hippuric acid in the urine (U.S. EPA, 1979). Elimination rates are slower for women than for men, perhaps because of the larger proportion of fatty tissue in women (U.S. EPA, 1979).

Excretion of toluene in experimental animals is similar to that found in man. In the rat, for example, elimination of toluene occurs more slowly from adipose tissue than from any other (Pyykko, et al. 1977; Carlsson and Lindqvist, 1977), including bone marrow, from which elimination is also relatively slow (U.S. EPA, 1979). Toluene is rapidly lost from the brain, as reflected in rapid recovery from toluene-induced CNS depression (Peterson and Bruckner, 1976; Savolainen, 1978).

IV.   EFFECTS

A.   Carcinogenicity

The data base on the carcinogenicity of toluene is extremely limited. No inhalation studies have been done. No accounts have been found in the literature in which cancer in

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humans has been attributed specifically to toluene. It is difficult to link cancer induction with any single solvent, as persons having occupational exposure to solvents are characterized by considerable job mobility and exposure to a variety of chemicals (U.S. EPA, 1979). Toluene was not demonstrated to be carcinogenic when applied to the skin of mice for one year (Doak, el al. 1976) or throughout a lifetime (Poel, 1963) (since toluene evaporates rapidly, this method is not appropriate). Toluene has not shown carcinogenicity when administered to rats by inhalation at concentrations of up to 300 ppm, 6 hours/day, 5 days/week for as long as 18 months (Gibson, 1979). Frei and Kingsley (1968) reported that toluene has a weak promoting effect on DMBA-initiated skin carcinogenesis in Swiss mice. The major metabolite of toluene, benzoic acid, is not carcinogenic, however, about 1 percent of toluene can be metabolized to o- and p-cresol, which are cancer promoters (Boutwell and Bosch, 1959).

    B.   Mutagenicity

        There is no conclusive evidence that toluene is mutagenic, although it has been reported to cause chromosome damage. For example, the incidence of chromosomal abnormalities in peripheral blood lymphocytes of humans who had been exposed to an average of 200 ppm toluene for as long as 15 years was no greater than in controls (Forni, et al. 1971). However, there have been two reports that toluene induced chromosomal aberrations in the bone marrow cells of rats (Lyapkalo, 1973; Dobrokhotov and Enikeev, 1977), and typographers exposed to toluene have a slightly increased frequency

of chromosome breaks as compared to controls (Funes-Cravioto et al. 1977). Toluene has not been tested in bacterial screening systems (Dean, 1978).

C. Teratogenicity

Although toluene should readily pass the placenta, no reports of teratogenic effects in humans are linked to toluene exposure (U.S. EPA, 1979). Toluene is teratogenic and embryotoxic in mice (Nawrot and Staples, 1979). It was shown to be teratogenic at 1.0 mg/kg, embryolethal at 0.3 ml/kg, and decreased fetal weight occurred at 0.5 ml/kg. There was no maternal toxicity at any dose level on days 6-15, but maternal weight gain was noted for doses given on days 12-15.

D. Other Reproductive Effects

Women occupationally exposed to multiple solvents including toluene through the use of varnishes had a relatively high incidence of menstrual disorders. Their offspring were said to experience more frequent fetal asphyxia, to be more underweight, and not to nurse as well as "normal" infants (Syrovadko, 1977). Dysmenorrhea was a frequent subjective complaint of female shoemakers chronically exposed to 60-100 ppm toluene (Matsushita, et al, 1975). In a single study, some retardation of body weight and skeletal growth were seen in fetuses of rats exposed continuously to 399 ppm toluene on days 1 to 8 of gestation; inhalation of lower levels of toluene had no effect (Hudak and Ungvary, 1978).

E.   Chronic Toxicity

The toxicity of toluene was recently reviewed (Lohr and
Stokholm, 1979). Its major toxic effects are on the central nervous
system, causing depression, headaches, confusion, dizziness, insomnia
and (at high exposure levels) death.

A study of 38 female shoemakers exposed chronically to
solvents including toluene at 60 to 100 ppm for about three years
revealed abnormal tendon reflexes, reduced grasping power, and
decreased finger agility when compared to controls (Matsushita,
et al., 1975). Reports reviewed by the National Institute for
Occupational Safety and Health (1973) have failed to demonstrate
adverse effects on the hematopoietic, hepatic, renal, or other
physiologic systems of workers routinely inhaling approximately 100
ppm toluene. Chronic exposure may also lead to disturbances in the
immune system, dermatitis, and permanent damage to the central
nervous system (Cohr and Stockholm, 1979; U.S. EPA, 1979).

F.   Other Relevant Information

The primary hazard associated with acute exposure to high
levels of toluene is excessive CNS depression (U.S. EPA, 1979).
Toluene is capable of altering the metabolism and bioactivity of
other chemicals which are metabolized by the mixed function oxidase
system. For example, simultaneous administration of toluene and
trichloroethylene or toluene and benzene to experimental animals
resulted in suppression of metabolism of both compounds (Ikeda,
1974; Ikeda, et al., 1972). Another showed marked reduction in the
concentration of benzene metabolites in various tissues, including

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bone marrow, after simultaneous administration of toluene, and
data that suggested that toluene might protect against benzene
myelotoxicity (Andrews, et al., 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

For freshwater fish, 96-hour static LC_{50} values ranged
from 12,700 ug/l for the bluegill (Lepomis macrochirus) to 59,300
ug/l for the guppy (Poecilia reticulatus) (U.S. EPA, 1978; Pickering
and Henderson, 1966). Only a single 48-hour LC_{50} value for Daphnia
magna of 313,000 ug/l has been obtained for toluene. In marine
fish, two 96-hour static LC_{50} values of 6,300 and 10,000-50,000
ug/l were obtained for striped bass (Morone saxatilis) and coho
salmon Oncorhynchus kisutch (Benville, et al., 1977). Among four
species of marine invertebrates, the bay shrimp (Crago franciscorum)
was most sensitive, with a 96-hour static LC_{50} value of 3,700 ug/l
(Benville, et al., 1977), while the mysid shrimp Mysidopsis bahia
was most resistant, with a 96-hour static LC_{50} value of 56,300 ug/l
(U.S. EPA, 1978).

B. Chronic Toxicity

No freshwater chronic data could be found in the available
literature. The only marine chronic value reported was 2,166 ug/l
for the sheepshead minnow (Cyprinodan variegatus) (U.S. EPA, 1978).

C. Plant Effects

The freshwater algae Chlorella vulgaris and Selenastrum
capricornutum were fairly insensitive to the action of toluene: EC_{50}
values for cell numbers range from 245,000 ug/l for Chlorella

(Kauss and Hutchinson, 1975) to 433,000 ug/l for _Selenastrum_
(U.S. EPA, 1978). Among five marine algal species tested, _Skeletonema_
costatum was the most sensitive with an adverse effect on growth at
8,000 ug/l (Dunstan, et al., 1975).

D.   Residues

No bioconcentration factors are available for toluene in
freshwater or marine organisms.

VI.   EXISTING GUIDELINES AND STANDARDS

Both the human health and aquatic criteria derived by U.S. EPA
(1979), which are summarized below, have not yet gone through the
process of public review; therefore, there is a possibility that
these criteria may be changed.

A.   Human

The NIOSH (1973) recommended standard for exposure to
toluene is 100 ppm, determined as a time-weighted average for an
8-hour workday, with a ceiling of 200 ppm.

The U.S. EPA (1979) draft criterion for toluene in ambient
water is 12.4 mg/l, corresponding to a calculated acceptable daily
intake of 29.5 mg. This criterion is based on chronic toxicological
test data for rats (maximum no-effect level of 590 mg/kg, 5 days/wk)
and the application of an uncertainty factor of 1000.

B.   Aquatic

The draft criterion for the protection of freshwater
organisms is 2,300 ug/l, as a 24-hour average, not to exceed 5,200
ug/l; and for marine life the draft criterion is 100 ug/l, as a
24-hour average, not to exceed 230 ug/l.

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TOLUENE

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No. 161

2,4-Toluenediamine

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.   20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

2,4-TOLUENEDIAMINE

Summary

2,4-Toluenediamine produced carcinogenic effects in rats and mice in a long-term National Cancer Institute (NCI) feeding study (50 ppm; 100 ppm). 2,4-Toluenediamine was found to be mutagenic, using mutants of _Salmonella typhimurium_, hamster embryo cell systems, and _Drosophila melanogaster_.

2,4-Toluenediamine was also found to be hepatotoxic to rats and mice in the NCI study on carcinogenicity. The compound also hastened the development of chronic renal disease and accelerated animal morbidity. Data concerning the teratogenicity of 2,4-toluenediamine was not found in the available literature. However, a closely related compound, the 2,5-diamino analog, is teratogenic in mice.

I. INTRODUCTION

2,4-Toluenediamine (molecular weight 122.17) is white solid that melts at 99.°C, has a boiling point of 292°C, a density of 1.047 g/cm at 100°C, heat of vaporization of 27.975 kJ/mol, heat of fusion of 19.874, and a specific heat of 2.572 J/g at 150°C (Milligan and Gilbert, 1978). This compound is very soluble in hot benzene, in hot water, and in both alcohol and ether (Weast, 1971). The major use for 2,4-toluenediamine is in the manufacture of 2,4-toluenediisocyanate (TDI), the major raw material for the producton of flexible polyurethane foams and elastomers (Milligan and Gilbert, 1978). The production of 2,4-toluenediamine has increased more than 100 percent since 1966 and was reported in 1976 at 2.05 X 10^5 tons, with a predicted growth rate of 8-12 percent per year (Milligan and Gilbert, 1978). 2,4-Toluenediamine can also be used in the manufacture of dyes and was an important ingredient in human hair dyes of the permanent, oxidative type until 1971, when its use was restricted after being implicated in the induction of liver carcinomas in rats (Ito, et al. 1969). Using mutants of Salmonella typhimurium, Ames, et al. (1975) found 2,4-toluenediamine to be mutagenic.

II. EXPOSURE

Two potential sources of exposure to 2,4-toluenediamine are in its manufacture and its use as an intermediate in the production of 2,4-toluene-diisocyanate. 2,4-Toluenediamine is manufactured by seven U.S. companies at nine U.S. locations (Muller, 1979; Gunn and Cooke, 1976), and most of the corresponding diisocyanate is produced by the same companies at the same locations. Capacity for the latter compound is 3.75 X 10^5 tons yearly (Muller, 1979). Some additional amounts are consumed in the production of dyes or are exported to manufacturers of 2,4-toluenediisocyanate outside the United States. The amount consumed as a dye intermediate is believed to be

quite small, and the magnitude of the exports of 2,4-toluenediamine is un-known (Gunn and Cooke, 1976). Monitoring data are not available concerning exposure to 2,4-toluenediamine dermally or by water, food, inhalation. Dermal carcinogenicity in mice is discussed below under "Effects" ("Chronic Toxicity").

III. PHARMACOKINETICS

Information on the absorption, distribution, metabolism, and ex-cretion of 2,4-toluenediamine was not found in the available literature.

IV. EFFECTS

A. Carcinogenicity

Carcinoma of the liver with invasion and metastases was observed in rats fed diets containing 0.1 or 0.06 percent 2,4-toluenediamine (Ito, et al. 1969). When the compound was fed at levels of 50 and 100 ppm to inbred barrier-raised F344 rats for 2 years, a statistically significant increase was observed in the incidence of hepatic neoplasia in males, and it induced a significant dose-related positive trend in the incidence of liver neo-plasms in both sexes. Hepatocellular changes considered to be associated with neoplasia were increased at a high level of statistical significance in both sexes. The compound also caused statistically significant increases in the incidence of mammary tumors in females, and an increase of mammary tumors in males, although not significant statistically, was believed related to the chemical (Cardy, 1979; Ulland, 1979). 2,4-Toluenediamine was also carcinogenic for female B6C3F1 mice, inducing hepatocellular carcinomas. The incidence of lymphomas in the female mice suggested that these tumors may have been related to administration of the test chemical as well (Ulland, 1979).

B.   Mutagenicity

Fahmy and Fahmy (1977) conducted a comparative assay in <u>Drosophila melangaster</u> for the assessment of the mutagenic efficiency of the hair dye components 2,4-toluenediamine and 4-nitro-o-phenylenediamine relative to benzidine, a human carcinogen which, like 2,4-toluenediamine, is also an aromatic amine. All compounds showed mutagenicity activity. Although activities of the chemicals on the different genetic sites varied between compounds and as a function of cell stage, mutagenic activity did not vary in response to changes in dose. The mutagenicities and selectivities of the test compounds for ribosomal DNA gradually decreased in the order benzidine greater than 2,4-toluenediamine greater than 4-nitro-o-phenylenediamine. For 2,4-toluenediamine a good correlation was found between mutagenicity in the <u>Salmonella</u>/microsome test and morphological transformation in a hamster embryo cell system (Shah, et al. 1977). For mutagenesis, the compound required metabolic activation by a rat liver microsomal enzyme (S9) preparation. In contrast, transformation of hamster cells was induced without activation by external enzymes. In the Ames assay there was no mutagenic activity in the strain TA100, indicating that the product is not a base pair mutagen. The dose response curves obtained with tester strain TA1538 and TA98 show that 2,4-toluenediamine is metabolized by the S9 to a frameshift mutagen (Shah, et al. 1977). In a study of the mutagenic effect of 2,4-toluenediamine in mice, Soares and Lock (1978) found no significant increase in dominant lethal mutations (seven weeks post-treatment) on males.

C.   Teratogenicity

Data concerning the teratogenic effects of 2,4-toluenediamine were not found in the available literature. However, 2,5-toluenediamine, a closely related compound which is a hair dye constituent, was found teratogenic in mice (Inouye and Murakami, 1977).

D. Other Reproductive Effects

Information on other reproductive effects was not found in the available literature.

E. Chronic Toxicity

Two reports primarily dealing with carcinogenicity provide information on chronic toxicity. Cardy (1979) found that 2,4-toluenediamine was hepatotoxic when fed at levels of 50 and 100 ppm to inbred, barrier-raised F344 rats for 2 years. The compound also accelerated the development of chronic renal disease in the strain, an effect that contributed to a marked decrease in the survival rate. Giles and Chung (1976), in a chronic toxicity study of 2,4-toluenediamine alone or in combination with selected hair dye complexes, found the compound to be nontoxic and noncarcinogenic to the skin of mice.

F. Acute Toxicity

Lewis and Tatken (1979) summarize the available information:

Oral-human LD_0: 50 mg/kg   Subcutaneous-rat LD_{Lo}: 50 mg/kg

Oral-rat LD_0: 500 mg/kg   Subcutaneous-dog TD_{Lo}: 200 mg/kg

Oral-rat TD_{Lo}: 11 g/kg   Subcutaneous-dog LD_{Lo}: 400 mg/kg

where LD_0--lethal dose to all animals; TD_{Lo}--lowest toxic dose (other than inhalation); LD_{Lo}--the lowest published lethal dose (other than LD_{50}) introduced by any other route than inhalation.

G. Other Relevant Information

Except as reported above, no additional information was found on the effects of 2,4-toluenediamine.

V. AQUATIC TOXICITY

A. Acute Toxicity, Chronic Toxicity, Plant Effects, and Other Relevant Information.

No information was found in the available literature on acute toxicity, chronic toxicity, plant effects, and other relevant information.

B. Residues

Veith, et al. (1979), in a method of estimating the bioconcentration factor of organic chemicals in fathead minnows (Pimephales promelas), report a log biocentration factor of 1.96 and log n-octanol/water partition coefficient of 3.16* for the fathead minnow in 32 days' exposure. A structure-activity correlation between the bioconcentration factor (BCF) and the n-octanol/water partition coefficient (P) is expressed by the equation—log BCF = 0.85 log P-70. According to the authors, this permits the estimation of the bioconcentration factor of chemicals to within 60 percent before laboratory testing.

VI. EXISTING GUIDELINES AND STANDARDS

No existing guidelines or standards were found in the available literature.

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*Under the same conditions the log n-octanol/water partition coefficient for heptachlor was 5.44; for hexachlorobenzene, 5.23; for mirex, 6.89; and for dipheylamine, 3.42.

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Toluene Diisocyanate

Health and Environmental Effects

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OCTOBER 30, 1980

DISCLAIMER

This report represents a survey of the potential health
and environmental hazards from exposure to the subject
chemical. The information contained in the report is drawn
chiefly from secondary sources and available reference
documents. Because of the limitations of such sources, this
short profile may not reflect all available information
including all the adverse health and environmental impacts
presented by the subject chemical. This document has undergone
scrutiny to ensure its technical accuracy.

TOLUENE DIISOCYANATE

Summary

Toluene diisocyanate (TDI) is used in the manufacture of polyurethane foam. TDI is formed through the reaction of 2,4-toluenediamine with phosgene. The TDI is then reacted with di- and poly-functional hydroxy compounds to form polyurethane foam.

TDI is readily reactive in water, forming carbon dioxide and polyurea derivatives. Environmental occurence of TDI is unlikely due to its high reactivity with hydroxy compounds and peroxy radicals.

Information on the teratogenicity of toluene diisocyanate was not found in the available literature. TDI after being tested by the National Cancer Institute for carcinogenicity using a standard bioassay protocol, was found not be carcinogenic. Additionally, toluene diisocyanate did not show mutagenic activity on testing of <u>Salmonell</u> <u>typhimurium</u> strains with and without a mammalian liver microsome activating system.

Extensive toxicologic data exists for TDI, primarily from occupational exposure studies. TDI produces respiratory effects, including mucous membrane irritation, bronchoconstriction, coughing, and wheezing. Exposure to high concentrations can result in pulmonary edema or death.

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The effects of chronic, low-level exposure to TDI vary.
Decreased lung function has been reported from inhalation
of 0.003 ppm TDI, but other investigators have not seen these
respiratory effects from inhalation of 0.02 ppm TDI.
Hypersensitivity to TDI has also been observed from occupational
respiratory exposure. Immunologic and pharmacologic reactions
have been proposed as the mechanism of action of TDI.

Other reported effects include memory loss, psychological
disturbances, and skin irritation. Uncertainty exists regard-
ing the frequency of these effects in those occupationally
exposed. Maintaining exposure below 0.005 ppm has proven
effective in protecting health of unsensitized workers.
Where an individual has previously been sensitized, a no-
threshold effect is indicated upon subsequent exposure to
TDI.

TOLUENE DIISOCYANTE

Environmental Fate

Toluene diisocyanate (TDI) readily reacts with hydroxy compounds. Its atmospheric half-life is approximately three days (Brown, et al. 1975). TDI readily hydrolyzes in neutral aqueous media, or more rapidly under acidic or basic conditions, to give unstable carbamic acids (Tennant, 1979). These acids tend to lose carbon dioxide, giving the corresponding amine which, in turn, reacts with the starting isocyanate to produce a urea derivative. This reaction produces a concurrent decrease in pH (Curtis, et al. 1979). TDI readily hydrolyzes in water, and has a half-life of 0.5 seconds to 3 days, depending on pH (Brown, et al., 1975). As temperature increases the reaction becomes more vigorous (Tennant, 1979).

Brown, et al. (1975) concluded that because of the short lifetime of toluene diisocyanate in water, its occurrence in this medium is unlikely.

Toluene diisocyanate is persistent in the atmosphere. Under atmospheric conditions reaction with ozone leads to an atmospheric half-life of 3,981 days. The reaction of TDI with peroxyradical groups has an environmental half-life of approximately 7.94×10^5 days in the water phase.

I. INTRODUCTION

This profile is based upon relevant literature identified through bibliographic searches in TOXLINE and Chemical Abstracts, and through manual searches. The National Institute for Occupational Safety and Health (NIOSH) has published a criteria document for diisocyanates (NIOSH, 1978). This report represents a comprehensive review of the available toxicologic literature on toluene diisocyanate (TDI) and was the source for much of the data described below.

Toluene diisocyanate is also reported as 2,4-diisocyanate-1-methylbenzene, tolylene diisocyanate, methylphenylene isocyanate, diisocyanotoluene, and stilbene diisocyanate. The compound is a colorless-to-pale yellow liquid. The chemical formula is $C_9H_6N_2O_2$. Physical properties of TDI are as follows: molecular weight, 174.16; melting point, 20 to 22°C; boiling point, 251°C; vapor pressure, 0.05 mm Hg at 25°C; and specific gravity, 1.22 at 25°C (NIOSH, 1978). TDI is soluble aromatic hydrocarbons, nitrobenzene, acetone, ethers, and esters.

The most common method of synthesizing toluene diisocyanate is through the primary reaction of diaminotoluene with phosgene. Toluene diisocyanate is then reacted with di- and poly-functional hydroxy compounds to form poly-urethane foams, coatings, elastomers, and spandex fibers (NIOSH, 1978).

Toluene diisocyanate production in the U.S. was 605 million pounds (Predicasts, Inc., 1980) in 1978, with an estimated 6.4 percent annual growth in production. Production capacity amounted to 775 million pounds per year in 1978.

II. EXPOSURE

Respiratory and dermal exposure to toluene diisocyanate has been well documented in occupation environments (NIOSH, 1978). Sources of occupational exposures include production processes of basic TDI manufacture, production of polyurethane foam, and accidental releases or spills in product synthesis, transportation, use, or disposal.

Non-occupational exposure to TDI through ingestion of contaminated food or water is unlikely since TDI released to the environment would readily react with other compounds, forming stable polyurea end products. For example, Curtis, et al. (1979) conducted acute aquatic toxicity studies of TDI and reported the immediate reaction of TDI with water resulting in the production of carbon dioxide and a polyurethane foam-like solid. Human exposures would most likely occur to these polyurea compounds and not TDI. Accidental releases and spills may result in respiratory TDI exposure of persons in the immediate vicinity. Dermal exposure may also occur in persons coming in direct contact with the compound.

III. PHARMACOKINETICS

Information on the abosrption, distribution, metabolism, and excretion of TDI was not identified in the available literature. NIOSH (1978), in describing the sensitization phenomenon of TDI exposure, hypothesized that this response may be the result of TDI reaction with _in vivo_ hydroxyl, amino, sulfhydryl, or similar compounds which form a hapten complex with TDI. This complex is believed to be responsible for the sensitization of individuals to TDI.

IV. EFFECTS

A. ·Carcinogenicity

TDI did not show carcinogenic activity after being tested by NCI using a standard bioassay protocol.

B. Mutagenicity

Toluene diisocyanate did not show mutagenic activity on testing _Salmonella_ _typhimurium_ strains with or without a mammalian liver microsome activating system ·(NIOSH, 1978).

C. Teratogenicity and Other Reproductive Effects

Information on teratogenic or other reproductive effects of toluene diisocyanate was not found in the available literature.

D. Chronic Effects

Inhalation of toluene diisocyanate represents the primary route of exposure and produces chronic effects; the mechanism of the chronic respiratory changes is uncertain.

Toluene diisocyanate induces a hypersensitive reaction in specific individuals. Predisposing factors may include both environmental and endogenous host factors (Adkinson, 1977). Intensity and duration of exposure are important in eliciting a hypersensitive reaction. Genetic factors controlling immune responsiveness, metabolic aberration were suggested as factors influencing the allergic reaction (Adkinson, 1977). However, Butcher, et al. (1976) found no pattern of prior hay fever or asthama, or of skin sensitization in clinically sensitized individuals.

Exposure to high concentrations has caused respiratory sensitization in workers (Walworth and Virchow, 1959; Bruckner, et al. 1968). These sensitization reactions were described earlier. The sensitization can progress to a condition resembling chronic bronchitis and pulmonary edema. Individuals sensitized to TDI present an asthmatic reaction upon reexposure to very low concentrations of TDI. Butcher, et al. (1979) described four specific types of responses in hypersensitive workers: (1) immediate; (2) late; (3) dual; and (4) dose-related. The responses were measured as percent change in one-second Forced Expiratory Volume (FEV_1) over time. Immediate response occurred within one hour of exposure, whereas late response exhibited a gradual decline in FEV_1 over five hours. The dual response elicited an early response within one hour and a late response after eight hours. The dose-related response was exhibited at 0.01 ppm, whereas exposure to 0.005 ppm did not show a significant decrease in FEV_1. The author suggested a pharmacologic basis for the hypersensitivity, but noted that an allergic mechanism could not be ruled out.

Porter, et al. (1975) reported sensitization correlated with the frequency and severity of significant exposures greater than 0.05 ppm. Once sensitized, an individual exposed to very low concentrations of TDI will produce asthmatic reactions upon subsequent TDI exposure.

Wegman (1977) reported decrements in FEV_1 in both sensitized and unsensitized workers. However, Adams (1975) and Butcher, et. al. (1977) did not show decreased FEV_1 after occupational exposures of 11 and 2.5 years, respectively. TDI concentrations were 0.02 ppm and below, with occasional excursions above this level. Consequently, the National Institute for Occupational Safety and Health (NIOSH) recommended an eight hour time-weighted average limit of 5 ppb, noting that the above studies and others had not reported significant effects on lung function at concentrations of 14-50 ug/m^3 (2.0-7.0 ppb).

Some authors have reported skin sensitization in persons occupationally exposed to TDI (Nava, et al. 1975; Karol, et al. 1978), but other investigators have not observed such skin sensitization reactions (Munn, 1960; Bruckner, et al. 1968).

Other chronic effects from TDI exposure include neurologic effects, eye irritation, and psychological symptoms. Le Quesne, et al. (1976) reported memory loss lasting 4 years in workers exposed to massive concentrations of TDI while fighting a fire at a polyurethane foam factory.

F. Acute Effects

Inhalation of TDI is the primary route of exposure which has demonstrated acute effects. Several authors have reported daily and cumulative decreases in lung function following respiratory exposure to TDI. Investigations of

acute effects from TDI exposure have produced contradictory results. Peters, et al. (1968) reported significant decreases in lung function upon exposure to 0.1-3.0 ppb, whereas Adams (1975) noted no significant decrease in lung function at 20 ppb.

Occupational exposure to high concentrations of TDI causes direct irritation of the respiratory tract (Walworth and Virchow, 1959; Maxon, 1964; Axford, et al. 1976; Gandevia, 1963).

Eye, nose, and throat irritation was observed upon atmospheric exposures to 500 ppb (Henschler, 1962). Nausea, vomiting, and abdominal pain may also occur (Key, et al. 1977). Dermal contact with liquid TDI may produce redness, swelling, and blistering. Contact with eyes may produce severe irritation and permanent damage. Ingestion of TDI may cause burns of the mouth and stomach (Key, et al. 1977).

Lewis and Tatken (1979) reported an inhalation LC_{50} for rats of 600 ppm following a 6-hour exposure; and an inhalation LC_{50} for mice of 10 ppm following a 4-hour exposure.

V.   AQUATIC TOXICITY

    A.   Acute Toxicity

        Curtis, et al. (1979) reported a 96-hour LC_{50} of 164.5 mg/l in the fathead minnow (Pimephales promelas). No significant mortality was noted in grass shrimp (Palaemonetes pugio) exposed to 508.3 mg/l. The authors noted that TDI

reacted with water of dilution, and concluded that TDI was toxic to the fathead minnow in the unreacted form only, as evidenced by all mortalities occurring during the first 12 hours of the test. However, the authors did note that a concurrent decrease in pH was observed as a result of carbon dioxide formation from TDI reactivity. Lewis and Tatken (1979) reported an aquatic toxicity rating, TLm_{96} (equivalent to a 96-hour LC_{50}) of 1.0-10.0 ppm. Thus TDI has moderate acute toxicity to aquatic organisms.

B. Chronic Toxicity, Plant Effects, and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

The Occupational Safety and Health Administration (OSHA) regulates TDI by specifying a PEL for airborne TDI of 0.14 mg/ m^3 (40 CFR 1910.1000) as a 15-minute exposure.

The American Conference of Governmental Industrial Hygienists (1979) has recommended a threshold limit value-time weighted average for toluene diisocyanate of 5 ppb (0.04 mg/m^3). NIOSH (1978) recommended a time-weighted-average limit for airborne toluene diisocyanate of 5 ppb, with a ceiling value of 20 ppb. NIOSH (1978) also reported occupational exposure limits for TDI in numerous countries. These limits ranged from 0.07 to 0.5 mg/m^3.

TOLUENE DIISOCYANATE

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Toxaphene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.   20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health
and environmental hazards from exposure to the subject chemi-
cal. The information contained in the report is drawn chiefly
from secondary sources and available reference documents.
Because of the limitations of such sources, this short profile
may not reflect all available information including all the
adverse health and environmental impacts presented by the
subject chemical. This document has undergone scrutiny to
ensure its technical accuracy.

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated
toxaphene and has found sufficient evidence to indicate
that this compound is carcinogenic.

163.3

TOXAPHENE

SUMMARY

Toxaphene is a mixture of polychlorinated camphenes. It is obtained from camphene by photochemical chlorination, which produces a heterogeneous mixture of chemicals (177) containing 67 to 69 percent chlorine. Toxaphene has not produced teratogenic effects in laboratory animals, but has been found to be mutagenic in two strains of <u>Salmonella typhimurium</u> with metabolic activation. A National Cancer Institute (NCI) 1979 study found that toxaphene significantly increased the incidences of hepatocellular carcinomas in mice.

The insecticide toxaphene has been demonstrated to be a potent toxin to a variety of aquatic life. For both freshwater and marine fish species, acute toxicity values of 0.8 to 28 μg/l were reported. Marine invertebrate species displayed considerable interspecies variation, with LC_{50} values ranging from 0.08 to 2,700 μg/l.

TOXAPHENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria document for Toxaphene (U.S. EPA, 1979).

Toxaphene is a commercially produced, broad spectrum, chlorinated hydrocarbon consisting primarily of chlorinated camphene and related compounds and isomers. It is currently the most heavily used insecticide in the U.S., with an annual production rate exceeding 50×10^3 tons (U.S. EPA, 1979).

On May 25, 1977, because of its carcinogenic effects, aquatic toxicity, and high bioconcentration factor, the U.S. EPA issued a notice of rebuttable presumption against registration and continued registration of pesticide products containing toxaphene.

Toxaphene is an amber, waxy solid with a mild terpene odor and an average molecular weight of 414. Its physical properties include: melting point of 65-90°C; vapor pressure, 0.17-0.40 mm Hg at 25°C; solubility in water, 0.4-3.0 mg/l; and is soluble in relatively non-polar solvents, with an octanol/water partition coefficient of 825 (U.S EPA, 1979).

The commercial product is relatively stable but may dehydrochlorinate upon prolonged exposure to sunlight, alkali, or temperatures above 120°C (Metcalf, 1966; Brooks, 1974). In natural water systems, toxaphene tends to be absorbed by the particulates present or to be taken up by living organisms and bioconcentrated. Thus, it is seldom found as a soluble component in receiving waters but can persist

in sediments or remain absorbed on suspended solids for prolonged periods (U.S. EPA, 1979).

II. EXPOSURE

    A.   Water

Toxaphene has been monitored in the U.S. since 1959. Although it has been detected at several locations, it is not found in all waters (U.S. EPA, 1979). Seven routine monitoring studies of U.S. surface water prior to 1975 did not detect toxaphene (U.S. EPA, 1979).

Nicholson, et al. (1964, 1966) detected toxaphene in the drinking water obtained from Alabama at levels ranging from 0.01-0.1 μg/l. A survey of commercial drinking water samples by the U.S. EPA (1976a) during 1975 and 1976 found no detectable levels of toxaphene (limit of detection 0.05 μg/l).

Toxaphene has been detected in water around areas where it is applied to crops as an insecticide. For example, it has been detected in surface waters in California at levels ranging from 0.02 to 7.9 μg/l, and in drainage effluents at levels of 0.130 to 0.950 μg/l (Johnston, et al. 1967; Bailey and Hammon, 1967). Several studies of an agricultural watershed in Alabama found that treatment of drinking water did not reduce toxaphene concentrations (U.S. EPA, 1979).

Toxaphene has been detected in the sediment samples of various waters even when it is not found in samples of the surface waters (Mattraw, 1975). Concentrations as high as 2.46 μg/l have been found in sediments (U.S. EPA, 1979).

Sediment samples at three locations downstream of a plant producing toxaphene had a maximum residue level of 15 µg/l toxaphene before dredging (Reimold and Durant, 1972).

B.   Food

The best available estimate of dietary intake of toxaphene is 0.021 µg/kg/day, based on the U.S. Food and Drug Administration basket survey between 1964 and 1970 (Duggan and Corneliussen, 1972). Based on recent market basket surveys indicating a decrease in the incidence of toxaphene contamination, a stable incidence of toxaphene in raw meat since 1969, and a two-fold increase in the incidence of toxaphene in unprocessed food samples between 1972 and 1976, the U.S. EPA (1979) estimates the current dietary intake to be 0.042 µg/kg/day.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for toxaphene to be 18,000 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on the measured steady-state bioconcentration studies in five species of fish and shellfish.

C.   Inhalation

The highest toxaphene residues in air have been found in areas where toxaphene is applied for agricultural purposes (especially cotton production in the Southern U.S.) (U.S. EPA, 1979). Studies indicate that airborne residues are highest during cotton growing season and decrease to low levels after harvesting, but spring tilling releases

soil residues to the air. Concentrations ranging from 0 to 2520 ng/m^3 have been measured in southern agricultural areas (Arthur, et al. 1976; Stanley, et al. 1971.) Mean monthly concentrations have been measured as high as 167 ng/m^3 (Arthur, et al. 1976).

Toxaphene has also been monitored in the atmosphere over the east coast near Bermuda and the open ocean (Bidleman and Olney, 1975). The mean concentrations were 0.79 and 0.53 ng/m^3, respectively. Using the maximum mean monthly concentration of 167 ng/m^3 (Arthur, et al. 1976), the average daily dose of toxaphene from air is approximately 0.057 µg/kg (U.S. EPA, 1979). This amount would reflect intake at a high toxaphene use area, whereas a more conservative value using a concentration of 0.53 ng/m^3 monitored over open ocean (Bidleman and Olney, 1975) would be an average daily intake of 0.18 ng/kg of toxaphene from air (U.S. EPA, 1979).

D.   Dermal

Toxicity studies with laboratory animals indicate that toxaphene can be absorbed across the skin in toxic amounts by humans (U.S. EPA, 1979). Incidence of dermal absorption of toxaphene by humans is restricted to occupational or accidental exposure.

III. PHARMACOKINETICS

A.   Absorption

The recently completed U.S. EPA (1978) study suggests that inhalation exposures to toxaphene do not result in sufficient absorption by humans to cause quantifiable levels in the blood.

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Animal studies show absorption of toxaphene across the alimentary tract, skin, and respiratory tract, as indicated by adverse effects elicited by oral, dermal, and inhalation exposures (U.S. EPA, 1979). The vehicle and mode of administration, as well as individual differences, affect the rate of absorption of toxaphene. The ratio of oral LD_{50} to dermal LD_{50} (in comparable lipophilic solvents) is about 0.1 (Lackey, 1949a,b; Conley, 1952; U.S. EPA, 1979).

B. Distribution

Toxaphene is readily distributed throughout the body, with highest residues found in fat tissue. Three hours after single intubations of Cl-36 labelled toxaphene, rats had detectable levels of Cl-36 activity in all tissues examined (kidney, muscle, fat, testes, brain, blood, liver, intestines, esophagus, spleen, and stomach), with the highest levels being found in the stomach and blood (Crowder and Dindal, 1974.) After 9 to 14 days, most of the activity is found in the fat, blood, kidney, liver, and intestines (Crowder and Dindal, 1974; Ohsawa, et al. 1975). The predominance of fat storage had been demonstrated in 12-week feeding studies with rats, and 2-year feeding studies with rats and dogs (Clapp, et al. 1971; Lehman, 1952; Hercules, Inc., undated). In the above studies, toxaphene residues were highest in fat tissues but always remained below the levels administered in the diet, thus suggesting that toxaphene is not biomagnified in terrestrial organisms (U.S. EPA, 1979).

C. Metabolism

Toxaphene undergoes reductive dechlorination, dehydrochlorination, and hydroxylation in mammalian systems (U.S. EPA, 1979). Studies by Crowder and Dindal (1974), Ohsawa, et al. (1975) and Khalifa, et al. (1976) have observed 50 percent dechlorination of toxaphene after administration by intubation to rats, or in vitro with rat liver microsomes and NADPH under anaerobic conditions. Toxaphene has been suggested as a substrate for the hepatic microsomal mixed-function oxidases because of type I binding spectra with cytochrome P-450, and NADPH dependence (Kulkarni, et al. 1975; Chandurkar, 1977).

Several investigators have noted that fat residues of toxaphene resemble whole toxaphene, while residues in both the liver and feces are consistently more polar (Pollock, 1978; Saleh, et al. 1977).

D. Excretion

The half-life of C-14 or Cl-36 labelled toxaphene in rats after single oral doses appears to be from one to three days, with most of the excretion occurring via the urine and feces (Crowder and Dindal, 1974; Ohsawa, et al. 1975). Only a small portion of the urine and fecal metabolites is eliminated as glucuronide or sulfate conjugates (Chandurkar, 1977).

A study of the blood levels of toxaphene in an individual consuming contaminated fish (52 μg toxaphene/g fish) revealed levels of 142 ppb, 47 ppb, <30 ppb on day 1, day 11, and day 14 of measurement (U.S. EPA, 1978).

IV.   EFFECTS

A.   Carcinogenicity

The National Cancer Institute (1979) has recently completed a carcinogenicity bioassay of toxaphene. The 80-week feeding study did not follow current NCI standards; only ten animals were used in each matched control group, and matched-fed control groups were not utilized (NCI, 1977). The feeding schedule was as follows: for rats - males, time weighted average (TWA) doses at 556 mg/kg and 1,112 mg/kg, and females, TWA doses at 540 mg/kg and 1,080 mg/kg; and for mice, males and females, TWA doses at 99 mg/kg and 198 mg/kg.

In male rats in the high dose group, a significant increase was noted in the incidence of follicular-cell carcinomas and adenomas of the thyroid. Of the nine thyroid tumors which were found in this group, two were carcinomas. A significant increase of follicular-cell adenomas of the thyroid was also noted in the high-dose group of female rats. No carcinomas of the thyroid were found in this group. In both of these groups, the development of thyroid tumors was dose-related.

In both male and female mice, significant increases were noted in the incidence of hepatocellular carcinomas and in the incidence of hepatocellular carcinomas combined with neoplastic nodules of the liver.

Based on the results of this study, the National Cancer Institute has concluded that "Toxaphene was carcinogenic in male and female B6C3F1 mice, causing increased

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incidences of hepatocellular carcinomas. The test results
also suggest carcinogenicity of toxaphene for the thyroid
of male and female Osborne-Mendel rats" (NCI, 1979).

Litton Bionetics, Inc. (1978) also reported a
significant excess of hepatocellular tumors (hepatocellular
adenoma plus hepatocellular carcinoma) in male mice fed
dietary levels of 50 ppm toxaphene.

B.   Mutagenicity

The mutagenicity of toxaphene has been tested
in bacterial systems using Salmonella typhimurium strains
TA1535, TA1537, TA1538, TA98, and TA100 (Hill, 1977). Posi-
tive test results were obtained for strains TA98 (frameshift
mutation) and TA100 (base pair substitution) only in tests
without metabolic activation. All other tests were nega-
tive. A "high temperature" toxaphene has elicited positive
dose response increases in strains TA98 and TA100 only with
metabolic activation. In other studies, toxaphene and toxa-
phene subfractions have been found to be mutagenic to strain
TA100 with or without metabolic activation (Hill, 1977).

A study conducted by the U.S. EPA (1973) found
no significant differences in the rates of chromosomal aber-
rations in leukocytes between groups of workers occupation-
ally exposed to toxaphene and those not exposed.

C.   Teratogenicity

Toxaphene did not produce teratogenic effects
when administered in the diet of rats, mice, and guinea
pigs (U.S. EPA, 1979). Kennedy, et al. (1973) found no
indication of teratogenic effects in F3 weanlings of rats

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fed toxaphene at levels of 25 mg/kg diet and 100 mg/kg diet.
Pregnant rats and mice fed 15 to 35 mg/kg/day of toxaphene
produced young with no teratogenic effects as did pregnant
guinea pigs fed 15 mg/kg body weight (Chernoff and Carver,
1976; DiPasquale, 1977).

D.   Other Reproductive Effects

Adverse effects on fertility, gestation, viability,
lactation, or survival indices were not observed in male
and female rats fed dietary levels of 25 mg/kg and 100 mg/kg
toxaphene (Kennedy, et al. 1973), or in mice fed dietary
levels of 25 mg/kg toxaphene (Keplinger, et al. 1970).

E.   Chronic Toxicity

Long term exposures to low dietary levels of toxa-
phene have been investigated in several studies involving
rats, dogs, and monkeys (U.S. EPA, 1979). All studies noted
some form of liver pathology in rats at dietary levels of
100 mg/kg or above. At 100 mg/kg, cytoplasmic vacuolization
was noted by Kennedy, et al. (1973). Increased liver weight
with minimal liver cell enlargement was noted in rats at
dietary levels of 25 mg/kg (Fitzhugh and Nelson, 1951).
The lowest dietary level of toxaphene producing unequivocal
liver damage over a two-year feeding period was 20 mg/kg
(U.S. EPA, 1979). Only at high concentrations, i.e., 1,000
mg/kg diet, does toxaphene elicit central nervous system
effects (Hercules, Inc., undated).

F.   Other Relevant Information

Induction of hepatic microsomal mixed-function
oxidase (MFO) appears to account for most of the interactions

of toxaphene with other compounds (U.S. EPA, 1979). Pre-
treatment with known MFO inducers, such as DDT, aldrin,
and dieldrin, increases oral LC_{50}'s two to three-fold (Deich-
man and Keplinger, 1970). Piperonyl butoxide, which inhibits
the metabolism of many toxicants by MFO, has been shown
to potentiate the toxicity of toxaphene in houseflies (Saleh,
et al. 1977).

Keplinger and Deichmann (1967) found that equitoxic
combinations of toxaphene with parathion, diazinon, or tri-
thion were less toxic than expected based on the assumption
of simple similar action.

Acute human intoxication by toxaphene-lindane
mixtures produces signs and symptoms that are not character-
istic of toxaphene or lindane poisoning (Pollock, 1958;
Masumura, 1975).

V.   AQUATIC TOXICITY

   A.   Acute

   Acute toxicity data of toxaphene to freshwater
fish are derived from 52 96-hour LC_{50} values for 18 species
resulting from 48 static and 4 flow-through assays. Observed
LC_{50} values for these species of fish range from 0.8 µg/l
for the channel catfish (Ictalurus punctatus) to 28 µg/l
for the goldfish, (Carassius auratus) (U.S. EPA, 1979).
No single family or species appeared to be dramatically
more resistant or sensitive to toxaphene. For freshwater
invertebrates, 17 static bioassays on 13 species resulted
in reported LC_{50} values of 1.3 µg/l for the stonefly (Cla-
asenia sabulosa) to 178 µg/l for the crayfish (Procambarus
simulans) (U.S. EPA, 1978).

For the marine fish, toxicity data were determined from five flow-through and two static assay procedures representing six species. Observed LC_{50} values ranged from 0.5 µg/l for the pinfish (Lagodon rhomboides) to 4.7 µg/l for the threespine stickleback (Gasterosteus aculeatus) (U.S. EPA, 1979). The toxicity of toxaphene to marine invertebrates shows considerable interspecific variation in 31 assays (10 flow-through and 21 static) with reported LC_{50} values ranging from 0.054 µg/l for larval stages of the driftline crab (Sesarma cineseum) to 2,700 µg/l for the blue crab (Callinecten sapilus).

B. Chronic

Chronic life cycle toxicity tests have produced chronic values of 0.037 and 0.059 µg/l for the fathead minnow (Pimephales promelas) and channel catfish (Ictalurus punctatus), respectively (Mayer, et al. 1977). Growth effects were noted in brooktrout chronically exposed to concentrations of 0.038 µg/l. Life cycle tests on freshwater invertebrates have been performed on three species with chronic values of 0.09, 0.18, and 1.8 µg/l reported for Daphnia magna; the scud (Gammarus pseudolimnaeus); and midge larvae (Chironomus plumosus), respectively (Sanders, in press). An embryo-larval test on the marine fish sheepshead minnow (Cyprinodon variegatus) produced a chronic value of 0.83 µg/l (Goodman, et al. 1978). A chronic value of 0.097 µg/l was obtained for the marine mysid shrimp (Mysidopsis bahia) (Nimmo, 1977).

C.   Plant Effects

No data for the effects of toxaphene were found for freshwater species. Effective concentrations for five species of marine plants ranged from 0.15 µg/l for reduced growth in the dinoflagellate (Monochrysis lutheri) to 150 µg/l for lethality in the dinoflagellate (Danaliella euchlora) and no growth of the algae (Protococcus) sp. (U.S. EPA, 1978).

D.   Residues

Bioconcentration factors for three species of fish were reported (Mayer, et al. 1975; Mayer, et al. 1977). Brooktrout fry (Salvelinus fontinalis) had the highest factor of 76,000 in 15 days, while yearling brooktrout had the lowest factor of 16,000 in 161 days. In the marine longnose killifish (Fundulas similis), bioconcentrations for a number of different life stages were reported as 29,450 for juveniles, 27,900 for fry, 5,400 for adults, and 1,270 to 3,700 for ova of exposed adults (Schimmel, et al. 1977).

VI.   EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A.   Human

The standards for toxaphene in air, water, and food which have been established or recommended by various groups and agencies were set before the results of the NCI bioassay for carcinogenicity were available (U.S. EPA, 1979).

The ACGIH (1977) recommends a time weighted average value of 500 mg/m^3 for the working environment and a tentative short-term exposure limit of 1 mg/m^3. The national interim primary drinking water standard for toxaphene is 5 µg/l (40 FR 11990; U.S. EPA, 1976b, 1976c). The National Academy of Sciences (1977) estimated the acceptable daily intake of toxaphene for man at 1.25 µg/kg and suggested no-adverse-effect levels from water at 8.75 µg/l (assigning 20 percent of the total ADI to water) or 0.44 µg/l (assigning 1 percent of the total ADI to water). Effluent standards for toxaphene manufacturers have been set at 1.5 µg/l for existing facilities and 0.1 µg/l for new facilities (U.S. EPA, 1976a). Tolerances established by the U.S. Food and Drug Administration for toxaphene in various agricultural products range from 0.1 mg/kg in sunflower seeds to 7 mg/kg in meat fat (U.S. EPA, 1979).

The U.S. EPA (1979) draft water quality criterion for toxaphene is 0.467 ng/l or 4.7 x 10^{-4} µg/l. This criterion is based on the NCI (1979) study that reported hepatocellular carcinoma and neoplastic nodules in mice fed toxaphene; the criterion was calculated to keep the lifetime cancer risk below 10^{-5} for humans.

B. Aquatic

A drafted criterion for the protection of freshwater aquatic organisms is 0.007 µg/l for a 24-hour average concentration, not to exceed 0.47 µg/l at any time. For marine aquatic life, the drafted criterion is 0.019 µg/l for a 24-hour average concentration not to exceed 0.12 µg/l at any time (U.S. EPA, 1979).

TOXAPHENE

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1,1,1-Trichloroethane

(Methyl Chloroform (MC))

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.   20460

October 30, 1980

DISCLAIMER

This report represents a survey of the potential health
and environmental hazards from exposure to the subject chemi-
cal. - The information contained in this 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.

1,1,1-TRICHLOROETHANE (MC)

SUMMARY

Results of an NCI carcinogenesis bioassay of MC was inconclusive due to experimental problems. NCI and a manufacturer are currently re-evaluating its carcinogenic potential. _In vitro_ studies have indicated that MC is slightly mutagenic with or without activation, and can cause mammalian cell transformation. Studies of the teratogenic potential of MC are suggestive; however, more studies are needed to make a conclusive statement. Inhalation exposure of healthy adults to the current PEL for MC (350 ppm) has generally resulted only in untoward psychophysiologic effects. Animal studies, as well as accidental human exposure have shown that MC, at high inhalation concentrations, produces microscopic pathology of liver and kidneys which is much less severe than that produced by carbon tetrachloride or tetrachloroethylene. MC is moderately toxic to aquatic life.

I. INTRODUCTION

The chlorinated ethanes are hydrocarbons in which one or more of the hydrogen atoms of ethane are replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. At room temperature, 1,1,1-trichloroethane (M.W. 133.4) is a liquid with a boiling point 74.1°C, a vapor pressure (20°C) of 100 torr, a melting point of -33°C, a specific gravity of 1.3492, and a low solubility in water (U.S. EPA, 1980a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds.

The 1976 production of 1,1,1-trichloroethane was: 3×10^3 kkg/year (U.S. EPA, 1980a).

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1980a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1980b).

II. EXPOSURE

The chloroethanes present in raw and finished waters are due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water

or treatment of sewage. Air levels of chloroethanes are
produced by evaporation of these compounds, widely used as
degreasing agents and in dry cleaning operations (U.S. EPA,
1980a). Occupational air monitoring studies have indicated
1,1,1-trichloroethane levels ranging from 1.5 to 396 ppm
(U.S. EPA, 1980a).

Sources of human exposure to chloroethanes include water,
air, ingestion of contaminated foods and fish, and dermal
absorption.

Human exposure to MC was estimated from ambient air
monitoring data. At 8 cities values of 0.02 to 1.86 ug/kg/day
were calculated. At one city, however, where an MC manufacturing
facility is located, 12-86 ug/kg/day was calculated (USEPA 1980).
Drinking water showed only traces (0.05-1.0 ppb) of MC,
except near a MC producing facility (USEPA, 1980).

An analysis of several foods indicated 1,1,1-trichloroethane
was present at levels of 1-10 ug/kg (Walter, et al., 1976).
Fish and shellfish have shown levels of 1,1,1-trichloroethane
in the nanogram range (Dickson and Riley, 1976).

The U.S. EPA (1980a) has estimated the weighted average
bioconcentration factor for 1,1,1-trichloroethane to be 21
for the edible portions of fish and shellfish consumed by
Americans. This estimate is based on the measured steadystate
bioconcentration studies in bluegills.

III. ATMOSPHERIC FATE AND TRANSPORT

Because of its volatility, its transformation into other
potentially harmful atmospheric components, its tropospheric
chemical reactivity, and its diffusion into the stratosphere,
MC is thought to pose a hazard to human health.

The volatilization of MC from water can be reversible
because it is stable in the atmosphere and is transported
back to surface water via rainfall. Tropospheric half-lives
of twenty weeks (Pearson and McConnell, 1975) to 8 years
(McConnell and Schiff, 1978) indicate that MC is highly stable
in the troposphere. Dilling et. al., (1976) estimated the de-
composition rate of MC under simulated atmospheric conditions
to be less than 5% in 23.5 hours. It is generally accepted
that the larger the tropospheric residence time of a chemical
species, the greater is the likelihood of its diffusion into
the stratosphere (U.S. EPA, 1980b). In a recent study of
the impact of chloro and chlorofluoro compounds on stratospheric
ozone, based on atmospheric measurement data, the NAS concluded
(1979) that MC contributes one quarter to one half as many
chlorine atoms to the stratosphere as do CFC's 11 and 12; at
the 1976 global emission rate MC is estimated (NAS, 1979) to
destroy 8 to 15 percent as much ozone as do both CFC 11 and
12. Thus, release from improperly disposed solid wastes
containing MC may pose a possible threat to the environment.

IV. PERSISTENCE

MC is inert to reaction with oxygen under normal conditions, except at high temperatures. There are two laboratory studies of the hydrolysis of MC (Dilling, 1975; Pearson and McConnel, 1975). These studies used two different methods for calculating the hydrolytic half life (U.S. EPA, 1980c). The hydrolytic half-life is about 5-9 months in freshwater, and about 39 months in sea water (Pearson and McConnel, 1975; U.S. EPA, 1980c).

At ambient temperatures MC hydrolyzes to acetic and hydrochloric acids. Vinylidene chloride (a CAG listed carcinogen) is a minor product, except at 10°C and at slightly alkaline pH when it is the major product of hydrolysis (Pearson and McConnell 1975, U.S. EPA, 1980c).

MC undergoes photochemical oxidation (Dilling et. al., 1975; Appleby, 1976; U.S. EPA, 1980c), yielding estimates for global average residence time of 1.4 to 12 years (U.S. EPA, 1980c). From these estimated lifetimes it was inferred that between 10 and 20 percent of the MC molecules produced will reach the stratosphere.

V. PHARMACOKINETICS

A. Absorption

The chloroethanes are rapidly absorbed following oral or inhalation routes of exposure (U.S. EPA, 1980a). Slow dermal absorption of 1,1,1-trichloroethane has been demonstrated in humans (Stewart and Dodd, 1964).

B. Distribution

Stahl, et al. (1969) have noted the presence of 1,1,1-trichloroethane in the liver, brain, kidney, muscle, lung and blood in post-mortem tissue samples following high levels of exposures. MC accumulates in the liver, kidney, and brain of the mouse following inhalation exposure (Holmberg, et. al., 1977).

C. Metabolism

The metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation to corresponding alcohols (U.S. EPA, 1979a). Oxidation reactions may produce unsaturated metabolites which are then transformed to the alcohol and ester (Yllner, 1971a,b,c,d). Trichloroethanol and trichloroacetic acid have been identified in the urine of rats following inhalation exposure to 1,1,1-trichloro-ethane (Ikeda and Ohtsuji, 1972). Metabolism appears to involve the mixed-function oxidase system (Van Dyke and Wineman, 1971).

D. Excretion

The chloroethanes are excreted primarily in the urine and expired air (U.S. EPA, 1980). Monster and co-workers (1979) reported that 60-80 percent of 1,1,1-trichloro-ethane inhaled by volunteers was expired unchanged; two urinary metabolites represented 3 percent of the uptake. Excretion of the chloroethanes is generally rapid, the major-ity of compound being eliminated within 24 hours (U.S. EPA, 1980a).

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VI. EFFECTS

A. Carcinogenicity

The NCI (1977) conducted a bioassay of MC using mice and rats. Although a variety of neoplasms were observed, no relationship was established bewteen dosage groups, species, sex type of neoplasm or site of occurence. The shortened life spans of the test animals due to the toxicity of the chemical made an assessment of carcinogenicity impossible (NCI, 1977). The NCI and a manufacturer of MC are currently retesting the compound for carcinogenicity.

Price et. al., (1978), have demonstrated in vitro transformation of rat embryo cells by MC. Injection of these cells in vivo produced undifferentiated fibrosarcomas at the site of inoculation in all tested animals.

B. Mutagenicity

Several groups have investigated the mutagenicity of MC in the Ames assay. Henschler et. al. (1977) found MC inactive both with and without addition of microsomes, using TA-100 strain of S. typhimurium. Simmon et. al. (1977) used slightly different assay conditions and reported that MC is slightly mutagenic to this strain. A dose response was evident, and metabolic activation did not alter mutagenicity.

C. Teratogenicity

Schwetz et. al. reported (1974, 1979) on inhalation studies (at 87.5 ppm) on pregnant mice and rats. A number of

skeletal abnormalities were noted, but these were of marginal

statistical significance. Additional studies are needed.

MC, when injected into the air space of fertilized chicken

eggs at 2, 3 and 6 days of incubation is embryotoxic (LD_{50}

of 50-100 mM/egg), and induces a variety of birth malfor-

mations (Elovaora et. al.: 1979). Both these studies suggest

that MC has teratogenic potential, and that further experiments

should be performed to confirm this potential toxicity.

D.   Other Reproductive Effects

Pertinent information could not be located in the

available literature on other reproductive effects of 1,1,1-

trichloroethane.

E.   Chronic Toxicity (U.S. EPA, 1980b)

Inhalation exposure of healthy adults to the current

TLV for MC (350 ppm) generally does not result in significant

untoward physiologic effects. Studies of human

exposure to 100-500 ppm have shown only subjective symptoms

of light-headedness, syncope, mild headache and nausea, and

objective symptoms of eye, nose and throat irritation. No

significant clinical chemistry organ function tests (e.g.

liver function) have been noted. However, adverse effects

on the performance of manual tasks have been documented.

At higher exposures (>10,000 ppm) MC produces anesthesia

and cardiovascular effects which can be lethal. Animal

studies, as well as accidental human exposure, have shown that

MC, at these high concentrations, produces a "chlorinated hydrocarbon" type of microscopic pathology of liver and kidneys (fatty infiltration and cellular necrosis) which is much less severe than that produced by carbon tetrachloride.

VI. AQUATIC TOXICITY

A. Acute Toxicity

For freshwater fish, 96-hour static LC_{50} values of 69,700 ug/l for the bluegill Lepomis macrochirus and 150,000 ug/l for the fathead minnow, Pimephales promelas, while a single 96-hour flow-through LC_{50} value of 52,800 ug/l was obtained for the fathead minnow, Pimephales promelas, (Alexander, et. al. 1978). For marine organisms, 96-hour static LC_{50} values ranged from 31,200 ug/l for the mysid shrimp, Mysidopsis bahia, to 70,900 ug/l for the sheepshead minnow, Cyprinodon variegatus, (U.S. EPA, 1978).

B. Chronic Toxicity and Plant Effects

Pertinent information could not be located in the available literature.

C. Residues

A bioconcentration factor of 9 was obtained for the bluegill (U.S. EPA, 1980a).

VIII. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1980a), 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 mammalian toxicology data, the EPA (1979a) has prepared a draft ambient water quality criterion to protect human health at the level of 15.7 mg/1 for 1,1,1-trichloroethane.

The 8-hour, TWA exposure standard established by OSHA for 1,1,1-trichloroethane is 350 ppm.

B.   Aquatic

The freshwater criterion has been drafted as 5,300 ug/1 as a 24-hour average, not to exceed 12,000 ug/1; while the criterion to protect marine life has been drafted as a 24-hour average concentration of 240 ug/1, not to exceed 540 ug/1.

1,1,1-TRICHLOROETHANE

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1,1,2,-Trichloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.   20460

APRIL 30, 1980

~~1981~~

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 1,1,2-trichloroethane and has found sufficient evidence to indicate that this compound is carcinogenic.

1,1,2-TRICHLOROETHANE

Summary

Results of a National Cancer Institute carcinogenesis bioassay indicate that oral administration of 1,1,2-trichloroethane produces an increase of several tumor types in rats and mice.

Information is not available to indicate if 1,1,2-trichloroethane has any mutagenic effects, teratogenic effects, or adverse reproductive effects.

Animal studies have indicated that exposure to 1,1,2-trichloroethane may produce liver and kidney toxicity.

Aquatic toxicity data for 1,1,2-trichloroethane is limited, with only two acute studies in freshwater fish and invertebrates available. Toxic doses ranged from 18,000 to 40,200 µg/l.

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1,1,2-TRICHLOROETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms of ethane are replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while both density and melting points increase. 1,1,2-Trichloroethane (molecular weight 133.4) is a liquid at room temperature with a boiling point of $113^{o}C$, a melting point of $-37.4^{o}C$, a specific gravity of 1.4405, and slightly soluble in water (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds.

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963) and all are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes are present in raw and finished waters primarily from industrial discharges. Small amounts of chloroethanes may be formed by chlorination of drinking water or treatment of sewage. A metropolitan water monitoring study has shown finished water levels from 0.1 to 8.5 µg/l for 1,1,2-trichloroethane (U.S. EPA, 1979a). Air levels of chloroethanes are produced by evaporation of volatile chloroethanes widely used as degreasing agents and in dry-cleaning operations (U.S. EPA, 1979a).

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976).

Pertinent information was not found in the available literature on 1,1,2-trichloroethane levels in food.

The U.S. EPA (1979b) has estimated the weighted bioconcentration factor for 1,1,2-trichloroethane to be 6.3. This estimate was based on the octanol/water partition coefficient for 1,1,2-trichloroethane.

III. PHARMACOKINETICS

A. Absorption

The chloroethanes are absorbed rapidly following oral or inhalation routes of exposure (U.S. EPA, 1979a). Dermal absorption of 1,1,2-trichloroethane may be extensive as indicated by lethal toxicity in animals following dermal exposure (Smyth, et al. 1969).

B. Distribution

Specific information on the distribution of 1,1,2-trichloroethane has not been found in the available literature. The reader is referred to a more general treatment of the chloroethanes (U.S. EPA, 1979b) which indicates widespread distribution of these compounds throughout the body.

C. Metabolism

The metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation to corresponding alcohols (U.S. EPA, 1979a). Oxidation reactions may produce unsaturated metabolites which are then transformed to the alcohol and ester (Yllner, 1971). Trichloroethanol and trichloroacetic acid have been identified in the urine of rats following inhalation exposure to 1,1,2-trichloroethanol (Ikeda and Ohtsuji, 1972). Metabolism appears to involve the activity of the mixed function oxidase system (Van Dyke and Wineman, 1971).

D. Excretion

The chloroethanes are excreted primarily in the urine and in expired air (U.S. EPA, 1979a) with excretion being generally rapid. Experiments conducted by Yllner (1971) indicate that following intraperatoneal injection of 1,1,2-trichloroethane into mice, more than 90 percent of the administered dose is excreted in 24 hours, with more than half found in the urine. Ten to twenty percent of injected compound is found in expired air.

IV. EFFECTS

A. Carcinogenicity

Results of an NCI carcinogenesis bioassay for 1,1,2-trichloroethane show that oral administration of compound produced an increase of several tumor types (NCI, 1978). Rats showed adrenal carcinomas, kidney carcinomas, and varied hemangiosarcomas, while mice showed an increase in hepatocellular carcinomas.

B. Mutagenicity, Teratogenicity and Other Reproductive Effects

Available information on this compound is very limited in these areas. A search of the literature did not reveal any pertinent data.

C. Chronic Toxicity

Animal studies have indicated that exposure to 1,1,2-trichloroethane may produce liver and kidney toxicity (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

A. Acute Toxicity

The only aquatic toxicity data for 1,1,2-trichloroethane are single static bioassays on the bluegill (Lepomis macrochirus) and Daphnia magna. The acute 96-hour LC_{50} value for the bluegill was 40,200 μg/l, while the 48-hour LC_{50} value for Daphnia magna was 18,000 μg/l (U.S. EPA, 1979). Marine studies are presently not available.

B. Chronic Toxicity, Plant Effects and Residues

Available information on this compound is very limited in these areas. A search of the literature did not reveal any pertinent data.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on the NCI carcinogenesis data, and using a linear, non-threshold model, the U.S. EPA (1979a) has estimated the level of 1,1,2-tri-chloroethane in ambient water that will result in an additional cancer risk of 10^{-5} to be 2.7 µg/l.

The 8-hr, TWA exposure standard for 1,1,2-trichloroethane is 10 ppm.

B. Aquatic

The draft criterion for protection of freshwater aquatic life is 310 µg/l as a 24-hour average; the concentration should not exceed 710 µg/l at any time (U.S. EPA, 1979a). No criterion for protection of saltwater aquatic life has been found.

1,1,2-TRICHLOROETHANE

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Trichloroethylene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.   20460

APRIL 30, 1980

#990-

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated

trichloroethylene and has found sufficient evidence to

indicate that this compound is carcinogenic.

DISCLAIMER

This report represents a survey of the potential health
and environmental hazards from exposure to the subject chemi-
cal. 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.

TRICHLOROETHYLENE

SUMMARY

Trichloroethylene is a colorless liquid used mainly as a degreasing solvent. Both acute and chronic exposure to high levels of trichloroethylene produce central nervous system depression and other neurological effects. Trichloroethylene also causes some kidney and liver damage. Trichloroethylene has not been shown to be a teratogen, and the data suggesting mutagenicity and carcinogenicity are weak. The studies of mutagenicity and carcinogenicity have been complicated by the presence of contaminants with known carcinogenic and mutagenic activity. However, the cancer assessment group has determined that Trichloroethylene is carcinogenic.

Only a few studies have been reported on trichloroethylene toxicity to aquatic species. Fathead minnows, when exposed in flow through and static tests, had 96 hour LC_{50} values of 40,700 and 66,800 µg/l, respectively. The 96 hour LC_{50} for the bluegill was 44,700 µg/l in static tests. The 48 hour LC_{50} for the freshwater invertebrate, Daphnia magna, was 85,200 µg/l. In the only reported chronic test, no adverse effects were observed in Daphnia magna exposed to 10,000 µg/l. Photosynthesis was reduced by 50 percent in the alga, Phaedactylan tricornutum, at a concentration of 8,000 µg/l. Trichloroethylene was bioconcentrated 17-fold by the bluegill after 14 days exposure. The half life of this compound in tissues was less than 1 day.

TRICHLOROETHYLENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Trichloroethylene (U.S. EPA, 1979).

Trichloroethylene (C_2HCl_3, 1,1,2-trichloroethylene, TCE, molecular weight 131.4) is a clear, colorless liquid. Trichloroethylene has a water solubility of 1,000 µg/ml; a vapor pressure of 77 mm Hg and a melting point of 83^0C (Patty, 1963). Trichloroethylene is mainly used as a degreasing solvent, and is used to lesser extents as a household and industrial dry-cleaning solvent, an extractive solvent in foods, and as an inhalable anesthetic during certain short-term surgical procedures (Huff, 1971).

Current Production: Annual production of trichloroethylene in the United States approximates 234,000 metric tons (U.S. EPA, 1979). The volatilization of trichloroethylene during production and use is the major source of environmental levels of this compound. Trichloroethylene is not expected to persist in the environment because of its rapid photooxidation in air, its low water solubility, and its volatility (Pearson and McConnell, 1975; Dillings, et al. 1976; Patty, 1963).

II. EXPOSURE

A. Water

The National Organics Monitoring Survey observed trichloroethylene in 28 of 113 drinking waters at a mean concentration of 21 µg/l in May through July, 1976 (U.S. EPA, 1979). Trichloroethylene may be formed during the chlorination of water (National Academy of Science, 1977; Bellar, et al. 1974).

B. Food

There is little information concerning the occurence of trichloro-
ethylene in U.S. foodstuffs. In England, trichloroethylene has been ob-
served at concentrations up to 10 μg/kg in meats, up to 5 μg/kg in fruits,
vegatables, and beverages (McConnell, et al., 1975); packets of tea were
found to contain 60 μg/kg (Fishbein, 1976). Little trichloroethylene would
be expected in other foodstuffs, except in the case where it is used as a
solvent for food extractions. The U.S. EPA (1979) has estimated the
weighted bioconcentration factor of trichloroethylene to be 39. This esti-
mate is based on measured steady-state bioconcentration studies in bluegills
and estimates of fish and shellfish consumption.

C. Inhalation

The only significant exposure to trichloroethylene in air occurs to
a relatively small, industrially exposed population (Fishbein, 1976).

III. PHARMACOKINETICS

A. Absorption

Trichloroethylene is readily absorbed by all routes of exposure.
In humans exposed to the compound by inhalation, steady state conditions are
approached within two hours. Absorption of trichloroethylene following in-
gestion has not been studied in humans. In rats, at least 80 percent of an
orally administered dose is systemically absorbed (U.S. EPA, 1979).

B. Distribution

In humans, trichloroethylene is distributed mainly to body fat (McConnell, et al. 1975). Laham (1970) demonstrated transplacental diffusion of trichloroethylene in humans.

C. Metabolism

Qualitatively the metabolism of trichloroethylene appears to be similar across species (Kimmerle and Eben, 1973). The principal products of trichloroethylene metabolism measured in urine are, trichloroethanol, trichloroacetic acid, and conjugated derivatives (glucuronides) of trichloroethanol. A reactive epoxide, trichloroethylene oxide, has been shown to be formed during the metabolism of trichloroethylene; it can alkylate nucleic acids and proteins (Van Duureen and Banerjee, 1976; Bolt and Filser, 1977). Patterns of metabolism of trichloroethylene in humans differ between male and female (Nomiyama and Nomiyama, 1971), and with age (U.S. EPA, 1979). Increased microsomal enzyme activity enhances the conversion of trichloroethylene to trichloroacetaldehyde (U.S. EPA, 1979). Ethanol interferes with the metabolism of trichloroethylene, causing ethanol intolerance in exposed workers (U.S. EPA, 1979).

D. Excretion

Trichloroethylene and its metabolites are excreted in exhaled air, urine, sweat, feces, and saliva (Kimmerla and Eben 1973; U.S. EPA, 1979). Trichloroethylene is lost from the body with a half-life of about 1.5 hours (Stewart, et al. 1962); however, its metabolites have longer half-lives ranging from 12 to 73 hours (Ikeda and Imamura, 1973; Ertle, et al. 1972).

IV. EFFECTS

A. Carcinogenicity

The National Cancer Institute (NCI, 1976) observed an increased incidence of hepatocellular carcinoma in mice (strain B6C3-F1) treated with trichloroethylene. Similar experiments in Osborne-Mendel rats failed to increase the incidence of tumors in this species. It has been pointed out that trichloroethylene used in the NCI bioassay (1976) contained traces of monofunctional alkylating agents, epichlorohydrin and epoxibutane, as stabilizers, and they might account for the observed carcinogenicity (U.S. EPA, 1979). No systematic study of humans exposed to trichloroethylene have revealed a correlation with cancer (Axelson, et al. 1978).

B. Mutagenicity

Trichloroethylene has been reported to be mutagenic, in the presence of mammalian liver enzymes, to a number of bacterial strains. These include E. coli K12, and S. typhimurium strain TA 100 (U.S. EPA, 1979; Simmon, et al. 1977), in addition to the yeast Saccharomyces cerevisiae (Shahin and VonBarstel, 1977). However, there is some doubt as to the mutagenicity of trichloroethylene due to epichlorohydrin and epoxibutane contamination. Henscher, et al. (1977) observed that these contaminants were potent mutagens in S. typhimurium strain TA100. Pure trichloroethylene was weakly mutagenic.

C. Teratogenicity

Exposure of mice and rats to 1600 mg/m^3 trichloroethylene for seven hours a day on days 6 through 15 of gestation did not produce teratogenic effects (Schwetz, et al. 1975).

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

Disturbances of the nervous system, which continue for at least a year after final exposure, were observed following industrial exposure to trichloroethylene (Nomiyama and Nomiyama, 1977; Bardodej and Vyskoch, 1956). Symptoms included headaches, insomnia, tremors, severe neuroasthemic syndromes coupled with anxiety states, and bradycardia. Prolonged occupational exposures to trichloroethylene have been also associated with impairment of the peripheral nervous system. This can include persistent neuritis (Bardodej and Vyskoch, 1956), temporary loss of tactile sense, and paralysis of the fingers (McBirney, 1954). Rare cases of hepatic damage have been observed following repeated abuse of trichloroethylene (Huff, 1971).

F. Other Relevant Information

Long-term toxicity of trichloroethylene appears to depend largely on its metabolic products (U.S. EPA, 1979). Chemicals that enhance or depress the mixed function oxidase system will have a synergistic or antagonistic effect, respectively, on the toxicity of trichloroethylene.

Trichloroethylene has been shown to induce transformation in a highly sensitive in vitro Fischer rat embryo cell system (F1706) (U.S. EPA, 1979). Following exposure of cells to 1 M trichloroethylene, the cells formed progressively growing foci made up of cells lacking contact inhibition, and the cells gained the ability to grow in semi-solid agar.

V. AQUATIC TOXICITY

A. Acute Toxicity

Alexander, et al. (1978) exposed fathead minnows (Pimephales promelas) to trichloroethylene in flow-through and static tests. The observed 96-hour LC_{50} values were 40,700 and 66,800 µg/l, respectively. The observed 96-hour LC_{50} for the bluegill (Lepomis macrochirus) is 44,700 µg/l in static tests (U.S. EPA, 1978). The 48 hour LC_{50} for Daphnia magna and is 85,200 µg/l (U.S. EPA, 1978). No saltwater fish or invertebrate acute toxicity data were found in the available literature.

B. Chronic Toxicity

In the only reported chronic test, no adverse effects were observed with Daphnia magna at the highest test concentration of 10,000 µg/l (U.S. EPA, 1978).

C. Plant Effects

There was a 50 percent decrease noted in ^{14}C uptake by the salt-water alga, Phaedectylum tricornutum, at a concentration of 8,000 µg/l (Pearson and McConnell, 1975).

D. Residues

Bioconcentration by bluegills was studied (U.S. EPA, 1978) using radiolabeled trichloroethylene. After 14 days the bioconcentration factor was 17. The half-life of this compound in tissues was less than one day.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The Food and Drug Administration (1974) has limited the concentration of trichloroethylene in final food products to 10 mg/kg in instant

coffee, 25 mg/kg in ground coffee and 30 mg/kg in spice extracts. The American Conference of Governmental Industrial Hygienists (ACGIH) TLV is 535 mg/m^3.

The Cancer Assessment Group (CAG) has determined that, at the present time, under existing policy, TCE is a carcinogen. The NCI bioassay (the results from which CAG has made their determination) is being repeated. When the data is available, it should be reviewed.

B. Aquatic

For trichloroethylene, the draft criterion to protect freshwater aquatic life is 1,500 ug/l as a 24-hour average; the concentration should not exceed 3,400 µg/l at any time. Criterion for saltwater species has not been developed because sufficient data could not be located in the available literature.

TRICHLOROETHYLENE

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No. 167

Trichlorofluoromethane, Dichlorodifluoromethane

and Trichlorotrifluoroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C.   20460

October 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documetns. 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.

TRICHLOROFLUOROMETHANE, DICHLORODIFLUOROMETHANE
AND TRICHLOROTRIFLUOROETHANE

SUMMARY

Trichlorofluoromethane (F-11), dichlorofluoromethane (F-12) and 1,1,2-trichloro-1,2,2-trifluoroethane (F-113) are not easily degraded in the environment. After release at the surface of the earth, F-11 and F-12 and F-113 mix with the atmosphere and rise slowly into the stratosphere where they are decomposed by ultraviolet radiation to release chlorine atoms. The chlorine atoms react with ozone, thereby reducing the total amount of ozone in the stratosphere and permitting an increased amount of biologically active ultraviolet radation to reach the earth's surface. The accumulation of F-11, F-12 and F-113 in the atmosphere also increases the absorption and emission of infrared radiation (the "greenhouse" efect).

F-11, F-12 and F-113 are absorbed via the lungs, gastrointestinal tract, and skin, however, most of that which is absorbed is eliminated unchanged in expired air.

F-11 was not found carcinogenic in a long-term mouse study. The carcinogenic potential of F-113 has not been tested by NCI, and few specific studies have been documented. F-11, F-12 and F-113 were negative in the Ames <u>Salmonella</u> test; F-12 was positive in a <u>Neurospora</u> <u>crassa</u> test system.

At high concentrations in air, these compounds have been shown to induce cardiovascular and pulmonary effects in animals.

In March 1979, fully halogenated chlorofluoroalkanes (including F-11, F-12 and F-113) were banned as propellants in the United States except for essential uses. The action was taken because the chlorofluoroalkanes may deplete the stratospheric ozone, leading to various adverse effects.

I. INTRODUCTION

This paper is based on an EPA report entitled "Environmental Hazard Assessment Report: Major One- and Two-Carbon Saturated Fluorocarbons" (U.S. EPA, 1976a).

Trichlorofluoromethane and dichlorofluoromethane are commonly referred to by their fluorocarbon numbers, which are F-11 and F-12, respectively. This convention will be followed in this paper. 1,1,2-Trichlo-1,2,2-trifluoroethane is dubbed F-113.

F-11, a colorless volatile liquid, F-12, a colorless gas, and F-113, a non-flammable colorless liquid, have the following physical/chemical properties (U.S. EPA, 1976a, Downning, 1966).

	F-11	F-12	F-113
Molecular Formula	CCl_3F	CCl_2F_2	$CCl_2F-CClF_2$
Molecular Weight	137	120	187
Boiling Point (°C)	23.8	-29.8	47.6
Freezing Point (°C)	-111	-158	--
Solubility (gm/100gm H_2O, 0°C, 1 atm.)	soluble in water and many organic solvents		0.017

A review of the production range (includes importation) statistics for trichlorofluoromethane (CAS No. 75-69-4) which is listed in the initial TSCA Inventory (1979) has shown that between 100 million and 200 million pounds of this chemical were produced/imported in 1977.*

A review of the production range (includes importation) statistics for dichlorodifluoromethane (CAS No. 75-71-8) which is listed inthe initial TSCA Inventory (1979) has shown that between 200 million and 300 million pounds of this chemical were produced/imported in 1977*

The major uses of F-11 and F-12 are as aerosol propellants, refrigerants, and foaming agents (U.S. EPA, 1976a).

II. EXPOSURE

A. Environmental Fate

Although F-11 and F-12 volatilize quickly from water and soils, they are considered persistent in the environment due to their resistance to biodegradation, photodecomposition, and chemical degradation (U.S. EPA, 1975a). AFter release at the surface of the earth, F-11, F-12 and F-113 (as well as other chlorofluoromethanes) mix with the atmosphere and rise

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*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

slowly into the stratosphere where they are decomposed by ultraviolet radiation to release chlorine atoms. Chlorine atoms and a subsequent reaction product, chlorine oxide, react with ozone and oxygen atoms, thereby reducing the total amount of ozone in the stratosphere and somewhat shifting the distribution of ozone toward lower altitudes. As a consequence, there is an increase in the amount of biologically active ultraviolet radiation (below 295 nm) reaching the earth's surface. In addition, the temperature distribution in the stratosphere is somewhat altered.

The accumulation of chlorofluoroalkanes in the atmosphere, at all levels, also increases the absorption and emission of infrared radiation (the "greenhouse" effect). This retards heat loss from the earth and thus affects the earth's temperature and climate. The amount of change in infrared absorption and emission is well known, however, the amount and details of the further effects on the earth's climate are uncertain. This effect is inevitably combined with the effects due to increased carbon dioxide in the atmosphere and works in the same direction (NAS, 1976, 1979).

B.   Bioconcentration

While chlorofluoroethanes are quite lipophilic and have the potential to bioaccumulate in organisms, their high volatility appears to preclude significant bioaccumulation (U.S. EPA, 1975a).

C. Environmental Occurrence

. Trichlorofluoromethane has been detected in finished drinking water, effluents from raw sewage and sewage treatment plants, and in rivers and lakes (U.S. EPA, 1976b). F-11 is formed in small quantities during chlorination and fluoridation of drinking water (U.S. EPA, 1975b).

The major routes by which the fluorocarbons reach the environment involve their commercial applications. Because of their characteristic high vapor pressures and low boiling points, it is expected that all losses of fluorocarbons would ultimately the atmosphere (U.S. EPA, 1976a).

III. PHARMACOKINETICS

The available data on fluorocarbon absorption and elimination indicate that they are absorbed across the alveolar membrane, gastrointestinal tract, and skin. Inhaled fluorocarbons are taken up readily by the blood. Fluorocarbons absorbed by any route are eliminated through expired air (U.S. EPA, 1976a).

Data from Allen and Hansbury, Ltd. (1971) show that sub-sequent to a five-minute exposure in ambient air, F-11 and F-12 are concentrated to the greatest extent in the adrenals, fat, and the heart of rats.

Eddy and Griffith (1971) observed metabolism in rats following oral administrations of ^{14}C-labelled F-12. About 2% of the total dose was exhaled as CO_2 and about 0.5% was excreted in urine; the balance was exhaled unchanged. Within thirty hours after administration, the fluorocarbon and its

metabolites were no longer present in the body. Blake and

Mergner (1974) have indicated that the apparent resistance of

F-11 and F-12 to biotransformation may be more a function of

their rapid elimination rather than their general stability.

IV. HEALTH EFFECTS

   A. Carcinogenicity

      A bioassay of F-11 for possible carcinogenicity was

conducted using rats and mice. Animals were subjected to F-11

by gavage for 78 weeks. The results of the bioassay in rats

were not conclusive because an inadequate number of animals

survived to the end of the study. Under the conditions of the

bioassay, F-11 was not carcinogenic in mice (NCI, 1978). The

carcinogenic potential of F-113 has not been dected by NCI, and

few specific studies have been documented. Epstein et. al.

(1967) observed a synergistic effect when piperonyl butoxide

and F-113 were sumultaneously injected in mice, producing an

increase in hepatoms.

   B. Mutagenicity

      Mutagenicity data on the fluorocarbons are scant.

Neither of the compounds was mutagenic in *Salmonella* tester

strains TA1535 or TA1538 with activation (Uehleke et al., 1977).

Sherman (1974) found no increase in mutation rates over controls

in a rat feeding study of F-12. Stephens et al., (1970) reported

a significant mutagenic activity of F-12 in a *Neurospora crassa*

test system. F-113 has not been shown to be positive in the

Ames test, and was reported not to be mutagenic in the dominant

lethal test in the mouse.

C. Other Toxicity

Taylor (1974) noted that exposure to 7% oxygen-15% trichlorofluoromethane (F-11) caused cardiac arrhythmias in all rabbits exposed. F-11 was subsequently shown to exert its toxicity at air concentrations of 0.5-5% in the monkey and dog, and from 1-10% in the rat and mouse. In all these animals it induced cardiac arrhythmias, sensitized the heart to epinephrine-induced arrhythmias, and caused tachycardia (increased heart rate), myocardial depression, and hypertension. The concentrations of F-12 that sensitized the dog to epinephrine and that influenced circulation in the monkey and dog were similar to those reported for F-11, however, F-12 differed in its effects on the respiratory parameters. It caused early respiratory depression and broncho-constriction which predominated over its cardiovascular effects (Aviado, 1975a,b).

A possible increased sensitivity to the fluorocarbons in humans with cardiac or respiratory illness may exist, but this is difficult to determine definitively on the basis of animal studies. Azar et al. (1972) noted that human inhalation of 1,000 ppm (4,949 mg/m^3) F-12 did not reveal any adverse effect, while exposure to 10,000 ppm resulted in a 7% reduction in a standardized psychomotor test score.

V. AQUATIC EFFECTS

No data were found.

VI. EXISTING GUIDELINES

As of March 17, 1979, fully halogenated chlorofluoroalkanes were banned as propellants in the United States except for essential uses. The action was taken because the chlorofluoro-alkanes (including F-11, F-12 and F-113) may deplete the stratospheric ozone, leading to an increase in skin cancer , climatic changes, and other adverse effects (43 CFR 11301).

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2,4,6-Trichlorophenol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.   20460

OCTOBER 30, 1980

DISCLAIMER

This report represents a survey of the potential health
and environmental hazards from exposure to the subject chemi-
cal. The information contained in the report is drawn chiefly
from secondary sources and available reference documents. Be-
cause 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.

2,4,6-TRICHLOROPHENOL

Summary

In a 1979 study N.C.I.-concluded that 2,4,6-trichlorophenol is carcinogenic in rats and mice. EPA's carcinogen Assessment Group has determined that there is substantial evidence that 2,4,6-trichlorophenol is carcinogenic in man.

2,4,6-Trichlorophenol is a convulsant and an uncoupler of oxidative phosphorylation.

2,4,6-Trichlorophenol is acutely toxic to freshwater fish with LC_{50} values ranging from 320 to 9,040 ug/l. No chronic or marine studies were available. Tainting of rainbow trout flesh has been noted at concentrations in water greater than 52 ug/l.

2,4,6-TRICHLOROPHENOL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Phenols (U.S. EPA, 1980).

2,4,6-Trichlorophenol (2,4,6-TCP) is a colorless, crystalline solid with the empirical formula $C_6H_3Cl_3O$ and a molecular weight of 197.5 (Weast, 1978). It has the following physical and chemical properties (Weast, 1978):

Melting Point:	69.5°C
Boiling Point:	246°C
Vapor Pressure:	1 mm Hg at 76°C
Solubility:	slightly soluble in water; soluble in alcohol and ether

Trichlorophenols are used as antiseptics and disinfectants, as well as for intermediates in the synthesis of other chemical products (U.S. EPA 1980).

It is generally accepted that chlorinated phenols will undergo photolysis in aqueous solutions as a result of ultraviolet irradiation and that photodegradation leads to the substitution of hydroxyl groups in place of the chlorine atoms and subsequent polymerization (U.S. EPA, 1980). For additional information regarding the chlorinated phenols, the reader is referred to the Hazrd Profile on Chlorinated Phenols (U.S. EPA, 1980).

II. EXPOSURE

Unspecified isomers of trichlorophenols have been detected in surface waters in Holland at concentrations of 0.003 to 0.1 ug/l (Piet and DeGrunt, 1975). 2,4,6-Trichlorophenol can be formed from the chlorination of phenol in water (Burttschell, et al. 1959). Exposure to other chemicals such as 1,3,5-trichlorobenzene,

lindane, the alpha- and delta-isomers of 1,2,3,4,5,6-hexachloro-cyclohexane, and hexachlorobenzene could result in exposure to 2,4,6-trichlorophenol via metabolic degradation of the parent compound.

The U.S. EPA (1980) has estimated the bioconcentration factor 2,4,6-trichlorophenol to be 110 for the edible portion of aquatic organisms. This estimate is based on the octanol/water partition coefficient for this chemical.

Trichlorophenols are found in flue gas condensates from municipal incinerators (Olie, et al. 1977).

A.   Absorption, Distribution and Metabolism

Information regarding the absorption, distribution and metabolism of 2,4,6-trichlorophenol could not be located in the available literature.

B.   Excretion

In rats, 82 percent of an administered dose (1 ppm in the diet for 3 days) of 2,4,6-trichlorophenol was eliminated in the urine and 22 percent in the feces. Radiolabelled trichlorophenol was not detected in liver, lung, or fat obtained five days after the last dose (Korte, et al. 1978).

IV.   EFFECTS

A.   Carcinogenicity

Early studies on the tumor-promoting or-initiating capacities of 2,4,6-trichlorophenol were negative or inconclusive (U.S. EPA, 1980). Based on the results of its recent study, however, the NCI concluded that this compound is carcinogenic in male F344 rats (inducing lymphomas and leukemias), and in both

sexes of $B_6C_3F_1$ mice, inducing hepatocellular carcinomas and adenomas. (National Cancer Institute, 1979).

B. · Mutagenicity

Ames tests using Salmonella, with and without mammalian microsomal activation, were negative for 2,4,6-trichlorophenol (Rasanen, et al. 1977). 2,4,6-Trichlorophenol increased the rate of mutations, but not the rate of intragenic recombination in a strain of Saccharomyces cerevisiae (Fahrig, et al. 1978). In addition, two of the 340 offspring from female mice injected with 50 mg/kg of 2,4,6-trichlorophenol during gestation were reported to have changes in hair coat color (spots) of genetic significance. At 100 mg/kg, 1 out of 175 offspring exhibited this response (U.S. EPA, 1980).

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Information regarding teratogenicity, other reproductive effects and chronic toxicity of 2,4,6-trichlorophenol could not be located in the available literature.

D. Other Relevant Information

2,4,6-Trichlorophenol is a convulsant (Farquharson, et al. 1958) and an uncoupler of oxidative phosphorylation (Weinbach and Garbus, 1965; Mitsuda, et al. 1963).

2,4,6-Trichlorophenol affects glucose metabolizing enzymes at low concentrations (U.S. EPA, 1980). At relatively high concentrations it affects the microsomal oxidizing system in vitro, which may have implication with respect to the liver's detoxification or cancer inducing abilities (U.S. EPA, 1980).

V. AQUATIC TOXICITY (U.S. EPA, 1980)

A. Acute Toxicity

Three assays have been conducted with 2,4-trichlorophenol to determine its acute toxicity to freshwater fish. A 96-hour static LC_{50} value of 600 ug/l has been obtained for the fathead minnow (Pimephales promelas). In a flow-through assay, a 96-hour LC_{50} value 9,040 ug/l was obtained for juvenile fathead minnows. The bluegill (Lepomis macrochirus) has been shown to be the most sensitive species studied, with a 96-hour static LC_{50} of 320 ug/l. Only one acute study has been performed on a freshwater invertebrate species. The result of a 48-hour static assay produced an LC_{50} value of 6,040 ug/l for Daphnia magna. There were no acute studies for any species of marine life.

B. Chronic Toxicity

2,4,6-Trichlorophenol is moderabely toxic to the fathead minnow (720 ug/l) (U.S. EPA, 1980).

C. Plant Effects

Complete destruction of chlorophyll in the algae, Chlorella pyrenoidosa, has been reported at concentrations of 10 ug/l. A chlorosis LC_{50} value of 5,923 ug/l was obtained for the duckweed, Lemna minor. Studies of the effects of 2,4,6-trichlorophenol on marine plants have not been reported.

D. Residues

No actual bioconcentration factors have been determined, but, based upon the octanol/water partition coefficient of 4,898, a bioconcentration factor of 380 has been estimated for those aquatic organisms having an eight percent lipid content.

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The weighted average bioconcentration factor for the edible portions of all organisms consumed by Americans is estimated to be 110.

E.   Miscellaneous

The tainting of fish flesh by 2,4,6-trichlorophenol has been observed in the rainbow trout (<u>Salmo gairdneri</u>). The highest estimated concentration of 2,4,6-trichlorophenol that will not impair the flavor of trout exposed for 48 hours to the chemical is 52 ug/l.

VI.   EXISTING GUIDELINES AND STANDARDS

A.   Human

Based on carcinogenicity the U.S. EPA (1980) has recommended 12 ug/l as the ambient for the 2,4,6-trichlorophenol water quality, criterion, for the ingestion of both fish and water (10^{-6} excess risk).

No other existing guidelines or standards were found for human exposure to 2,4,6-trichlorophenol.

B.   Aquatic

The ·   criterion to protect freshwater organisms 970 ug/l, is the chronic exposure value. Data were insufficient to derive a criterion for marine organisms (U.S. EPA, 1980).

2,4,6-TRICHLOROPHENOL

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1,2,3-Trichloropropane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.   20460

APRIL 30, 1980

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1,2,3-TRICHLOROPROPANE

Summary

Pertinent data are not available on the possible carcinogenicity, muta-
genicity, teratogenicity; or chronic toxicity of 1,2,3-trichloropropane.
Acute toxicity studies with animals suggest harmful effects to the liver.
1,2,3-Trichloropropane is reported to be irritating to the eyes and mucous
membranes of humans.

Pertinent data on the toxicity of trichloropropane to aquatic organisms
are not available.

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1,2,3-TRICHLOROPROPANE

I. INTRODUCTION

1,2,3-Trichloropropane (CAS registry 96-18-4) is a colorless, clear liquid made from the chlorination of propylene. It has the following chemical and physical properties (Windholz, 1976; Hawley, 1971; Verschueren, 1977):

Formula:	$C_3H_5Cl_3$
Molecular Weight:	147.43
Melting Point:	-14.7^oC
Boiling Point:	156.85^oC
Density:	1.3889^{20}_{4}
Vapor Pressure:	2.0 torr @ 20^oC
Solubility:	Sparingly soluble in water, soluble in alcohol and ether.

1,2,3-Trichloropropane is used as a paint and varnish remover, solvent, and degreasing agent (Hawley, 1971), in addition to its use as a cross-linking agent in the elastomer Thiokol ST (Johnson, 1971).

II. EXPOSURE

A. Water

1,2,3-Trichloropropane has been detected in drinking water (U.S. EPA, 1975) and also in 6 of 204 surface water samples taken in various locations throughout the United States (U.S. EPA, 1977). No information concerning concentration was available.

B. Food

Pertinent data were not found in the available literature.

C.   Inhalation

Pertinent data were not found in the available literature; how-
ever, fugitive emissions from manufacturing and production facilities pro-
bably would account for the major portion of 1,2,3-trichloropropane if found
in air.

D.   Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

Pertinent data were not found in the available literature.

IV. EFFECTS

A.   Carcinogenicity, Mutagenicity, Teratogenicity,
     Reproductive Effects, Chronic Toxicity.

Pertinent data were not found in the available literature.

B.   Acute Toxicity

Exposure to trichloropropane at high concentrations is irritating
to the eyes and mucous membranes and causes narcosis.

McOmie and Barnes (1949) exposed 15 mice to 5000 ppm trichloro-
propane for 20 minutes. Seven of the mice survived exposure; however, four
of these mice died from liver damage 7 to 10 days later. Seven of ten mice
exposed to 2500 ppm trichloropropane for 10 minutes per day for 10 days
died. McOmie and Barnes (1949) found that liquid trichloropropane applied
to the skin of rabbits produced irritation and erythema, followed by slough-
ing and cracking. Repeated application of 2 ml of trichloropropane caused a
painful reaction, including subdermal bleeding, and the death of one of
seven rabbits treated.

Silverman, et al. (1946) reported eye and throat irritation and an
objectional odor to human volunteers exposed to 100 ppm trichloropropane for

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15 minutes. McOmie and Barnes (1949) found that ingestion of 3g of tri-chloropropane by humans caused drowsiness, headache, unsteady gait, and lumbar pain.

V.   AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A.   Human

The American Conference of Governmental Industrial Hygienists recommends a threshold limit value of 50 ppm for occupational exposure to 1,2,3-trichloropropane (ACGIH, 1977).

B.   Aquatic

No guidelines on standards to protect aquatic organisms from 1,2,3-trichloropropane toxicity have been established because of the lack of pertinent data.

1,2,3-TRICHLOROPROPANE

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o,o,o-Triethyl Phosphorothioate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.   20460

APRIL 30, 1980

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O,O,O-TRIETHYL PHOSPHOROTHIOATE

Summary

There is no information available on the possible carcinogenic, muta-
genic, teratogenic, or adverse reproductive effects of O,O,O-triethyl phos-
phorothioate. Triethyl phosphate, a possible metabolite of the compound,
has shown weak mutagenic activity in <u>Salmonella</u>, <u>Pseudomonas</u>, and <u>Drosophila</u>.

Like other organophosphates, O,O,O-triethyl phosphorothioate may be ex-
pected to produce cholinesterase inhibition in humans.

No pertinent data are available on the aquatic effects of the compound.

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O,O,O-TRIETHYL PHOSPHOROTHIOATE

I.   INTRODUCTION

O,O,O-Triethyl phosphorothioate (CAS registry number 126-68-1), also known as triethyl thiophosphate, is a colorless liquid with a characteristic odor. It has the following physical and chemical properties (Hawley, 1971):

Formula:	$C_6H_{15}O_3PS$
Molecular Weight:	198
Boiling Point:	93.5°C-94°C (10 torr)
Density:	1.074

O,O,O-Triethyl phosphorothioate is used as a plasticizer, lubricant additive, antifoam agent, hydraulic fluid, and as a chemical intermediate (Hawley, 1971).

II. EXPOSURE

A.   Water and Food

Pertinent data were not found in the available literature.

B.   Inhalation

Pertinent data were not found in the available literature; however, fugitive emissions from production and use would probably constitute the major source of contamination (U.S. EPA, 1977).

D.   Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A.   Absorption

Pertinent data were not found in the available literature. Acute toxicity studies with a number of organophosphate insecticides indicate that these compounds are absorbed following oral or dermal administration

(Gaines, 1960). March, et al. (1955) have reported rapid absorption of the structurally similar insecticide demeton from the gastrointestinal tract of mice following oral administration.

B. Distribution

Pertinent data were not found in the available literature.

C. Metabolism

Pertinent data were not found in the available literature. The thiono isomer of the insecticide demeton may be metabolized via oxidative desulfuration by the liver at the P=S bond in mammals (March, et al. 1955) to form the thiolo derivative. Thus, O,O,O-triethyl phosphorothioate may be converted to triethylphosphate $\underline{in}$ $\underline{vivo}$ (Matsumura, 1975).

D. Excretion

Pertinent data were not found in the available literature. March, et al. (1955) have reported that following oral administration of demeton, the large majority of compound was eliminated as urinary metabolites, with small quantities detected in the feces. Elimination was rapid following oral administration.

IV. EFFECTS

A. Carcinogenicity

Pertinent data were not found in the available literature.

B. Mutagenicity

Pertinent data were not found in the available literature. The insecticide oxydemeton methyl has been shown to produce mutations in Drosophila, E. coli and Saccharomyces (Fahrig, 1974). Triethyl phosphate, a possible metabolite of O,O,O-triethyl phosphorothioate, has produced weak mutagenic effects in Salmonella and Pseudomonas (Dyer and Hanna, 1973) and recessive lethals in Drosophila (Hanna and Dyer, 1975).

C. Teratogenicity

Pertinent data were not found in the available literature. A single intraperitoneal injection of demeton (7 to 10 mg/kg) between days seven and twelve of gestation has been reported to produce mild teratogenic effects in mice (Budreau and Singh, 1973).

D. Other Reproductive Effects

Pertinent data were not found in the available literature. Embryotoxic effects (decreased fetal weights, slightly increased fetal mortality) have been reported following intraperitoneal administration of demeton (7 to 10 mg/kg) to pregnant mice (Budreau and Singh, 1973).

E. Chronic Toxicity

Pertinent data were not found in the available literature. O,O,O-triethyl phosphorothioate, like other organophosphates, may be expected to produce symptoms of cholinesterase inhibition in humans (NAS, 1977).

v. AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Pertinent data were not found in the available literature.

O,O,O-TRIETHYL PHOSPHOROTHIOATE

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Trinitrobenzene

Health and Environmental Effects

171-1

DISCLAIMER

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TRINITROBENZENE

Summary

Information on the carcinogenicity, mutagenicity, teratogenicity, or adverse reproductive effects of trinitrobenzene was not found in the available literature.

Trinitrobenzene has been reported to produce liver damage, central nervous system damage, and methemoglobin formation in animals.

Slight irritant effects have been reported for marine fish exposed to trinitrobenzene at concentrations of 100 ug/l.

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TRINITROBENZENE

I. INTRODUCTION

This profile is based on the Investigation of Selected Potential Environmental Contaminants: Nitroaromatics (U.S. EPA, 1976).

Trinitrobenzene (1,3,5-trinitrobenzene, molecular weight, 213.1) is a crystalline solid with the following physical properties: melting point, 122.5°C; specific gravity, 1.76. The compound is explosive upon rapid heating. Trinitrobenzene is insoluble in water, but soluble in alcohol or ether (Windholz, 1976).

Trinitrobenzene is used as an explosive, and as a vulcanizing agent for natural rubber (U.S. EPA, 1976).

Hydrolysis of trinitrobenzene under neutral pH conditions is not expected to be rapid; as pH increases, hydrolysis would be favored (Murto, 1966). Photolytic degradation of trinitrobenzene has not been demonstrated in aqueous solutions (Burlinson, et al. 1973).

A bioconcentration factor is not available for trinitrobenzene; however, the work of Neely, et al. (1974) on several nitroaromatics would suggest a low theoretical bioconcentration of the compound.

Biodegradation of trinitrobenzene by acclimated microorganisms has been reported by Chambers, et al. (1963).

II. EXPOSURE

Pertinent information on levels of exposure to trinitrobenzene from occupational contact or from non-occupational sources of exposure (air, water, food) was not found in the available literature.

III. PHARMACOKINETICS

Pertinent information on the absorption, distribution, metabolism, or excretion of trinitrobenzene was not found in the available literature. The

reader is referred to a discussion of the pharmacokinetics of dinitro-benzenes, which may show pharmacokinetic similarities (U.S. EPA, 1979).

Acute oral toxicity studies conducted with dogs indicate that trinitro-benzene is effectively absorbed by this route (Fogleman, et al. 1955).

IV. EFFECTS

Pertinent information on the carcinogenic, mutagenic, teratogenic, or adverse reproductive effects of trinitrobenzene was not found in the available literature.

A series of toxicity studies in rats, mice, and guinea pigs have indicated that orally administered trinitrobenzene causes liver damage and central nervous system damage (Korolev, et al. 1977). The acute toxicity study of Fogleman, et al. (1955) has shown that trinitrobenzene, like dini-trobenzenes, induces methemoglobin formation in vivo.

V. AQUATIC TOXICITY

The only study reporting the effects of trinitrobenzene to aquatic life has been presented by Hiatt, et al. (1957). Slight irritant effects i.e., excitability, violent swimming, opercular movement increases suggesting res-piratory distress upon short term exposure to marine fish Kuhlia sandvicensis were observed at exposure levels of 100 ug/l, while moderate and violent reactions to the chemical were produced at exposures of 1,000 and 10,000 µg/l. No effects were noted on exposures to concentrations of 50 or 10 ug/l.

VI. EXISTING GUIDELINES

There is no available 8-hour, TWA exposure limit for trinitrobenzene. The compound has been declared a hazardous chemical by the Department of Transportation (Federal Register, January 24, 1974).

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TRINITROBENZENE

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Aniline

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 environment 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.

ANILINE SUMMARY

Aniline is an aromatic amine. Like many members of this group it is characterized by an outstanding property: the ability to form methemoglobin in mammalian organisms. Aniline and some of its analogues have been suspected as carcinogens since the turn of the century. An increased incidence of urinary bladder tumors has been noted in workers in the aniline and aniline dyestuff industries. Oral feeding studies conducted by the National Cancer Institute have shown aniline to be carcinogenic in rats. Aniline is reported not to be mutagenic to six strains of S. typhimurium, however, several aniline analogues and derivatives are mutagenic.

ANILINE

I. INTRODUCTION

Aniline (aminobenzene) is a liquid at room temperature. Its physical properties can be summarized as follows: (Hawley, 1977; Weast, 1977-78; Strecher, 1968):

Molecular formula	$C_6H_5NH_2$
Molecular weight	93.13
Melting point	-6.2°C
Boiling point	184.4°C
Flash point	158.0°F (Closed Cup)
Solubility in cold water	35.0 grams/liter (0.38 M).
Temperature at which vapor pressure equals 1 mm/Hg	34.8°C
pKa	4.63

Of particular interest is aniline's water solubility - i.e., aniline is soluble even in cold water.

The Stanford Research Institute's <u>Chemical Economics Handbook</u> cites the nitrobenzene reduction process as the current method of aniline synthesis (McCaleb, 1976). It is estimated that 270,000 kkg of aniline was produced in 1978 (Slimak, et. al., 1980). Aniline was reported to be used for the following uses:

synthesis of isocyanate (50% of total consumption), of rubber chemicals (27%), dyes and intermediates (6%), hydroquinone (5%), drugs (37%), and miscellaneous chemicals including herbicides (9%).

II. EXPOSURE

   A. Water

   Aniline levels in surface or drinking water was not reported in the available literature. However, overall emission of aniline to receiving waters as a result of the production of aniline, consumptive use, carry-over as impurities in manufactured products, and degradation of manufactured products was estimated in 1978, to be 9970 kkg (Slimak, et. al., 1980).

   B. Food

   Pertinent data on aniline concentrations could not be located in the available literature.

   C. Inhalation

   Pertinent data on aniline concentrations could not be located in the available literature. However, overall emissions of aniline to air as a result of aniline, isocyanates, rubber chemicals, dyes and intermediates, hydroquinone, and miscellaneous products production is estimated to be 69.4 kkg in 1978 (Slimak, et. al., 1980). Aniline is also reported to occur in cigarette smoke (Gosselin, et. al., 1976).

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PHARMACOKINETICS

A.   Absorption

Both inhalation and dermal absorption are important
exposure routes in humans (Pietrowski, 1957).   At air concen-
trations of up to 20 mg/m^3, absorption is about equal by
both routes, that is, 6 mg/hr; at higher concentrations the
respiratory pathway becomes progressively a more important
factor.   Dermal contact with liquid aniline also results in
rapid systemic absorption: 0.2-0.7 mg/cm^2 of skins/hr has
been shown to occur (Pietrowski, 1957).

B.   Distribution

Aniline is rapidly absorbed into the blood stream;
its subsequent systemic distribution has not been reported.
Its metabolic transformations (see below) are mainly dependent
on liver enzymes.

C.   Metabolism

Aniline is metabolized in the liver by oxidation
and conjugation.   Hepatic microsomal oxidizing enzymes cause
metabolic transformation to N-acetylaminophenol and to o- and
p-aminophenol.   Conjugating enzymes then cause metabolic
transformation to the glucuronide and sulfonate (Casarett and
Doull, 1975).

D.   Excretion

The administration of aniline leads to urinary excretion
of glucuronic acid and sulfonic acid conjugates and of its
metabolites, o- and p-aminophenol (Williams, 1959; Parke,

1960). In addition, small amounts of free aniline, phenyl

sulfamic acid, aniline- glucuronide, aminophenyl and

acetylaminophenyl, mercaptonic acids, phenylhydroxylamine,

and acetanilide are excreted in varying amounts by different

species tested (Parke, 1960). The conjugates of p-amino-

phenol are the most important urinary metabolites of aniline

(Williams, 1959). The urinary excretion of these

metabolites gives an accurate measure of the absorption of

aniline vapor (Pietrowski, 1972). It is probable that the

other aniline metabolites mentioned above also appear in the

urine of people exposed to aniline (IARC, 1974).

IV. EFFECTS

A. Carcinogenicity

The carcinogenic potential of aniline has been of

great interest because, since 1895, an increased incidence of

urinary bladder tumors has been noted in workers in the

aniline dye industry (IARC, 1974). It has subsequently been

shown that other amines which occur in the environment, such

as 2-naphthylamine, 4-aminobiphenyl and benzidine, are probably

more important in the causation of these occupational cancers

(IARC, 1974). Although most animal studies appear to have

exonerated aniline as a human carcinogen (IARC, 1974), an NCI

study showed a dose-related increase in fibrosarcomas or

sarcomas in the spleen and in several organs of the body

cavity. Although the results were not statistically signifi-

cant, the rarity of these tumors and their dose-dependency

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led to the conclusion that aniline is carcinogenic in female
Fisher 334 rats. The male rats showed a statistically
significant increase in the incidence of hemangiosarcomas of
the spleen and a significant increase in the combined incidence
of fibrosarcomas and sarcomas of the spleen and in multiple
body organs (NCI, 1978).

B.   Mutagenicity

In the Ames assay aniline is not mutagenic toward
any of the six standard S. typhimurium strains, when tested
in the presence or absence of microsomes (Geomet, 1980).
However, in the presence of nor-harman (a 2-carboline derivative),
significant mutagenicity has been observed (Nagao, et. al.,
1977; Sugimura, 1979).

C.   Teratogenicity

Pertinent data could not be located in the available
literature. However, cyanotic effects such as those produced
by aniline can adversely affect the fetus, leading the ITC
to recommend that reproductive effect tests be conducted (44
FR 31871).

D.   Other Reproductive Effects

Aniline can cross the placenta to form methemoglobin
in the fetus, affecting its development (Gosselin, 1976).
Courtney, (1979), reported that, after treatment of CD-1
mouse dams with aniline (150 to 200 mg/kg) during gestation
and lactation, CPK and LDH isozyme patterns in serum and

cardiac tissue in offspring were altered on days 1 and 20 postpartum. The serum CPK pattern was markedly altered on day 1 postpartum and by day 20, an additional enzyme appeared.

E.   Acute and Chronic Effects

Aniline is moderately lethal to the rat: the oral LD50 is 440 mg/kg. The LD50 value via the dermal route is 1400 mg/kg in the rat. For human beings the oral LDLO is reported as 50 mg/kg (NIOSH, 1979). The no-effect level for humans has been estimated as 0.25 mg/kg (NIOSH, ref. 169).

Aniline absorption causes anoxia due to the formation of methemoglobin. Most of the signs and symptoms of overexposure to aniline can be attributed to methemoglobin formation. Such symptoms include fatigue, headache, irritability and dizziness (Proctor and Hughes, 1979). In addition there may be direct effects of aniline on the central nervous system (e.g., insomnia, paresthesias) and cardiotoxic effects (Patty, 1979; Sax, 1979).

Chronic exposure induces amenia (Patty, 1979; Sax, 1979; Proctor and Hughes, 1979). Other chronic effects of aniline exposure are hepatic injury, (perhaps caused by an aniline metabolite) (Jenkins, 1972; Geomet, 1980) and splenic hemosiderosis (NCI, 1978).

V.   AQUATIC TOXICITY

The lethal concentration and threshold concentration for aniline with respect to _Chironomus dorsalis_ Meig. larvae are 6 and 3 mg/l, respectively (Puzikova and Markin, 1975).

Aniline also produces toxic effects in Daphnia, at 0.4 mg/l (Verschueren, 1977).

B.   Chronic Toxicity

Lakhnova 1975, reported that aniline at a concentration of 0.2 mg/l is lethal to Daphnia magna Straus within nine days. Therefore, Lakhnova recommended a maximum permissible limit of 0.02 mg/l.

VI.   EXISTING GUIDELINES AND STANDARDS

A.   Human

The maximum allowable concentration in class I waters for the production of drinking water in the U.S. is 5 mg/l. Several European countries have set lower limits: 0.1 mg/l (USSR), 5 ppm (Federal German Republic), 2.6 ppm (Deutsche Demokratische Republik), and 1.3 ppm (CSSR) (Verschueren, 1977).

B.   Aquatic

Data were insufficient to draft a criterion for protection of freshwater or marine life. Lakhnova (1975) recommended a maximum permissible limit of 0.02 mg/l.

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