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

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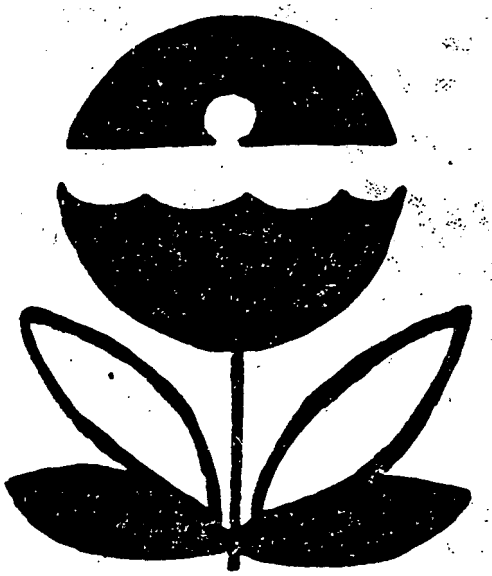

APRIL 30, 1980

U.S. ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF SOLID WASTE

No. 151

Quinones

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.

QUINONE

Summary

Quinone has been reported to produce neoplasms, but insufficient data are available to assess its carcenogenic potential. Quinone was not mutagenic to Orosophila melanogaster, human leukocytes, nor Neurospora.

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.

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.

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

Drosophila 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 pressure, and death by paralysis of the medullary centers (Patty, 1967).

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

-1810-

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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-

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,

moderate to severe irritation was followed in 24 hours by slight hyperkeratosis. Surviving rats showed reduced weight but no internal gross lesions upon necropsy.

Flickinger (1976) reported that resorcinol is a severe eye irritant (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 resorcinol 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 feasibility of control technology. Herbes and Beauchamp (1977) compared toxic interactions of two coal conversion effluents, resorcinol and 6-methylquinaline. 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 report 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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No. 153

Selenium

Health and Environmental Effects

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

APRIL 30, 1980

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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.

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 [illegible]ding 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 Drosophila melanogaster (Ting and Walker, 1969; Walker and Bradley, 1969). However, these

and 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.

SELENIUM

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No. 154

Silver

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.

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 argyria. 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 determined 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, Daphnia magna 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-

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 mucociliary 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

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

(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 Hemicentrotus pulcherrimus. 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 adequate diets or aggravating deficiency symptoms when the animal's diet lacks one or more of the nutrients. The effects have been described in dogs, sheep, pigs, rats, chicks, turkey, 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 hardness and experimental variability on these nonreplicated results.

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 tested, and the mysid shrimp is the most resistant.

B. Acute Toxicity

Davies, et al. (1978) conducted an 18-month mortality test with rainbow trout and found the no-effect concentration 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 retardation in the freshwater alga, Chlorella vulgaris, 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, Skeltonema costatum, 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 determined 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 recommendation.

B. Aquatic

For silver the draft criterion to protect freshwater 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 criterion 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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No. 155

TCDD

Health and Environmental Effects

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

APRIL 30, 1980

DISCLAIMER

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

2,3,7,8-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 contaminant 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-trichlorophenoxyacetic acid (2,4,5-T) (U.S. EPA, 1979).

Characteristically, TCDD ($C_{12}H_4Cl_4O_2$) is a white crystalline 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 conditions (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, 1[illegible]).

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.

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 µg/kg of diet for up to 78 weeks. In 50 animals receiving diets ranging from 0.005 µg/kg to 5 µg/kg 13 benign and 15 malignant tumors were observed. No tumors were found in controls or those fed a dietary level of 0.0001 µg/kg. Animals fed diets of 50 µg/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 µg/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).

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 freshwater 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} µg/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 the range of 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding draft criteria are 4.55×10^{-7} µg/l, 4.55×10^{-8} µg/l, and 4.55×10^{-9} µg/l, respectively.

B. Aquatic

No drafted criterion is available to protect fresh and saltwater species from TCDD toxicity.

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No. 156

1,1,1,2-Tetrachloroethane

Health and Environmental Effects

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

APRIL 30, 1980

-1862-

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

1,1,1,2-Tetrachloroethane is potentially formed during chlorination of drinking water and has been identified at a concentration of 0.11 µg/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-tetrachloroethane 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-tetrachloroethane. 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 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).

D. Excretion

Murine studies show that, after i.p. injection of 1,1,1,2-tetrachloroethane, 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-tetrachloroethane/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-hydroxybutyrate dehydrogenase activities were enhanced. Except for creatine phosphokinase, 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 microvacuolizations 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

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WASHINGTON, D.C. 20460

APRIL 30, 1980

-1872-

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 evidence to indicate that this compound is carcinogenic.

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.

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 Daphnia magna. In marine fish and invertebrates, the studies yielded a 96-hour static LC_{50} value of 12,300 µg/l for the sheepshead minnow (Cyprinodon variegatus), and of 9,020 µg/l for the mysid shrimp (Mysidopsis bahia).

B. Chronic Toxicity

Pertinent information could not be located in the available literature.

C. Plant Effects

When the freshwater algae Selenastrum capricornutum 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 Skeletonema costatum was tested for these adverse effects, 96-hour EC_{50} values were 6,440 and 6,230 µg/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 estimated 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).

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No. 158

Tetrachloroethylene

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 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 $\mu g/m^3$ in urban areas and less than 0.013 $\mu g/m^3$ in rural areas (Lillian, et al., 1975). By far the most significant exposure to tetrachloroethylene is in the industrial environment (Fishbein, 1976). Significant dermal 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 phenomenon, 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 (Savolainen, et al., 1977), tetrachloroethylene tends to accumulate 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 E. coli K_{12} with tetrachloroethylene. However, Cerna and Kypenova (1977) tested PCE and found elevated mutagenic activity in 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 decreases 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 teratogenic (U.S. EPA, 1979).

D. Other Reproductive Effects

No information available.

E. Chronic Toxicity

Repeated exposure to tetrachloroethylene has resulted 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). Occasional reports have even associated tetrachloroethylene exposure with the symptomatology of more serious chronic diseases such as Raynaud's disease (Lob, 1957; Sparrow, 1977). Sparrow (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 approximately 400 mg/m^3 (one for 15 years), subjective complaints, 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 reported 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 µg/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 µg/l	0.20 µg/l	2.0 µg/l
Consumption of fish and shellfish only.	0	0.040 µg/l	0.40 µg/l	4.0 µg/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.

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No. 159

Thallium

Health and Environmental Effects

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WASHINGTON, D.C. 20460

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-1897-

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 teratogenic, 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 concentrations as low as 20 µg/l. Algae are also sensitive, with effects produced at concentrations as low as 100 µg/l.

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 ointments 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 exposure and fatal exposure in man, there is a tendency for thallium to concentrate in the kidneys, colon and hair (Weinig and Zink, 1967; Cavanagh, et al. 1974).

Thallium crosses the placenta freely from the maternal 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	µg 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 mutagenic 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 toxicity 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, weariness, loss of hair, disturbance of sensation, psychic trouble albuminuria and nephritis (Meyer, 1928).

Rats fed thallous acetate in their diet for 105 days experienced 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

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-l- 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 µg/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.

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No. 160

Toluene

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.

TOLUENE

Summary

Toluene has not been reported to be carcinogenic or teratogenic in humans or animals. There is no conclusive evidence that toluene is mutagenic. 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 has been shown to be acutely toxic to freshwater fish at concentrations of 6,940 to 32,400 µg/I and to marine fish at concentrations from 4,470 to 12,000 µg/l. A single chronic value of 2,166 µg/l has been reported for marine fish. Aquatic plants appear to be resistant to the action of toluene with effective concentrations ranging from 8,000 to 433,000 µg/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 92113) is a clear, colorless, non corrosive 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 freshwater and 379.3 + 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 respresentative 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 µg/l to 19 µg/l. Benzaldehyde and benzoic acid, metabolites of toluene, were also detected. Benzaldehyde was found in the water of five cities, and in two of these cities was measured at levels of 0.1 and 0.5 µg/l. Benzoic acid at 15 µg/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 µg 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 metablite 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 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 μg/ml in persons inhaling 100 ppm and 2 μg/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 retained more toluene than thin ones. In their study, the average uptake of toluene vapor during exercise was approximately 49 percent for obese subjects 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 glycine to form hippuric acid (U.S. EPA, 1979). There has also been a report, however, of glucuromide 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 meteabolism of toluene results in detoxication.

D. Excretion

Toluene is rapidly excreted from the body following inhalaton 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, probably 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

No accounts have been found in the literature in which cancer in 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 has not been demonstrated to be carcinogenic when applied to the skin of mice for one year (Doak, et al. 1976) or throughout a lifetime (Poel, 1963). 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).

B. Mutagenicity

There is no conclusive evidence that toluene is mutagenic. 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). Toluene has not been tested in bacterial screening systems (Dean, 1978).

C. Teratogenicity

Although toluene should readily pass the placenta, there are no reports of teratogenic effects in humans or laboratory animals linked to toluene exposure (U.S. EPA, 1979). For example, toluene is not teratogenic in rats or chickens (Roche and Hine, 1968), or in rats or mice (Hudak and Ungvary, 1978).

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

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. Numerous subacute and chronic studies on a variety of experimental animals have failed to show evidence of severe cumulative toxicity (U.S. EPA, 1979).

F. Other Relevent 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 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 µg/l for the bluegill (Lepomis macrochirus) to 59,300 µg/l for

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 µg/l has been obtained for toluene. In marine fish, two 96-hour static LC_{50} values of 6,300 and 10,000-50,000 µg/l were obtained for striped bass (Morone saxatilis) and coho salmon Oncorhynchus kisutch (Benville, et al. 1977; Morrow, et al. 1975). 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 µg/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 µg/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 µg/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 ranging from 245,000 µg/l for Chlorella (Kauss and Hutchinson, 1975) to 433,000 µg/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 µg/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 criterion for the protection of freshwater organisms is 2,300 µg/l, as a 24-hour average, not to exceed 5,200 µg/l; and for marine life the draft criterion is 100 µg/l, as a 24-hour average, not to exceed 230 µg/l.

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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

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 2.05×10^5 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-toluenediisocyanate. 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 3.75×10^5 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 unknown (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 excretion 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 neoplasms 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 Drosophila melangaster 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 Salmonella/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.

*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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No. 162

Toluene Diisocyanate

Health and Environmental Effects

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

APRIL 30, 1980

-1935-

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 occurrence of TDI is unlikely due to its high reactivity with hydroxy compounds and peroxy radicals.

Information on the carcinogenicity and teratogenicity of toluene diisocyanate was not found in the available literature. As of September 1978, TDI was being tested by the National Cancer Institute for carcinogenicity using a standard bioassay protocol, but results have not been reported. Toluene diisocyanate did not show mutagenic activity on testing of Salmonella typhimurium 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.

The effects from 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 inahlation 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 regarding 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 carbonic acids (Tennant, 1979). The 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 water pH (Curtis, et al. 1979). TDI readily hydrolyzes in water, with a half-life of 0.5 seconds (Brown, et al. 1975). As temperature increases the reaction becomes more vigorous (Tennant, 1979).

Toluene diisocyanate reactions with ozone progress more slowly than the hydroxy reaction, with an atmospheric half-life of 3,981 days. The reaction of TDI with RO_2 peroxyradical groups has an environmental half-life of approximately 7.94×10^5 days in the water phase.

Brown, et al. (1975) concluded that the short lifetime of toluene diisocyanate in various media makes environmental occurrence unlikely.

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 effects 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 in 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 polyurethane 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

Repiratory and dermal exposure to toluene diisocyanate has been well documented in occupational 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 absorption, 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 reacton 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

Information on the carcinogenic effects of toluene diisocyanate was not found in the available literature. Lewis and Tatken (1979) reported that TDI is currently being tested by NCI for carcinogenicity by standard bioassay protocol as of September 1978.

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 which has produced chronic effects, although 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 processes, atopic diathesis, and coexisting disease states and 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 asthma, or of atopy (by skin testing) 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 will 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 $\mu g/m^3$ (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 a reaction with TDI occurred when added to the dilution water.

The authors 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.

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 enforcing a limit for airborne TDI of 0.14 mg/cu m (40 CFR 1910.1000) as a 15-minute exposure.

The American Conference of Governmental Industrial Hygienists (1979) has published 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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No. 163

Toxaphene

Health and Environmental Effects

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

APRIL 30, 1980

-1949-

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

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 Salmonella typhimurium 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 x 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.

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

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). Positive test results were obtained for strains TA98 (frameshift mutation) and TA100 (base pair substitution) only in tests without metabolic activation. All other tests were negative. A "high temperature" toxaphene has elicited positive dose response increases in strains TA98 and TA100 only with metabolic activation. In other studies, toxaphene and toxaphene 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 (1978) found no significant differences in the rates of chromosomal aberrations in leukocytes between groups of workers occupationally 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

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 toxaphene 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 (Deichman 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 trithion 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 characteristic 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 (Claasenia 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 4.7×10^{-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).

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No. 164

1,1,1-Trichloroethane

Health and Environmental Effects

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

APRIL 30, 1980

-1970-

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.

1,1,1-TRICHLOROETHANE

SUMMARY

Results of an NCI carcinogenesis bioassay have indicated that oral administration of 1,1,1-trichloroethane produced a variety of neoplasms. Retesting of this compound is underway since a high incidence of premature deaths in this initial study was observed.

There is no evidence to indicate that 1,1,1-trichloroethane has mutagenic or teratogenic activity.

Human toxic effects seen after exposure to 1,1,1-trichloroethane include central nervous system disorders. Animal studies indicate that toxic effects may be produced in the central nervous system, pulmonary system, heart, kidney, and liver.

Relatively little aquatic toxicity data is available. In acute studies both freshwater and marine fish are comparably sensitive, with LC_{50} values ranging from 69,700 to 105,000 µg/l.

-1972-

I. INTRODUCTION

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

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 of 74.1°C, a melting point of -33°C, a specific gravity of 1.3492, and a low solubility in water (U.S. EPA, 1979a).

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

The 1976 production of 1,1,1-trichloroethane was: 315×10^3 ton/year (U.S. EPA, 1979a).

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

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

II. EXPOSURE

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

are produced by evaporation of these compounds, widely used as degreasing agents and in dry cleaning operations (U.S. EPA, 1979a). Occupational air monitoring studies have indicated 1,1,1-trichloroethane levels ranging from 1.5 to 396 ppm (U.S. EPA, 1979a).

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. An analysis of several foods indicated 1,1,1-trichloroethane was present at levels of 1-10 µg/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 (1979a) 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 steady-state bioconcentration studies in bluegills.

III. PHARMACOKINETICS

A. Absorption

The chloroethanes are absorbed rapidly following oral or inhalation routes of exposure (U.S. EPA, 1979a). 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 level exposures. Animal studies have indicated that the compound 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-trichloroethane (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 expired air (U.S. EPA, 1979a). Monster and coworkers (1979) reported that 60-80 percent of 1,1,1-trichloroethane inhaled by volunteers was expired unchanged; two urinary metabolites represented 3 percent of the uptake. Excretion of the chloroethanes is generally rapid, the majority of compound being eliminated within 24 hours (U.S. EPA, 1979a).

IV. EFFECTS

A. Carcinogencity

An NCI bioassay for carcinogenicity (1977) has indicated that 1,1,1-trichloroethane induced a variety of

neoplasms. A high incidence of deaths in test animals has led to the retesting of this compound by NCI. Price, et al. (1978) have demonstrated *in vitro* transformation of rat embryo cells with 1,1,1-trichloroethane; injection of these cells *in vivo* produced undifferentiated fibrosarcomas in all tested animals.

B. Mutagenicity

Pertinent information could not be located in the available literature on the mutagenicity of 1,1,1-trichloroethane.

C. Teratogenicity

Inhalation studies with 1,1,1-trichloroethane in mice and rats have shown the production of some soft tissue and skeletal anomalies (Schwetz, et al. 1974). These were not shown to be statistically significant by the Fisher Exact probability test.

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

Human toxic effects seen after exposure to 1,1,1-trichloroethane include several central nervous system disorders. These include changes in reaction time, perceptual speed, manual dexterity, and equilibrium (U.S. EPA, 1979a).

Animal studies have indicated that 1,1,1-trichloroethane produces toxic effects in the central nervous system,

cardiovascular system, and pulmonary system, and induces liver and kidney damage (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

A. Acute Toxicity

For freshwater fish, 96-hour static LC_{50} values of 69,700 µg/l for the bluegill Lepomis macrochirus and 150,000 µg/l for the fathead minnow, Pimephales promelas, while a single 96-hour flow-through LC_{50} value of 52,800 µg/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 µg/l for the mysid shrimp, Mysidopsis bahia, to 70,900 µg/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, 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 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/l 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 µg/l as a 24-hour average, not to exceed 12,000 µg/l; while the criterion to protect marine life has been drafted as a 24-hour average concentration of 240 µg/l, not to exceed 540 µg/l.

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No. 165

1,1,2,-Trichloroethane

Health and Environmental Effects

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

APRIL 30, 1980

-1981-

DISCLAIMER

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-1982-

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.

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°C, a melting point of -37.4°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-trichloroethane 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.

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No. 166

Trichloroethylene

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

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°C (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 trichloroethylene in U.S. foodstuffs. In England, trichloroethylene has been observed 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 estimate 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 ingestion 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 Duuren 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.

8. Aquatic

For trichloroethylene, the draft criterion to protect freshwater aquatic life is 1,500 µg/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.

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No. 167

Trichlorofluoromethane and Dichlorodifluoromethane

Health and Environmental Effects

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

APRIL 30, 1980

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TRICHLOROFLUOROMETHANE AND DICHLORODIFLUOROMETHANE

SUMMARY

Trichlorofluoromethane (F-11) and dichlorodifluoromethane (F-12) are not easily degraded in the environment. After release at the surface of the earth, F-11 and F-12 mix with the atmosphere and rise slowly into the stratosphere where they are decomposed by ultraviolet radiation to release chlorine atoms. The chlorine atoms remove ozone catalytically, thereby reducing the total amount of ozone in the stratosphere and permitting an increased amount of biologically active ultraviolet radiation to reach the earth's surface. The accumulation of F-11 and F-12 in the atmosphere also increases the absorption and emission of infrared radiation (the "greenhouse effect").

F-11 and F-12, while fairly lipophilic, are not expected to bioaccumulate because of their high volatility. The compounds 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. F-11 and F-12 were negative in the Ames Salmonella test; F-12 was positive in a Neurospora crassa test system.

At high concentrations in the air, F-11 and F-12 have been shown to induce cardiovascular and pulmonary effects in animals.

In March 1979, fully halogenated chlorofluoroalkanes (including F-11 and F-12) 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.

F-11, a colorless volatile liquid, and F-12, a colorless gas, have the following physical/chemical properties (U.S. EPA, 1976a):

	F-11	F-12
Molecular Formula	CCl_3F	CCl_2F_2
Molecular Weight	137.37	120.92
Boiling Point (°C)	23.82	-29.79
Freezing Point (°C)	-111	-158
Solubility	Both are soluble in water and many organic solvents	

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 in the 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 will volatilize quickly from water and soils, they are considered persistant 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 and F-12 (as well as other chlorofluoromethanes) mix with the atmosphere and rise slowly into the stratosphere where they are decomposed by ultraviolet radiation to release chlorine atoms. Chlorine atoms and a subsequent reaction product, chlorine oxide, remove ozone catalytically, thereby reducing the total amount of ozone in the stratosphere

*/ 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).

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 chlorofluoromethanes 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 F-11 and F-12 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). It is known that F-11 will form 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 reach the atmosphere (U.S. EPA, 1976a).

III. PHARMACOKINETICS

The available data on fluorocarbon absorption and elimination indicate that fluorocarbons 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 the expired air (U.S. EPA, 1976a).

Data from Allen and Hanburys, Ltd. (1971) show that subsequent to a five-minute exposure in ambient air to rats, F-11 and F-12 are concentrated to the greatest extent in the adrenals, the fat, and the heart.

Eddy and Griffith (1971) observed metabolism in rats following oral administration of ^{14}C-labelled F-12. About 2% of the total dose was exhaled as CO_2 and about 0.5% was excreted in the urine; the balance was exhaled unchanged. Within thirty hours after administration, the fluorocarbon and its metabolities 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).

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 el al., 1977). Sherman (1974) found no increase in mutation rates over controls in a rat feeding study of F-12. Stephens el al. (1970) reported significant mutagenic activity of F-12 in a Neurospora crassa test system.

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 bronchoconstriction 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 only 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 chlorofluoroalkanes (including F-11 and F-12) may deplete the stratospheric ozone, leading to an increase in skin cancer, climatic changes, and other adverse effects (43CFR11301).

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No. 168

2,4,6-Trichlorophenol

Health and Environmental Effects

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

APRIL 30, 1980

-2014-

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 2,4,6-trichlorophenol and has found sufficient evidence to indicate that this compound is carcinogenic.

SPECIAL NOTATION

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

2,4,6-TRICHLOROPHENOL

Summary

Little is known about the chronic effects of 2,4,6-trichlorophenol on mammals. 2,4,6-Trichlorophenol did not promote skin cancer in skin painting studies with mice, but gave evidence of mutagenicity in two assay systems. No information was available on teratogenicity or subacute or chronic toxicities. 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 µg/l. No chronic or marine studies were available. Tainting of fish flesh has been estimated at concentrations in the water greater than 52 µg/l.

2,4,6-TRICHLOROPHENOL

I. INTRODUCTION

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

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, 1979).

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

II. EXPOSURE

Unspecified isomers of trichlorophenols have been detected in surface waters in Holland at concentrations of 0.003 to 0.1 µg/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-hexachlorocyclohexane, and hexachlorobenzene could result in exposure to 2,4,6-trichlorophenol via metabolic degradation of the parent compound (Kohli, et al. 1976; Foster and Saha, 1978; Tanaka, et al. 1977).

The U.S. EPA (1979a) has estimated the bioconcentration factor of 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 also found in flue gas condensates from municipal incinerators (Olie, et al. 1977).

III. PHARMACOKINETICS

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

2,4,6-Trichlorophenol did not increase the incidence of papillomas or carcinomas when applied repeatedly at a high concentration to the skin of mice after initiation with dimethylbenzanthracene (Boutwell and Bosch, 1959).

Results from a study of mice receiving 2,4,6-trichlorophenol in the diet throughout their lifespans (18 months) showed an increased incidence of tumors. This increased incidence, however, was in an uncertain range such that conclusive interpretation could not be made (Innes, et al. 1969).

B. Mutagenicity

However, 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, 1979a).

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).

V. AQUATIC TOXICITY

A. Acute Toxicity

Three assays have been conducted with 2,4,6-trichlorophenol to determine its acute toxicity to freshwater fish. A 96-hour static LC_{50} value of 600 µg/l has been obtained for the fathead minnow (Pimephales promelas) (U.S. EPA, 1972). In a flow-through assay, a 96-hour LC_{50} value of 9,040 µg/l was obtained for juvenile fathead minnows (Phipps, et al., manuscript). The bluegill (Lepomis macrochirus) has been shown to be the most sensitive species studied, with a 96-hour static LC_{50} of 320 µg/l (U.S.

EPA, 1978). 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 µg/l for Daphnia magna (U.S. EPA, 1978). There were no acute studies for any species of marine life.

B. Chronic Toxicity

There were no chronic data for any freshwater or marine organisms for 2,4,6-trichlorophenol.

C. Plant Effects

Complete destruction of chlorophyll in the algae, Chlorella pyrenoidosa, has been reported at concentrations of 10,000 µg/l (Huang and Gloyna, 1968). A chlorosis LC_{50} value of 5,923 µg/l was obtained for the duckweed, Lemna minor (Blackman, et al. 1955). 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. Thus, the weighted average bioconcentration factor for the edible portions of all organisms consumed by Americans is estimated to be 110 (U.S. EPA, 1979a).

E. Miscellaneous

The tainting of fish flesh by 2,4,6-trichlorophenol has been observed in the rainbow trout (Salmo gairdneri). 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 µg/l (Shumway and Palensky, 1973).

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 U.S. EPA (1979a) has recommended a draft criterion of 100 µg/l for 2,4,6-trichlorophenol in ambient water for the prevention of adverse organoleptic effects.

No other existing guidelines or standards were found for exposure to 2,4,6-trichlorophenol.

B. Aquatic

The draft criterion to protect freshwater organisms is a 24-hour average concentration of 52 µg/l not to exceed 150 µg/l. Data were insufficient to derive a criterion for marine organisms (U.S. EPA, 1979a).

2,4,6-TRICHLOROPHENOL

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No. 169

1,2,3-Trichloropropane

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

-2026-

DISCLAIMER

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1,2,3-TRICHLOROPROPANE

Summary

Pertinent data are not available on the possible carcinogenicity, mutagenicity, 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.

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°C
Boiling Point:	156.85°C
Density:	1.3889^{20}_{4}
Vapor Pressure:	2.0 torr @ 20°C
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; however, fugitive emissions from manufacturing and production facilities probably 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 trichloropropane 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 sloughing 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

15 minutes. McOmie and Barnes (1949) found that ingestion of 3g of trichloropropane 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.

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No. 170

o,o,o-Triethyl Phosphorothioate

Health and Environmental Effects

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O,O,O-TRIETHYL PHOSPHOROTHIOATE

Summary

There is no information available on the possible carcinogenic, mutagenic, teratogenic, or adverse reproductive effects of O,O,O-triethyl phosphorothioate. Triethyl phosphate, a possible metabolite of the compound, has shown weak mutagenic activity in Salmonella, Pseudomonas, and Drosophila.

Like other organophosphates, O,O,O-triethyl phosphorothioate may be expected to produce cholinesterase inhibition in humans.

No pertinent data are available on the aquatic effects of the compound.

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 in 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

References

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Trinitrobenzene

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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.

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.

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 dinitrobenzenes, which may show pharmacokinetic similarities (U.S. EPA, 1979).

Acute oral toxicity studies conducted with dogs indicate that trinitrobenzene 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 dinitrobenzenes, 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 respiratory 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 µg/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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