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PROGRAM MANAGER FOR ROCKY MOUNTAIN ARSENAL

U.S. ARMY
MATERIEL COMMAND

— COMMITTED TO PROTECTION OF THE ENVIRONMENT —

FINAL
HUMAN HEALTH EXPOSURE ASSESSMENT
FOR ROCKY MOUNTAIN ARSENAL
VOLUME III-A
TOXICITY ASSESSMENT
VERSION 4.1
SEPTEMBER 1990
CONTRACT NO. DAAA15-88-D-0024
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ROCKY MOUNTAIN ARSENAL

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VOLUME III-A
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U.S. ARMY PROGRAM MANAGER'S OFFICE
FOR THE ROCKY MOUNTAIN ARSENAL CONTAMINATION CLEANUP

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DISCLAIMER STATEMENT

The toxicity profiles contained in Volume II-A and Volume III-A were provided by Shell Oil Company. They are intended to provide additional toxicity information for certain chemicals. The numerical estimates of toxicity used in the PPLVs computed in the Human Health Exposure Assessment for Rocky Mountain Arsenal are those contained in the toxicity profiles prepared by the Army in Volume II and Volume III.

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TABLE OF CONTENTS

<u>Toxicity Profile</u>	<u>Page</u>
FLUOROACETIC ACID	1
HEXACHLOROCYCLOPENTADIENE	11
ISODRIN	29
MERCURY (INORGANIC)	39
METHYLENE CHLORIDE	56
SUPONA	77
1,1,2,2-TETRACHLOROETHANE	90
TETRACHLOROETHYLENE	102
1,1,2-TRICHLOROETHANE	120
TRICHLOROETHYLENE	139

FLUOROACETIC ACID

Summary

Fluoroacetic acid and its sodium salt, sodium fluoroacetate (Compound 1080), are acutely toxic to birds and mammals. Fluoroacetic acid will be present in the body as the anion of the sodium salt, so information about fluoroacetate is appropriate. Fluoroacetate is used primarily as a rodenticide, but is also used to kill coyotes in western North America. Most of the literature about its toxicity describe its mechanism of action and the consequent metabolic changes it induces in rodents. Fluoroacetate apparently induces toxicity through two mechanisms: a) inhibition of the tricarboxylic acid cycle through lethal synthesis of fluorocitrate and b) interference with the mitochondrial citrate transport systems. These effects result in an accumulation of citrate and ultimately in lethal depression of cellular respiration. Few data on fluoroacetate's reproductive, teratogenic, mutagenic and carcinogenic effects, and environmental persistence are currently available. However, fluoroacetate is found as a natural constituent in at least 36 species of plants indigenous to the southern hemisphere.

CAS Number:	144-49-0
Chemical Formula:	CH_2FCOOH
IUPAC Name:	2-Fluoroacetic Acid
Important Synonyms and Trade Names:	Fluoroethanoic Acid; Gifblaar Poison; MFA; Monofluoroacetic Acid.

Chemical and Physical Properties

Molecular Weight:	78.04 (Merck 1983)
Boiling Point:	165°C (Sax 1979)

Melting Point:	33°C (Merck 1983)
Specific Gravity:	1.369 (USEPA 1985)
Solubility in Water:	Soluble (Merck 1983)
Solubility in Organics:	Slightly soluble in petroleum ether
Log Octanol/Water Partition Coefficient (K_{ow}):	Not Located
Soil/Water Partition Coefficient (K_{oc}):	Not Applicable
Bioconcentration Factor:	Not Applicable
Vapor Pressure:	Not Located
Henry's Law Constant:	Not Applicable

Transport and Fate

Little information is available on the transport and fate processes of fluoroacetic acid or its sodium salt, sodium fluoroacetate. Both the acid and the salt are water soluble (USEPA 1985; Gosselin 1976). Sodium fluoroacetate is also nonvolatile (Gosselin 1976) and therefore losses from environmental media due to evaporation would not be expected to occur. Under normal conditions of Ph in soil and water it is likely that the compound will be present as a salt rather than as a free acid. Potassium fluoroacetate is a natural toxic constituent of the South African plant *Dichaepetalum cymosum* (Peters et al. 1981). Fluoroacetate is also a natural constituent of some poisonous plants, notably *Acacia georginae*, a perennial shrub found in Australia (Gosselin 1976). Neither plant is likely to occur naturally in the United States.

Although no data on the stability of fluoroacetic acid (or its sodium salt) in air, soil, water or its potential for bioaccumulation were located in the available literature, some soil microbes (Walker and Lien, 1981) and plants (Ward and Huskisson, 1972) apparently metabolize fluoroacetate via defluorination, glutathione conjugation, or

both. Given the soluble nature of fluoroacetic acid and its sodium salts, bioconcentration would not be expected to occur.

Health Effects

The data presented are for sodium fluoroacetate, the salt of fluoroacetic acid. Numerous in vivo and in vitro studies with laboratory animals have shown that its toxicity is derived from its metabolic conversion to fluorocitric acid (fluorocitrate), a potent inhibitor of the tricarboxylic acid cycle (TCA)--an essential mechanism in energy production in mammalian cells (Gosselin 1976). The block results from the inhibition of aconitase (a TCA enzyme) which regulates the conversion of citrate to isocitrate, causing the accumulation of large quantities of citrate in various tissues (Casarett and Doull, 1980). Spencer and Lowenstein (1966) showed that fluoroacetate increases the citrate content of kidney but not of liver in rats under various dietary and physiological conditions. Further evidence to support TCA cycle inhibition by fluoroacetate was reported by Zhou et al. 1984, when they observed a 5-fold increase of hepatic citrate and a 50-90% reduction in hepatic glycolysis and glycogenolysis in the perfused livers of fluoroacetate-pretreated rats (5 mg/kg). Tisdale and Brennan (1985) reported indirect evidence of fluoroacetate's inhibiting capacity after studying the cytotoxic effects of fluoroethylnitrosoureas (FENUS) in mice. Their results suggest that some of the antitumorigenic effects of FENUS result from fluoroacetate production, ultimately resulting in the inhibition of the TCA cycle. Berhane and Casida (1989) provided supporting evidence of TCA cycle inhibition in mice, but they also showed that fluoroacetate undergoes defluorination and subsequent conjugation with glutathione. Sykes et al. (1987) provided additional evidence of the defluorination of fluoroacetate, after intravenously dosing mice with 0.4 mg/kg [^{18}F] - fluoroacetate. With the exception of the accumulation of [^{18}F] in bone (10% of the dose, an indication of defluorination) over 4 hours, fluoroacetate was rapidly excreted by the mice (40% of the dose eliminated after 4 hours; plasma elimination half-life,

1.6 hours). Thus, fluoroacetate can proceed through two pathways of metabolism: a) conversion to fluorocitrate and b) defluorination and glutathione conjugation.

Szerb and Issekutz (1987) reported a potential biochemical consequence of fluoroacetate poisoning on the CNS. Fluoroacetate apparently reduces glutamine synthesis and glutamate uptake in the glial cells of rat hippocampal slices. However, the absence of a dose-response relationship makes this finding tenuous. Nonetheless, the results do suggest a potential mechanism for the convulsive action of fluoroacetate. Other evidence from in vitro experiments suggests that the inhibition of the TCA cycle cannot account for all the toxic effects of fluoroacetate. For instance, mitochondrial incubations of heart, kidney, and brain prepared from fluoroacetate - intoxicated rats show differential effects to gluconeogenic substrates (Corsi and Granata, 1967). However, most of the evidence from in vitro experimentation supports the hypothesis that the primary biochemical lesion produced by fluoroacetate is TCA cycle inhibition. Wiedemann et al. (1983) demonstrated this with incubations of isolated rat kidney tubules. Fluoroacetate inhibited gluconeogenesis in these cells after they were exposed to a number of gluconeogenic substrates (again, however, a dose-response relationship was not established). Because the metabolic lesion involves inhibiting oxidative energy metabolism, the heart and the central nervous system are the critical tissues affected (Casarett and Doull 1980). Symptoms of poisonings include nausea, vomiting, cardiac irregularities, cyanosis, and convulsions. Death is usually the result of ventricular fibrillation or respiratory failure. The estimated lethal dose for humans ranges from 2 to 10 mg/kg (Casarett and Doull 1980).

Species differences are reported in the types of symptoms which precede death. Dogs usually die of convulsions or respiratory failure; however, in man, monkeys, horses and rabbits, central nervous system effects are often incidental with the principal complication arising from ventricular fibrillation (Casarett and Doull 1980).

Few data are available on the effects of chronic poisoning with sodium fluoroacetate; however, renal changes similar to nephrosis have occurred in rats

administered acutely lethal or repeated sublethal injections of fluorocitrate (Gosselin 1976). In one reported case of chronic poisoning, a rabbit exterminator exposed repeatedly over a period of 10 years exhibited severe and progressive lesions of the renal tubular epithelium and milder hepatic neurologic and thyroid dysfunctions (Gosselin 1976).

No data on the reproductive effects, teratogenicity, carcinogenicity, or mutagenicity of fluoroacetic acid or related compounds was located in the available literature. The oral LD₅₀ values in rats, mice and guinea pigs are 4.7, 7, and 0.47 mg/kg, respectively (NIOSH 1982). The subcutaneous LD₅₀ value in rats is 5.0 mg/kg (Hayes et al. 1973).

Toxicity to Wildlife and Domestic Animals

Some poikilothermic animals are reported to be resistant to fluoroacetate notably, the S. African clawed toad (*Xenopus laevis*) and some fish such as the bass and the bream (Bauermeister et al. 1977). The intraperitoneal LD₅₀ of fluoroacetate in rainbow trout (*Salmo gairdneri*) is 500 μ mole/kg (Bauermeister et al. 1977).

Acute oral toxicities (LD₅₀) are presented below for a variety of species (Hudson et al. 1984).

<u>Species</u>	<u>LD₅₀ (mg/kg)</u>
bullfrogs (<i>Rana catesbeiana</i>),	54.4 mg/kg
mallard ducks (<i>Anas platyrhynchos</i>),	9.11 mg/kg
California quail (<i>Callipepla californica</i>),	4.63 mg/kg
Japanese quail (<i>Coturnix c. japonica</i>),	12.8 mg/kg
ring-necked pheasant (<i>Phasianus colchicus</i>),	6.46 mg/kg
Chukar (<i>Alectoris chukar</i>),	3.51 mg/kg
turkeys (<i>Meleagris gallopavo</i>),	4.76 mg/kg
domestic pigeons (<i>Columba livia</i>)	4.24 mg/kg
house sparrows (<i>Passer domesticus</i>)	3.0 mg/kg
domestic ferrets (<i>Mustela putorius</i>)	1.41 mg/kg
mule deer (<i>Odocoileus h. hemionus</i>)	0.33-1.0 mg/kg

Hudson et al. (1984) reported secondary toxicity in fasted ferrets fed live or dead mice previously dosed with 1, 2, 4, or 8 mg/kg sodium fluoroacetate. Only one ferret survived; this following the ingestion of one of two low-dose (2 mg/kg) mice.

Regulations and Standards

OSHA Permissible Exposure Limit: $TWA^1 = 0.05 \text{ mg/m}^3$ (sodium salt)

ACGIH Threshold Limit Value: $TWA = 0.05 \text{ mg/m}^3$ (sodium salt)

$STEL^2 = 0.15 \text{ mg/m}^3$ (sodium salt)

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For fluoroacetic acid, the D_T value is derived from an acute oral toxicity value (LD_{50}) in guinea pigs. The D_T is computed as the product of the acute value and an application factor of 1×10^{-3} (Layton et al., 1987). The application factor allows the derivation of an interim acceptable long term intake rate (D_T) based on the results of acute tests (LD_{50}) in the absence of more suitable long term studies (i.e., No-Observed-Effect-Level, NOEL, studies). The application factor corresponds to the cumulative percentile on a log-normal distribution of NOEL/ LD_{50} ratios for various chemicals. The percentile was chosen to reduce the probability that the calculated dose rate would be above a toxic level; the 5th cumulative percentile was used by Layton et al. (1987) and was found to be equal to 10^{-3} . The application factor also includes a safety factor of 100 to address interspecies and intraspecies variability;

¹ Time Weighted Average.

² Short Term Exposure Limit.

therefore, an interim estimate of D_T is obtained when the acute value is multiplied by the application factor. Derivation of the D_T value is as follows:

$$\begin{aligned} D_T &= \text{Acute oral LD}_{50} \times \text{Application Factor} \\ &= 0.47 \text{ mg/kg/day} \times 1 \times 10^{-5} \\ &= 0.0000047 \text{ mg/kg/day} \end{aligned}$$

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HEXACHLOROCYCLOPENTADIENE

Summary

Hexachlorocyclopentadiene is used as a chemical intermediate for insecticides and flame retardants (USEPA 1988). Human exposure is most likely to occur during its manufacture or during production of HCPD containing products with inhalation being the primary exposure mode (USEPA 1980a). The compound acts as an irritant to the eyes, skin, mucous membranes and respiratory tract of humans. Accidental over-dosing may cause necrosis of the brain, heart, adrenals, liver, and kidneys.

HCPD has been detected in water near points of industrial discharge at levels ranging from 0.156 to 18 mg/l (USEPA 1979 in USEPA 1980a). It is not expected to remain in flowing water due to its low solubility, photolability, and tendency to volatilize. HCPD has been identified in a few samples of fish from waters near the Hooker Chemical Plant in Michigan (Spehar et al. 1977 in USEPA 1980a). USEPA has estimated the weighted average bioconcentration factor of HCPD for the edible portions of fish for human consumption to be 3.2 (USEPA 1979 in USEPA 1980a).

Hexachlorocyclopentadiene (HCPD) has not presently been shown to be carcinogenic in animals or humans; however, the National Cancer Institute has selected HCPD for testing. No evidence of mutagenicity has been established for HCPD in either mammalian or bacterial test systems. In animal studies, HCPD given orally resulted in toxic nephrosis in female mice and in male and female rats. Rats exposed to high concentrations of HCPD via inhalation experienced mortality, depressed body weights, increased kidney weights (females only) and pulmonary degenerative changes. HCPD has not resulted in teratogenic or embryotoxic effects following its administration to rabbits and rats; however, maternal toxicity was observed in treated rabbits.

A subchronic study whereby HCPD was given by gavage revealed increased incidence of stomach lesions and toxic nephrosis and increased mortality in rats of

both sexes; the rat NOAEL for stomach lesions of 10 mg/kg body weight was used to set the reference dose of 7×10^{-3} mg/kg/day (Abdo et al. 1984).

CAS Number: 77-47-4

Chemical Formula: C_5Cl_6

IUPAC Name: 1,2,3,4,5,5'-Hexachloro-1,3-cyclopentadiene

Important Synonyms and Trade Names: HCPD, Perchlorocyclopentadiene;
PCL; C56; Graphlox; HRS 1655;
NCI-C55607 (USEPA 1985)

Appearance and Odor: Yellow-green liquid with a pungent odor (USEPA 1988)

Conditions or Materials to Avoid: Reacts slowly with water to form hydrochloric acid but the reaction is not hazardous; corrodes iron and other metals in the presence of moisture (USEPA 1988).

Chemical and Physical Properties

Molecular Weight: 272.77 (U.S. EPA 1985)

Melting Point: -9.6°C

Boiling Point: 239°C at 753 mm Hg (Hawley 1977; Stevens 1979)
 234°C (Irish 1963)

Specific Gravity: 1.715 at 15.5°C (Hawley 1977)

Solubility in Organic Solvents: Miscible in hexane (Bell et al. 1978)

Solubility in Water: 2.1 mg/liter at 25°C (Dal Monte and Yu 1977)
1.8 mg/liter at 28°C (Wolfe et al. 1982)
0.805 mg/liter at 25°C (Lu et al. 1975)
2.1 mg/liter at 25°C (USEPA 1986a)

Log Octanol/Water Partition Coefficient (K_{ow}): 3.52 (Lyman et al. 1982)
Fragment Method
5.04 (Wolfe et al. 1982)

Soil/Water Partition Coefficients (K_{oc}): 13,140 Lyman et al. (1982)
Eqn 4-8 ($\log K_{ow} = 5.04$)
24,330 Lyman and Loreti
(1987) ($\log K_{ow} = 5.04$)
4,800 USEPA (1986a)

Bioconcentration Factor:

29	Veith et al. (1979) (experimental)
11	USEPA (1980b)
279	Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 3.52$)
195	Davies and Dobbs (1984) Eqn B ($\log K_{ow} = 3.52$)
107.6	Davies and Dobbs (1984) Eqn C ($\log K_{ow} = 3.52$)
179	Davies and Dobbs (1984) Eqn A ($S = 9$)
717	Davies and Dobbs (1984) Eqn C ($\log K_{ow} = 5.04$)
1,570	Davies and Dobbs (1984) Eqn B ($\log K_{ow} = 5.04$)
3,980	Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 5.04$)

Vapor Pressure: 0.08 mm Hg at 25°C (Irish 1963)
0.975 mm Hg at 62°C (Stevens 1979)

Vapor Density (AIR = 1): 9.4 (USEPA 1988)

Henry's Law Constant: 0.0137 atm-m³/mole (USEPA 1986a)
5.76 x 10⁻¹ Dimensionless
0.027 atm-m³/mole (Atallah et al. 1980, Wolfe et
al. 1982)
1.13 Dimensionless

Transport and Fate

Hexachlorocyclopentadiene (HCPD) is known to volatilize rapidly from water (USEPA 1984); however, it is not likely to persist following its release to air. The estimated tropospheric residence time (Cupitt 1980) is approximately five hours based on reactions with hydroxyl radicals and ozone (USEPA 1984). Atmospheric photolysis of HCPD is likely since HCPD has a chromophore which absorbs light in the solar spectrum. The degradation products are thought to be ClCO, diacylchlorides, ketone and free Cl radical (USEPA 1984).

HCPD is known to photolyze in aqueous media. In flowing bodies of water, photolysis, hydrolysis, volatilization and biodegradation will all contribute to the loss of HCPD. The photolytic half-life of HCPD in shallow water (<5 cm depth) is estimated to be 10 minutes (USEPA 1984). Hydrolysis is much slower with a half-life ranging from 3-11 days at pHs of 5-9 and temperatures between 25 and 30°C (Wolfe et al. 1982). These authors conclude that the results of model simulation of the fate and transport of HCPD in various ecosystems suggests that it is transformed mainly via photolysis and to a lesser extent hydrolysis (Wolfe et al. 1982). In river systems export from the ecosystem will predominate but in lakes and ponds transformation will dominate. Sediments in defined sediment-water systems do not significantly affect the disappearance rate constants for the hydrolytic and photolytic processes. Fate and transport assessment indicates that HCPD will not likely reach substantial steady-state concentrations in the various compartments of the simulated ecosystems (Wolfe et al. 1982).

The fate and transport of HCPD in soils is affected by its strong tendency to adsorb onto organic matter (USEPA 1984). A range of estimated soil/water partition coefficients (K_{oc}) is reported above and indicates that sorption of HCPD to soil/sediments and dissolved organic material will occur. The combined low water solubility and high organic partitioning for HCPD suggests that this compound will not be an environmental mobile contaminant. HCPD is known to be metabolized by a number of soil microorganisms (USEPA 1984).

A range of estimated and experimental bioconcentration factors (BCFs) for HCPD is also reported above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the estimated concentration or biomagnification of HCPD residues would occur; however, experimental data appear to indicate that uptake is not considerable (USEPA 1984).

In reviewing the major pathways of HCPD in air, water, and soil, researchers have concluded that HCPD in air would be rapidly photolyzed to CO₂ and HCl; HCPD in water would be mainly volatilized with that which remains being slowly degraded to CO₂; and HCPD in soil would be either volatilized or adsorbed (Atallah et al. 1981). The HCPD volatilized from soil or water would be immediately photolyzed as HCPD is a highly reactive compound. These authors found the hydrolytic t_{1/2} to be <2 hours at Ph 12 and 11 days at Ph 3-6; photolysis t_{1/2} was <30 minutes (Atallah et al. 1981). HCPD was found to be biodegradable under both aerobic and anaerobic conditions with the octanol/water partition coefficient indicating only a moderate potential for bioconcentration.

Health Effects

Few data are available on the health effects of HCPD exposures in humans. The compound is very irritating to the eyes and mucous membranes and induces lacrimation, sneezing, and salivation. Repeated contact with the skin causes blistering burns, and inhalation causes pulmonary edema (USEPA 1984). Exposure may also cause headaches and throat irritation (USEPA 1988). One study of an accidental human exposure suggests that the liver may be a target organ (USEPA 1988).

HCPD is acutely toxic to experimental animals, causing pulmonary hyperemia and edema, degenerative and necrotic changes in the brain, heart, and adrenal glands, and necrosis of the liver and kidney tubules under severe exposure situations (USEPA

1988). A rat oral LD₅₀ of 113 mg/kg and a rabbit dermal LD₅₀ of 430 mg/kg have been reported in RTECS (NIOSH, 1984).

Mice and rats were found to be approximately equal in susceptibility to the toxic effects of HCPD given by gavage in subchronic testing (Abdo et al. 1984). Ten rats per sex received 0, 10, 19, 38, 75, or 150 mg HCPD/kg body weight by gavage for 5 days/week for 13 weeks. At high doses an increased incidence and severity of stomach (male dose: >38 mg/kg; female dose: >19 mg/kg), and toxic nephrosis (dose > 38 mg/kg) occurred in both sexes. In addition, mortality increased with increasing dose for both sexes.

Similarly, female mice experienced toxic nephrosis (dose >75 mg/kg) but 19 mg/kg/day was the NOEL and 38 mg/kg/day was the LOAEL for stomach lesions in both male and female mice (Abdo et al. 1984). The highest treatment group (300 mg/kg/day) experienced mortality which was much greater for males (10/10) than for females (3/10).

Applying an uncertainty factor of 1,000 (10 for uncertainty in the subchronic NOAEL x 10 for interspecies conversion x 10 for sensitive human subpopulations) to the rat NOAEL for stomach lesions of 10 mg/kg body weight, or 7 mg/kg/day, yields a reference dose (RfD) of 7×10^{-3} mg/kg/day (USEPA 1988). However, confidence in this RfD is low because it is not based on chronic exposure data and inhalation and dermal studies have shown much more toxicity (lung damage and skin lesions) with steep dose response curves (USEPA 1988). No RfD for chronic inhalation exposure is available at this time.

Other subchronic results showed minimal to mild acute inflammatory response in the respiratory tract and minimal squamous-cell metaplasia of the nasal cavity epithelium in rats exposed to 0.5 ppm HCPD for 13 weeks (USEPA 1988). Mice exposed at this level had moderate to severe subchronic inflammation of the mucosa of the bronchi and bronchioles and squamous cell metaplasia of the larynx, trachea, bronchi, and bronchioles; the severity of these effects lessened over the treatment period (USEPA 1988).

Rats and monkeys exposed subchronically (14 weeks) to HCPD via inhalation at doses of 0, 0.1, 0.05, and 0.20 ppm exhibited no treatment related abnormalities in gross pathology, histopathology, hematology, or clinical chemistry. However, slight but statistically insignificant increases in hemoglobin concentration and erythrocyte counts were seen in the 0.01 and 0.20 ppm male rats and the 0.05 ppm female rats (USEPA 1984).

Male and female rats chronically exposed (30 weeks) via inhalation to doses of 0, 0.05, 0.1, and 0.5 ppm HCPD 6 hours/day, 5 days/week exhibited a number of effects (USEPA 1984). At the highest dose level, mortalities of males and females occurred. Males in this dose group exhibited depressed weight gain following the seventh week of exposure and for the remainder of the study. Females in the medium and high dose groups also exhibited depressed body weights. Pulmonary, kidney and liver degenerative changes were observed in both sexes at the high dose. Kidney weights of high dose females were significantly increased.

A study designed to examine the difference in toxicity of HCPD as a function of route of exposure by determining the absorption, distribution, and fate of HCPD following acute oral, inhalation, and i.v. exposure of rats revealed that the direct damage to lung tissue by inhaled HCPD and low bioavailability of orally administered HCPD contributes substantially to higher inhalation toxicity (Lawrence and Dorrough 1982). For all exposure routes, the lungs were the major site of HCPD toxicity upon post-mortem exam in this study.

Chronic toxicity studies have revealed that daily administration of 1/30 the median lethal dose (20 mg/kg) for 6 months resulted in the death of 2/10 animals (Naishstein and Lisovskaya 1965 in USEPA 1980a). These same researchers found no adverse effects from applying 0.5 - 0.6 ml of a solution containing 20 ppm HCPD daily to the skin of rabbits for 10 days (Naishstein and Lisovskaya 1965 in U.S. EPA 1980a). However, degenerative changes of the brain, heart, lungs, liver, kidneys, and adrenal glands, and chronic skin inflammation, acanthosis, hyperkeratosis, and epilation occurred among rabbits having 430-610 mg/kg HCPD applied to their skin for 24 hours; this was also the minimum lethal dose (Treon et al. 1955). Guinea

pigs, rabbits, and rats exposed to 0.15 ppm HCPD daily for 7 hours over 7 months survived but 4/5 mice died (Treon et al 1955).

Mice, rats, rabbits, and guinea pigs exposed to 0.34 ppm HCPD for 7 hours/day for 5 days/week had variable survival: mice and rats survived for 20 exposure periods; guinea pigs survived for 30 periods; 4/6 rabbits died by the 25th period (Treon et al. 1955). Lethal inhalation doses were: rabbits = 1.5 ppm for 7 hours; mice = 1.4 ppm for 3 7-hour periods; rats = 1.0 ppm for 5 7-hour periods; guinea pigs = 3.2 ppm for 2 7-hour periods.

The acute oral LC_{50} of HCPD in rats ranges from 500-630 mg/kg (USEPA 1980b). Treon et al. (1955) reported an LD_{50} for HCPD of 505 mg/kg body weight for male rats. Oral administration to rats or rabbits induced diarrhea, lethargy, and a retarded respiratory rate. Rabbits and rats given lethal oral dosages exhibited diffuse degenerative lesions in the brain, heart, liver, adrenal glands, and kidneys, and edema and hyperemia of the lungs. HCPD at a dose of 0.01 - 0.05 ml in Ultrasene solutions at concentrations ranging from 0.001 - 90% were applied to the skin of a monkey; the threshold concentration which induced irritation of intact skin was between 10-20% (Treon et al. 1955).

No reproductive impairment or evidence of teratogenicity was observed in pregnant rats orally administered HCPD at doses of 3, 10 or 30 mg/kg/day during days 6-15 of gestation (USEPA 1984). No evidence of teratogenicity was apparent in mice or rabbits orally dosed with 0, 5, 25 or 75 mg/kg/day HCPD during days 6-15 (mice) of gestation (USEPA 1984). Fertility was not significantly different in either dosed mice or rabbits. No maternal toxicity or embryotoxicity occurred in treated mice; however, maternal toxicity did occur at 75 mg/kg/day in rabbits. No embryotoxic effects were noted at any dose level in rabbits (USEPA 1984). HCPD was not teratogenic by oral gavage in rats, mice, and rabbits (USEPA 1988). Teratogenic effects were not reported at doses up to 100 mg/kg/day in rats receiving HCPD on days 6-15 of gestation (IRDC 1978 in USEPA 1980a).

No evidence of the carcinogenicity of HCPD has been demonstrated in animals or humans (USEPA 1984); however, the National Toxicology Program (NTP) began

carcinogenicity testing in 1986 (NTP 1986) using F344 rats and B6C3F₁ hybrid mice (USEPA 1988). It has not been shown to be mutagenic in a variety of bacterial (*E. coli*, *S. typhimurium*) and mammalian cell cultures (mouse lymphoma). HCPD was relatively toxic to cells but without significant carcinogenic activity in a malignant transformation assay using BALB/373 cells (Litton Bionetics 1977 in USEPA 1980a). U.S. EPA is evaluating HCPD for evidence of human carcinogenicity (USEPA 1988).

Toxicity to Wildlife and Domestic Animals

Very little information is available on the toxicity of HCPD to wild and domestic animals. The acute oral LD₅₀ of HCPD in rabbits ranges between 420 and 620 mg/kg (USEPA 1980b). Freshwater and marine aquatic organisms exhibit acute toxic effects at concentrations of HCPD as low as 7 µg/liter, while freshwater organisms exhibit chronic effects at concentrations of 5 µg/l (USEPA 1986b).

HCPD can be toxic to certain bacteria and fungi but not those in the soil (Atallah et al. 1981). Acute toxicity of HCPD to aquatic organisms is generally high with the most sensitive species, *Daphnia*, having a 48-hour LC₅₀ of 52 ppb. However, its extremely short half-life greatly reduces the hazard to aquatic life and it is only slightly bioconcentrated and very slightly biomagnified if at all (Atallah et al. 1981). HCPD is rapidly degraded in the gut of mammals with only small amounts being absorbed; 90% of orally consumed HCPD is excreted in feces within 7 days with <1% remaining in body tissues (Atallah et al. 1981).

Acute toxicity studies of the fathead minnow reported 96-hour LC₅₀ values of from 7.0 - 104 µg/l under static and flow-through conditions with larval and adult fish (USEPA 1978 in USEPA 1980a). The lowest chronic value was 2.6 µg/l. The 30-day exposure of this species to > 7.3 µg/l of hexachlorocyclopentadiene resulted in a 96-hour LC₅₀ of 7.0 µg/l and a 30-day LC₅₀ of 6.7 µg/l (Spehar et al. 1979). Residues of HCPD in 30-day-old minnows were <0.1 µg/l resulting in a BCF of <11.

Regulations and Standards

Ambient Water Quality Criteria (USEPA 1986b, 1988):

The available data are not adequate for establishing criteria. However, EPA does report the lowest values known to be toxic in aquatic organisms.

Aquatic Life (Freshwater)

Acute Toxicity: 7 $\mu\text{g/liter}$

Chronic Toxicity: 5.2 $\mu\text{g/liter}$

Aquatic Life (Saltwater)

Acute Toxicity: 7 $\mu\text{g/liter}$

Chronic Toxicity: Data are insufficient

Human Health

Water and Fish Consumption: 1.0 $\mu\text{g/liter}$ (using organoleptic data for controlling undesirable taste and odor)

Health Criterion: 206 $\mu\text{g/liter}$

ACGIH Threshold Limit Value (1980): TWA = 0.1 mg/m^3

SUPERFUND (CERCLA) Reportable Quantity for Release into the Environment: 10 pounds (Proposed 1987)

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For HCPD, the oral D_T value is based on the current EPA Reference Dose (RfD) (USEPA 1988). The oral RfD is based on the subchronic oral (gavage) toxicity study previously discussed in which male and female rats were administered HCPD at doses of 0, 10, 19, 38, 75, or 150 mg/kg/day, 5 days/week for 13 weeks (Abdo et al. 1984). The No-Observed-Adverse-Effect-Level (NOAEL) identified from this study was 7 mg/kg/day. [Note: EPA multiplies the actual NOAEL of 10 mg/kg/day by a conversion factor of 5/7 days to account for the less than continuous exposure duration in determining the final NOAEL level.] An Uncertainty Factor (UF) of 1,000 is included to address the extrapolation of results to humans (10), intraspecies variability (sensitive subgroups) (10) and to account for the use of a subchronic rather than a chronic experimental exposure (10). Derivation of the D_T value for HCPD is as follows:

$$\begin{aligned}
 D_T &= \frac{\text{NOAEL (mg/kg/day)}}{\text{UF}} \\
 &= \frac{7}{1,000} \\
 &= 0.007 \text{ mg/kg/day}
 \end{aligned}$$

The inhalation D_T for HCPD is based on a chronic inhalation study in rats (Clark et al. 1982) and has been used by EPA as the basis for the Acceptable Intake Chronic (AIC) for HCPD (USEPA 1984; USEPA 1986a). In the study rats were exposed 6 hours/day, 5 days/week for 30 weeks to concentrations of 0, 0.05, 0.1 or 0.5 ppm HCPD, followed by a 14-week recovery period. Male and female mortalities were observed at the high dose level. Body weights were depressed in these animals and pulmonary degenerative effects were observed, with males being most affected. Mild degenerative changes were observed in the livers and kidneys of females at 0.5 ppm. At 0.1 ppm reduced body weights were noted in females. No effects were observed in either sex at 0.05 ppm (0.066 mg/kg/day).

An uncertainty factor (UF) of 1,000 is used in the derivation of the AIC to address: 1) interspecies extrapolation (10); 2) intraspecies variability (10); and 3) discrepancies in the available data for HCPD toxicity levels. Derivation of the inhalation D_T for HCPD is as follows:

$$\begin{aligned} D_T &= \frac{\text{NOAEL (mg/kg/day)}}{\text{UF}} \\ &= \frac{0.066}{1,000} \\ &= 6.6 \times 10^{-5} \text{ mg/kg/day} \end{aligned}$$

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ISODRIN

Summary

Isodrin is a chlorinated cyclodiene pesticide and an endo-endo isomer of the well characterized aldrin. It is a broad spectrum pesticide that is no longer used commercially in the U.S. This compound would be expected to share some of the toxic properties of aldrin as well as the related compound endrin. There is no data available on the carcinogenicity, teratogenicity, mutagenicity, or chronic or reproductive toxicity of isodrin. One report of an acute oral toxicity test in young male and female rats (90 days of age) gives an LD₅₀ of 7 mg/kg for females and 15 mg/kg for males (Gaines, 1969).

CAS Number:	465-73-6
Chemical Formula:	C ₁₂ H ₈ Cl ₆
IUPAC Name:	1,2,3,4,10,10-hexachloro - 1,4,4a,5,8,8a -hexahydro -1,4,5,8 - endo-endo-dimethanonaphthalene
Important Synonyms and Trade Names:	Isodrin, Compound 711

Chemical and Physical Properties

Molecular Weight:	364.90
Melting Point:	240 - 242°C (Merck 1983)
Solubility in Water:	0.16 mg/liter (Lyman et al. 1982) Estimated 1.4 mg/liter; 0.02 mg/liter (Lyman et al. 1982) (Eqn. 2-3 log K _{ow} = 4.38; 6.51)
Log Octanol/Water Partition Coefficient (K _{ow}):	6.51 (Lyman et al. 1982) Fragment Method

**Soil/Water Partition
Coefficient (K_{ow}):**

5,751; 82,880	Lyman et al. (1982) Eqn. 4-8 ($\log K_{ow} = 4.38$; 6.51)
7,448; 339,900	Lyman and Loreti (1987) $\log K_{ow} = 4.38$; 6.51)
8,759; 294,900	Kadeg et al. (1986) ($\log K_{ow} = 4.38$, 6.51)

Bioconcentration Factor:

11,708	Davies and Dobbs (1984) Eqn B ($\log K_{ow} = 6.5$)
51,286	Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 6.5$)
4,436	Davies and Dobbs (1984) Eqn C ($\log K_{ow} = 6.5$)
1,737	Davies and Dobbs (1984) Eqn A ($S = .16$)
233	Davies and Dobbs (1984) Eqn C ($\log K_{ow} = 4.38$)
635	Davies and Dobbs (1984) Eqn B ($\log K_{ow} = 4.38$)
1,260	Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 4.38$)

Vapor Pressure: $< 1 \times 10^{-4}$ mm Hg [estimated for 25°C] (Cogley and Foy 1978)

Henry's Law Constant:

4.8×10^{-4} atm - m^3 /mole (calculated)
 3.4×10^{-5} atm - m^3 /mole (calculated)
 1.4×10^{-3} dimensionless
 3.2×10^{-3} atm - m^3 /mole (calculated)
 1.3×10^{-1} dimensionless

Transport and Fate

Very little information is available on the fate and transport of isodrin under environmental conditions; indeed, the physical/chemical properties of this compound have not yet been fully characterized. Photodrin formation has been observed following reactions of isodrin with acid, bromine, hydrogen bromide and ultraviolet (UV) light in the laboratory (Berkowitz et al. 1978). However, under field conditions, photoconversion of isodrin to photodrin is not expected as the maximum

UV absorption of isodrin (198 nm) occurs in a region of the atmosphere where solar radiation is attenuated by both the ozone layer and by water (Berkowitz et al. 1978).

Isodrin is estimated to have a very low vapor pressure and a relatively low solubility in water (Cogley and Foy 1978). Therefore, it appears reasonable to assume that volatilization of isodrin to air, and leaching of isodrin contaminated soil residues to groundwater will not occur to an appreciable extent. A range of estimated soil/water partition coefficients (K_{ow}) is reported above and indicates that sorption of isodrin to soils/sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of chlorinated hydrocarbon pesticides is very high. The combined low estimated water solubility and high organic partitioning indicate that isodrin will exhibit little environmental mobility. The persistence of isodrin in various soils under varying experimental conditions, as summarized by Berkowitz et al. (1978), indicates that detectable residues may be present in excess of 13 years post-application.

No residues of isodrin were found in soybeans, corn, or oats grown in soil treated with isodrin (Nash et al. 1973). Ten weeks following application of isodrin (0.19 ppm) to soils, up to three percent of the applied quantity was recovered unchanged in the leaves of exposed carrots while 41 percent remained unchanged in the soils (Berkowitz et al. 1978 cite Klein et al. 1973). Conversion products which accounted for a majority of the remaining residues were identified as endrin. The half-life of isodrin in soil has been estimated at 6 years.

A range of estimated bioconcentration factors (BCFs) for isodrin is also reported above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the concentration factors suggests that appreciable bioconcentration or biomagnification of isodrin residues can occur. In fact, isodrin is known to convert to epoxides in body fat and is reported to accumulate faster than most halogenated hydrocarbons (Anonymous, 1987).

Health Effects

No information on the toxicity of isodrin to humans was located in available literature. Additionally, no data on the carcinogenicity, mutagenicity, or subchronic, chronic or reproductive toxicity were available for animals in the literature reviewed.

Acute oral and dermal toxicity data are available for mice, rats, rabbits and chickens, and the LD₅₀ values are listed in the following table.

<u>Species</u>	<u>Sex</u>	<u>Route of Administration</u>	<u>LD₅₀ Value (mg/kg)</u>
Rat	Male	Oral	15.0 ^a
	Female	Oral	7.0 ^a
Rat	Male	Dermal	35.0 ^a
	Female	Dermal	23.0 ^a
Mouse	Male	Oral	8.8 ^b
Rabbit	----	Oral	6.0 ^c
		Dermal	< 94 ^b
Chicken	----	Oral	2.7 ^c

^a as cited in Gaines, T.B. 1969

^b as cited in Berkowitz et al. 1978

^c as cited in Anonymous, 1987.

Toxicity to Wildlife and Domestic Animals

There is little information on the toxicity of isodrin in wild and domestic animals. Endrin, an isomer of isodrin, was consistently the most toxic chemical among 89 chemicals tested in bobwhite, pheasants, mallards, and Japanese quail

(Health et al. 1972). Isodrin would be expected to exhibit somewhat similar toxic properties.

Unlike other cyclodiene insecticides, the photoisomer of isodrin (photoisodrin) which is produced by sunlight and ultraviolet light exposure is less toxic than its parent compound (Georgacakis et al. 1971), indicating that the toxicity of isodrin is not related to its metabolism to more toxic lipophilic ketones. Reported LC_{50} values for freshwater fish were 2.5, 6.0, 6.0 and 1.5 ppb in bass, bluegill, golden shiners and goldfish, respectively (Berkowitz et al. 1978).

Regulations and Standards

None located.

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For isodrin, the D_T value is derived from an acute oral toxicity value (LD_{50}) in female rats. The D_T is computed as the product of the acute value and an application factor of 1×10^{-5} (Layton et al., 1987). The application factor allows the derivation of an interim acceptable long term intake rate (D_T) based on the results of acute tests (LD_{50}) in the absence of more suitable long term studies (i.e., No-Observed-Effect-Level, NOEL, studies). The application factor corresponds to the cumulative percentile on a log-normal distribution of NOEL/ LD_{50} ratios for various chemicals. The percentile was chosen to reduce the probability that the calculated dose rate would be above a toxic level; the 5th cumulative percentile was used by Layton et al. (1987) and was found to be equal to 10^{-3} . The application factor also includes a safety factor of 100 to address interspecies and intraspecies variability; therefore, an

interim estimate of D_T is obtained when the acute value is multiplied by the application factor. Derivation of this D_T value is as follows:

$$\begin{aligned} D_T &= \text{Acute oral LD}_{50} \times \text{Application Factor} \\ &= 7.0 \text{ mg/kg/day} \times 1 \times 10^{-5} \\ &= 0.00007 \text{ mg/kg/day} \end{aligned}$$

There is some uncertainty associated with the derivation of this D_T value for isodrin due to a lack of toxicological data. There are no published studies which carefully examined either the acute or chronic dose-response effects of this pesticide, and no reports of true NOAEL or LOAEL values. Further, there are no reports in the literature which address the question of mutagenicity or carcinogenicity of isodrin.

There are fairly good estimates of health risk for two structurally similar pesticides, aldrin and dieldrin, and the toxicological data available for isodrin indicate that their potency is similar. If D_T values are derived for these two pesticides based simply on their oral reference doses (as reported by USEPA 1988), the results would be as follows:

DIELDRIN

$$D_T = \text{RfD} = \frac{\text{NOAEL}}{\text{uncertainty factor}} = \frac{0.005 \text{ mg/kg/day}}{100} \quad (\text{Walker et al. 1969})$$

$$D_T = 0.00005 \text{ mg/kg/day}$$

ALDRIN

$$D_T = \text{RfD} = \frac{\text{LOAEL}}{\text{uncertainty factor}} = \frac{0.025 \text{ mg/kg/day}}{1000} \quad (\text{Fitzhugh et al.})$$

$$D_T = 0.00003 \text{ mg/kg/day}$$

If these D_T values are compared to the D_T derived for isodrin above (0.00007 mg/kg/day), it seems that the value is similar and may be acceptable. However, use

of the D_T estimate for isodrin should be with the understanding that it was derived from a minimum of data specific for the compound.

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MERCURY (INORGANIC)

Summary

Mercury is an element that occurs naturally in the environment, but is also found in a large number of manufactured products such as electrical equipment and instruments, dental implants, mildewcides and fungicides, paint, and even some pharmaceuticals (ATSDR 1988; Stokinger 1981). Mercury and its derivatives caused a range of toxic effects depending upon its form, duration of exposure and dose. Inorganic mercury is reported to be teratogenic and embryotoxic in studies with experimental animals. Human data indicates that prenatal exposure to mercury vapors in the work place (unspecified concentrations) increased rates of spontaneous abortions, labor complications, and infant mortalities (Mishonova et al. 1980). The major target organs for inorganic mercury compounds at low levels of exposure are the kidney and central nervous system while at high exposure levels respiratory, cardiovascular and gastrointestinal effects are also prominent (ATSDR 1988). Data on the mutagenic effects of mercury in mammalian cell cultures have been inconclusive. The biogeochemical cycle of mercury includes transport in the atmosphere (often long distance), deposition in the soil and surface water, sorption to soil and sediment particulates, and bioaccumulation in both terrestrial and aquatic food chains (ATSDR 1988). Typical U.S. air levels have been reported to average $0.01 \mu\text{g}/\text{m}^3$ to $0.02 \mu\text{g}/\text{m}^3$ (USEPA 1980), with higher levels near industrial sources (up to $15 \mu\text{g}/\text{m}^3$). Typical concentrations of mercury in rainwater are below $0.2 \mu\text{g}/\text{L}$ (USEPA 1984a), in marine waters $0.005 \mu\text{g}/\text{L}$ (Matsunaga et al. 1979), and in drinking water less than $0.025 \mu\text{g}/\text{L}$ (USEPA 1984a). Soil concentrations, averaged from a number of countries, range from 20-625 ng/g and varies with depth (ATSDR 1988).

CAS Number: 7439-97-6

Chemical Formula: Hg

IUPAC Name: Mercury

Chemical and Physical Properties

Atomic Weight:	200.59 (Merck 1983)
Boiling Point:	356.72°C (Merck 1983)
Melting Point:	-38.87°C (Merck 1983)
Specific Gravity:	13.534 (Merck 1983)
Solubility in Water:	56.2 µg/liter at 25°C (Merck 1983)
Solubility in Organics:	Depends on chemical species
Vapor Pressure:	0.0012 mm Hg at 20°C (USEPA 1984a) 0.002 mm/Hg at 25°C (Merck 1983)

Transport and Fate

Inorganic mercury can exist in three oxidative states in the environment, including metallic (Hg^0), mercurous (Hg_2^{++}), and mercuric (Hg^{++}). In general, the mercurous salts are much less soluble than the more commonly found mercuric salts. The nature and solubility of the chemical species that occur in an environmental system will depend on the redox potential and the Ph of the environment. Metallic mercury is a liquid at ambient temperature, readily vaporizes, and is the principal form in the atmosphere (WHO, 1976). Mercuric mercury is the predominant form in surface waters.

Mercury can volatilize to the atmosphere from both aquatic and terrestrial sources and this degassing of the lithosphere and hydrosphere can occur at a rate of 25,000 - 150,000 m tons/year (WHO, 1976). Other sources of atmospheric mercury which include industrial processes, mining and smelting of mercury ones, and combustion of fossil fuels can contribute up to 3000 m tons/year (Lindberg, 1984). Estimates on residence time of mercury in atmosphere range from 6-90 days to 0.3 to 2.0 years (ATSDR 1988). Volatilization of mercury is reduced by conversion of

metallic mercury to complexed species and by deposition of HgS in reducing sediments. Precipitation (wet/dry) is an important mechanism for removal of mercury from the atmosphere (USEPA 1984a). Photolysis is the main transformation process in the atmosphere and may also be important in some aquatic systems. However, even with these varied systems for removal and breakdown of airborne mercurials, atmospheric transport is a major environmental distribution pathway for mercury (USEPA 1984a).

The transport and fate of mercury in surface waters and soil is influenced by the form the element takes. Adsorption onto suspended and bed sediment is probably the most important process determining the fate of mercury in the aquatic environment. Sorption is strongest onto organic material for the Hg_2^{++} species. Mercury in soils is generally complexed to organic compounds. Mercury is not readily leached from either organic rich or mineral rich soils (Rosenblatt et al. 1975). Therefore, freshwater and marine sediments are important repositories for inorganic mercury. Uptake of mercury in plants can also occur with the highest concentrations found in bulb or root crops (Rosenblatt et al. 1975). Turf grass exposed to a mixture of mercurous and mercuric chloride added to the root zone did not accumulate mercury (USEPA 1984a), while uptake of mercury vapor by wheat leaves has been reported (USEPA 1984a).

Virtually any inorganic mercury compound can be remobilized via methylation by a variety of microorganisms found in soil and water, under both aerobic and anaerobic conditions. Conditions reported to enhance biomethylation include large amounts of available mercury, large numbers of bacteria, the absence of strong complexing agents, near neutral Ph, high temperatures, and moderately aerobic environments. The resulting products, methyl and dimethyl mercury, are then rapidly accumulated by aquatic food chains. Thus, the concentrations of mercury can be magnified by an order of 10^3 to 10^5 over the concentrations normally found in surface waters (ATSDR 1988). For example, bioconcentration factors (in freshwater) for mercury in mercuric chloride range from 1,800 in rainbow trout (*Salmo gairdneri*) to 4,994 in the fathead minnow (*Pimephales promelas*) (USEPA 1984b). ASTM (1985)

indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the reported concentration factors suggests that appreciable bioconcentration or biomagnification of mercury can occur, and indeed is of interest as the most important source of nonoccupational mercury exposure in humans (ATSDR 1988).

With the prevalence of mercury compounds in soil, water, air and foodstuffs there have been many reports of quantitative determinations of mercury concentrations in the environment. Following is a list of the ranges of mercury concentrations that have been reported.

<u>Medium</u>	<u>Range of Hg Concentrations</u>	<u>Citation</u>
Air		
ambient	.01 - .02 $\mu\text{g}/\text{m}^3$	USEPA 1980
emission sources	.01 - .015 mg/m^3	USEPA 1984a
Water		
rainwater	< .2 $\mu\text{g}/\text{L}$	USEPA 1984a
unpolluted marine waters	.005 - .006 $\mu\text{g}/\text{L}$	Matsunaga et al.
1979		
estuarine waters	.002 - .45 $\mu\text{g}/\text{L}$	Fitzgerald 1979
well water	~ .5 $\mu\text{g}/\text{L}$	USEPA 1985
drinking water	< .025 $\mu\text{g}/\text{L}$	USEPA 1984a
Soil	20-625 ng/g	Andersson 1979
Non-fish foodstuffs	< .02 $\mu\text{g}/\text{g}$	ATSDR 1988
Fish	< .2 $\mu\text{g}/\text{g}$	ATSDR 1988

Health Effects

Exposure to inorganic mercury and mercury containing products can occur by inhalation, ingestion, or skin contact due to the prevalence of the element in air,

water, and soil. There is information available on acute and chronic mercury exposure in both humans and animals.

Human Data

The acute toxicity of mercury depends on the form of the absorbed compound and its dose. Insoluble inorganic monovalent mercury salts are relatively nontoxic due to poor absorption by the gastrointestinal system. In general, divalent salts are more toxic than monovalent salts, and ionizable salts are more toxic than salts that do not ionize. Symptoms associated with ingestion of ionizable salts of mercury include pharyngitis and difficulty swallowing, abdominal pain, nausea, vomiting, bloody diarrhea, and shock, followed by swelling of the salivary gland, loosening of teeth, nephritis, anuria, and hepatitis (Stokinger 1981). Acute effects from inhalation of mercury vapors include acute pneumonitis and lung tissue damage (high doses, $> 1 \text{ mg/m}^3$; USEPA 1984a), metallic taste in mouth, abdominal pain and diarrhea, headache, albuminuria, gingivitis, lip and cheek ulceration, and a line of HgS on the gums (Stokinger, 1981). Contact dermatitis may result from exposure to liquid metallic mercury (USEPA 1984a). Absorption of organic mercury compounds (i.e. methylmercury) via the gastrointestinal tract is almost 100%, thus many deaths and poisonings have occurred from its ingestion.

Occupational studies indicate that the chronic exposure to mercury vapor affects primarily the central nervous system and the kidneys (increased urinary excretion of high molecular weight proteins or proteinuria, USEPA 1984a). At high exposure levels, extreme irritability, excitability, delirium with hallucinations, melancholia, anxiety, and manic depressive psychosis have been reported (NIOSH, 1977). Workers exposed to average air concentrations of 0.1 to 0.2 mg/m^3 experienced both mental disturbances and objective tremors (NIOSH 1977). The kidney is the primary target for divalent inorganic salts, regardless of the route of exposure. Chronic inhalation of $0.2 - 0.3 \text{ mg/m}^3$ of mercuric chloride is associated with proteinuria (NRC, 1977). Kidney autoimmune responses and the related

development of nephrosis have also been observed in humans in response to skin application of 1% to 10% ammoniated mercury ointments, exposure to paint additives, and oral treatment with mercurials (Becker et al. 1962; Mandema et al. 1963; Adner and Jans 1978; Kazantzis 1978; Bigazzi, 1985).

Little is known about the reproductive and developmental effects of inorganic mercury in humans, although there have been case reports of spontaneous abortions and infant mortality among women exposed to mercury vapor during pregnancy (USEPA 1984a). Prenatal exposure to methyl mercury has been linked to fetal fatalities and severe neurological problems among survivors, with some evidence that the fetus is more sensitive to methyl mercury than adults (WHO, 1976; Inskip and Piotrowski 1985). Infants 4 to 30 months seem to be more susceptible than adults and older children to the effects of mercury vapors (USEPA 1984a).

Mutagenic responses of nonmammalian cell cultures to mercuric salts in vitro have been varied and inconclusive (USEPA 1984a). Chromosomal aberrations have been observed in lymphocytes of persons occupationally exposed to mercury vapors (average levels in air year before study were 0.15 to 0.44 mg/m³; USEPA 1984a), but people exposed to mercury vapors over several months in Iraq did not show similar changes (Kazantzis, 1981). While some mercury compounds produce somatic cell genetic changes, there is no evidence of inheritable genetic damage to germ cells in humans. Carcinogenesis in humans has not been associated with occupational exposure to mercury vapors (USEPA 1984a). Mercury has been classified according to EPA's Guidelines for Carcinogenic Risk Assessment in EPA's Group D (not classified) based upon inadequate data in humans and animals (50 Federal Register 46972, Wed. Nov. 13, 1985).

Animal Data

There have been numerous studies on all aspects of mercury exposure and its health effects in animals, with central nervous system and kidney effects being the principal results of exposure. Inorganic mercury salts have been shown to be diuretic

in dogs (USEPA 1980). Monovalent salts are less toxic than divalent salts and the oral route is less toxic than intramuscular injection. The lowest acute effect level for elemental mercury is 1 $\mu\text{g/g}$ brain tissue in rabbit and 1.9 $\mu\text{g/g}$ brain tissue in the rat (USEPA 1980). Rats exposed to mercury acetate in their diet for 2 years showed morphological changes in their kidney (dietary levels of 2 mg/kg/day and above; Fitzhugh et al. 1950). In dogs, no kidney effects were observed after 83 weeks of inhalation of 0.1 mg/m³ mercury vapor; however, 0.86 mg/m³ resulted in both brain and kidney injury which disappeared when exposure ended (Stokinger, 1981).

There are also a number of studies in animals exploring the reproductive and developmental effects of mercury. Rats exposed to mercury vapors (2.5 mg/m³, 6 hr/day, 5 day/week) exhibited longer estrus cycles (USEPA 1984a). In a study involving an aborted monkey fetus, mercury had crossed the placenta and was present in all examined tissues except amniotic fluid, indicating no mercury elimination by the fetus (Stokinger 1981). In rats exposed prenatally to mercury vapor, death occurred within 6 days of birth (USEPA 1980). However, no conclusive results concerning the teratogenic effects of mercury vapor are available (ATSDR 1988), although parenteral administration of inorganic mercury salts has produced abnormalities in experimental animals. For example, Gale (1981) reported a number of abnormalities in hamster fetuses given a subcutaneous dose of mercury acetate on day eight of gestation, including pericardial cavity distension, cleft palate, hydrocephalus and heart defects. A further study by the same group showed that zinc sulfate administered simultaneously with mercuric acetate partially or markedly reduced the embryotoxic effects of mercury (Gale 1984).

There is one report of carcinogenic actions of mercury in animals. Rats given metallic mercury by intraperitoneal injection developed malignant sarcomas in those tissues in direct contact with the metal (Druckrey et al. 1957).

Pharmacokinetics and Metabolism

Inorganic salts of mercury vary in degree of absorption. Less than 15% of an administered dose is absorbed via the gastrointestinal tract in mice and about 7% absorption occurred in a study of human volunteers (Goyer 1986). Rats can absorb 10-30% of water-soluble inorganic mercurials via the gastrointestinal tract. Only about 5% of mercuric chloride solutions applied to the skin of guinea pigs is absorbed (Friberg and Nordberg 1971). Elemental mercury vapor is rapidly absorbed from the lungs, with 74% of an inhaled dose retained in man in a study of 5 volunteers exposed for 14-24 minutes at levels of 62-100 $\mu\text{g}/\text{m}^3$ (Stokinger 1981). Liquid metallic mercury is poorly absorbed (less than 0.01%) from the gastrointestinal tract (Stokinger 1981).

Inorganic salts and mercury vapor are most highly concentrated in the kidneys following exposure, but organic mercury appears to concentrate most heavily in the brain. Mercury vapor has a greater affinity for the central nervous system than inorganic mercury salts, but less than organic forms of mercury (Goyer 1986). In animals, 90% of an absorbed dose accumulates in the kidney where it induces metallothionein production. The production of metallothionein, which is toxicologically inactive, may be responsible for the tolerance to mercury sometimes observed among workers and repeatedly exposed rats (Stokinger 1981). Exposure to mercury vapor leads to distribution of mercury throughout the body in a variety of chemical and physical states. Elemental mercury dissolves in the blood upon inhalation and is then oxidized to its divalent cation. The distribution then parallels the distribution of mercury salts, with the exception of the brain, which can accumulate up to 10 times more mercury after vapor exposure than upon ingestion of a mercury salt (Berlin and Johansson 1964). Mercury can also penetrate the placenta and be passed to the fetus.

The urine and feces are the main pathways for excretion of mercury in humans. Some elemental mercury is also excreted in exhaled air and in perspiration. Excretion of mercury shortly after exposure is mainly in the feces, but as more is

deposited in the kidney, urinary excretion predominates. Human data suggest that urinary mercury does not derive from filtration of plasma mercury, but rather from the release of mercury stored in the kidney. At levels of exposure of 0.1 mg/m^3 , urinary mercury levels serve as good indicators of vapor exposure in rabbits and dogs. Prolonged exposures, however, may actually decrease urinary mercury excretion due to kidney injury (Stokinger 1981). In humans, a 2.9 mg/liter increment in urinary mercury excretion has been predicted for each 1 mg/m^3 increment in the time-weighted air concentration; this prediction was estimated from the 0.06 mg/liter increase in the urinary excretion rate for each $1 \text{ } \mu\text{g}/100 \text{ ml}$ change in the blood mercury level that has been reported to occur (USEPA 1980). However, there is great interindividual variation in urinary excretion of mercury, as well as problems with urine analysis for mercury. Thus, the usefulness of urinary levels as an indicator of dose in humans is uncertain (Stokinger 1981; USEPA 1980).

Toxicity to Wildlife and Domestic Animals

Mercury has been identified as a serious pollutant in aquatic environments. Elemental mercury was previously considered to be relatively inert, and it was believed that it would quickly settle to the bottom of a body of water and not pose a hazard to aquatic life. However, as discussed previously, both elemental and inorganic salts can be methylated by sediment microorganisms (USEPA 1985). Therefore, mercury can adversely affect aquatic life through direct toxicity and through bioaccumulation.

The aquatic toxicity of inorganic mercury compounds has been investigated. Among freshwater species, the 96-hour LC_{50} values for inorganic salts range from $0.02 \text{ } \mu\text{g/liter}$ for crayfish to $2,000 \text{ } \mu\text{g/liter}$ for caddishfly larvae (USEPA 1980). Mercuric chloride is acutely toxic to rainbow trout at about $300 \text{ } \mu\text{g/liter}$ at 10°C (USEPA 1984a).

The acute oral lethal dose (low) in rabbits is 40 mg/kg (NIOSH 1982). Chronic dietary exposure of chickens to mercuric chloride at growth inhibitory levels causes immune suppression with a differential reduction effect on specific immunoglobulins (Bridger and Thaxton 1983). The lethal concentration (LC₅₀) values for mercuric chloride administered in the diets of Japanese quail (*Coturnix japonica*), ringed-neck pheasants (*Phasianus colchicum*) and mallard ducks (*Anas platyrhynchos*) were 5,926, 3,790, and >5,000 ppm, respectively (Hill et al., 1975).

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For inorganic mercury the D_T value for oral exposure is based on the Reference Dose (RfD) reported in the Health Effects Assessment Summary Table (3 x 10⁻⁴ mg/kg/day) (USEPA 1989). Though details on the underlying study were not available, the effect of concern was central nervous system effects associated with a blood mercury level of 200 mg/ml (USEPA 1989). An uncertainty factor of 10 was included in the derivation of the RfD, presumably to protect sensitive human subgroups.

$$D_T = RfD$$

$$D_T = 3 \times 10^{-4} \text{ mg/kg/day}$$

Regulations and Standards

WHO	Guidelines for drinking water	0.001 mg/L	ATSDR, 1988
	Provisional tolerable weekly intake	0.3 mg total Hg	ATSDR, 1988
OSHA	Ceiling	0.1 mg/m ³	ATSDR, 1988
FDA	Permissible level in bottled water	0.002 mg/L	ATSDR, 1988
NIOSH	Recommended exposure limit for occupational exposure Immediately dangerous to health level	0.05 mg/m ³ 28 mg/m ³	ATSDR, 1988 ATSDR, 1988
OSHA	Ceiling Standard for skin contact	0.1 mg/m ³	ATSDR, 1988
ACGIH	Threshold limit values for vapor TWA	0.05 mg/m ³	ATSDR, 1988
	TWA (aryl and inorganic compounds)	0.1 mg/m ³	ATSDR, 1988
National Primary Drinking Water Standard (USEPA)		0.003 mg/L	
Ambient Water Quality Criteria			USEPA 1986
	Aquatic Life (Freshwater)		
	acute toxicity	2.4 µg/L	
	chronic toxicity	0.012 µg/L	
	Aquatic Life (Saltwater)		
	acute toxicity	2.1 µg/L	
	chronic toxicity	0.025 µg/L	
	Human Health criterion	144 ng/L	

An inhalation D_T has also been developed for inorganic mercury because of its potential for volatilization. The inhalation D_T is based on the data used by EPA to compute the Acceptable Intake Chronic for inhalation exposure (USEPA 1984c; 1986b). The intake value is derived from a Threshold Limit Value (TLV) for mercury vapor of 0.05 mg/m^3 (ACGIH 1983). In using this value as a basis for an acceptable intake, EPA has first added an extra margin of safety to the TLV by incorporating an UF of 10. The TLV is thus reduced to 0.005 mg/m^3 . The acceptable intake chronic is then computed by using an estimated breathing rate (BR-- $10 \text{ m}^3/\text{day}$) and multiplying by $5/7$ days to correct for continuous exposure. An additional UF of 10 is included by EPA to protect sensitive subgroups and a 70 kg reference weight is included for adult humans. Derivation of the D_T for inhalation exposure to inorganic mercury vapor is as follows:

$$\begin{aligned}
 D_T &= \frac{\text{TLV/UF} \times \text{BR} \times 5/7 \text{ days}}{70 \text{ kg} \times \text{UF}} \\
 &= \frac{0.005 \text{ mg/m}^3 \times 10 \text{ m}^3/\text{day} \times 5/7 \text{ days}}{70 \text{ kg} \times 10} \\
 &= 0.000051 \text{ mg/kg/day}
 \end{aligned}$$

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METHYLENE CHLORIDE

Summary

Methylene chloride (dichloromethane) is a widely used chlorinated hydrocarbon solvent. It is used commercially as a blowing agent for polyurethane, as a propellant in aerosols such as insecticides, hair sprays, and paints, as a solvent in the manufacture of photographic and synthetic fibers, as a major component in paint stripping formulations, as an insecticidal fumigant for grains, as an extraction solvent for naturally occurring substances in food processing, and as a coolant and refrigerant. Methylene chloride is volatile; therefore, inhalation is the main route of human exposure. In humans, methylene chloride irritates the eyes, mucous membranes, and skin. Higher doses cause central nervous system depression as evidenced by reports of sluggishness, irritability, lightheadedness, nausea, and fatigue (USEPA 1985). In experimental animals, methylene chloride is reported to cause kidney and liver damage, convulsions and paresis (incomplete paralysis). Methylene chloride is also a mutagen and a carcinogen in animals.

CAS Number: 75-09-2

Chemical Formula: CH_2Cl_2

IUPAC Name: Dichloromethane

Important Synonyms and Trade Names: Methylene dichloride, methane dichloride, DCM, methylene bichloride

Chemical and Physical Properties

Molecular Weight: 84.93

Boiling Point: -40°C (USEPA 1979)

Melting Point: -95.1°C

Specific Gravity: 1.3266 at 20°C

Solubility in Water: 13,200-20,000 mg/liter at 25°C (USEPA 1979)

19,000 mg/liter (Valvani et al. 1980)

Solubility in Organics: miscible with alcohol and ether

Log Octanol/Water Partition Coefficient: 1.25 (USEPA 1979)

1.30 (USEPA 1986)

Soil/Water Partition Coefficient (K_{ow}):

27.5 Sabljic (1984) (experimental)

114; 121 Lyman et al. (1982) eqn 4-8 ($\log K_{ow} = 1.25$; 1.3)

27; 30 Lyman and Loreti (1987) ($\log K_{ow} = 1.25$; 1.3)

8.8 USEPA (1986)

Bioconcentration Factor:

2.9 - 2.3 Davies and Dobbs (1984) Eqn A ($S = 13,200 - 20,000$)

5.25 Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 1.25$)

8.6 Davies and Dobbs (1984) Eqn C ($\log K_{ow} = 1.25$)

5.81 Davies and Dobbs (1984) Eqn B ($\log K_{ow} = 1.25$)

16.4 Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 1.9$)

21 Davies and Dobbs (1984) Eqn B ($\log K_{ow} = 1.9$)

14.2 Davies and Dobbs (1984) Eqn C ($\log K_{ow} = 1.9$)

Vapor Pressure: 362 mm Hg at 20°C (USEPA 1986)

436 mm Hg at 25°C (Berkowitz et al. 1978)

Vapor Density: 2.93

Henry's Law Constant: 2.6×10^{-3} atm-m³/mole (calculated)

2.03×10^{-3} atm-m³/mole (USEPA 1986)

8.53×10^{-2} dimensionless

Methylene chloride is a colorless liquid that looks like water, has a mild, sweet odor and rapidly volatilizes into the atmosphere. It is slightly soluble in water, but completely miscible with most common organic solvents. This compound is

commercially produced by chlorination of methane or methyl chloride.

Approximately 2.65×10^4 kilograms of methylene chloride were produced in the U.S. in 1983, with its use in aerosol products and as a paint remover accounting for more than 50% of its use.

Transport and Fate

Volatilization to the atmosphere appears to be the major mechanism for removal of methylene chloride from surface waters and is its primary environmental transport process (USEPA 1979). This compound is not expected to accumulate in the atmosphere, however, because of reaction with hydroxyl radicals, the primary tropospheric chemical degradation process for methylene chloride (USEPA 1985). Estimates of the atmospheric half-life for methylene chloride range from a few months to 1.4 years (ATSDR 1988). Attack by hydroxyl radicals in the troposphere results in the formation of carbon dioxide, and to a lesser extent, carbon monoxide and phosgene. Phosgene is readily hydrolyzed to hydrochloric acid and carbon dioxide. About one percent of tropospheric methylene chloride would be expected to reach the stratosphere where it would probably undergo photodissociation resulting from interaction with high energy ultraviolet radiation. Methylene chloride would also be expected to be transported unchanged for some distance from its source, which is partly responsible for its relatively wide environmental distribution. Atmospheric methylene chloride may also be returned to the earth in precipitation.

In contrast to surface waters where volatilization is important, transport is likely to be an important fate process in groundwater due to the moderate solubility of methylene chloride. Hydrolysis does not appear to be significant in groundwater, but biodegradation may occur under both aerobic and anaerobic conditions (USEPA 1985). For example, methylene chloride was shown to support growth of sewage microorganisms in culture when the medium was supplemented with sodium bicarbonate (Rittman and McCarty 1980). Klecka (1982) demonstrated the aerobic degradation of methylene chloride in a system simulating a waste treatment plant.

Anaerobic degradation was also shown in a study using sediment-water samples spiked with methylene chloride (Wood et al. 1981). A range of soil-water partition coefficients (Koc) is reported above and indicates that some sorption of methylene chloride to soils/sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of volatile organic compounds will range from low to moderate.

A range of bioconcentration factors for methylene chloride is also reported above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the concentration factors suggest that appreciable bioconcentration or biomagnification of methylene chloride residues is not likely to occur.

Background Exposure

Methylene chloride occurs in ambient air throughout the U.S. at levels of approximately 30 to 50 ppt (USEPA 1985). The predicted maximum annual average to which people may be exposed has been reported to be 14.3 ppb (0.50 mg/m³) for people living near source facilities (USEPA 1985). Urban levels of methylene chloride exposure may be in the range of 500 ppb (Brodzinsky and Singh 1983). A background mixing ratio of approximately 38 ppt is reported as the average for the northern hemisphere, with a global average of 29 ppt (Singh et al. 1983).

Methylene chloride is also prevalent in drinking water, surface water and groundwater throughout the U.S. Average concentrations in drinking water have been reported to be less than 1 µg/liter, with maximum concentrations less than 3 µg/liter (USEPA 1975a, 1975b). In heavily industrialized river basins, methylene chloride concentrations greater than 1 ppb have been reported in surface water (Ewing et al. 1977). The EPA database system STORET reported levels for the period 1978 to 1981 to range from 0 to 120 µg/liter in ambient waters (USEPA 1981). At 36 Superfund hazardous waste sites, methylene chloride was detected in groundwater at

levels up to 8.4 mg/liter, and is ranked 16th out of 25 substances that were most frequently detected (ATSDR 1988).

There is no information available on the levels of methylene chloride present in soil outside of hazardous waste sites. There is also little information on the levels of this compound in food, although the FDA has placed a limit of 10 ppm of methylene chloride in decaffeinated coffee (50 FR 51551, December 18, 1985).

Pharmacokinetics and Metabolism

Methylene chloride is readily absorbed after either inhalation or oral exposure, but more slowly following dermal exposure. Following an 8 hour inhalation exposure to concentrations of methylene chloride ranging from 50-200 ppm, humans have been found to absorb between 55 and 75% of the total dose (USEPA 1985). This agent is distributed to all tissues. In a radioactive tracer study, highest concentrations were found in liver, kidney, lung, and brain (McKenna and Zempel 1981). Methylene chloride has also been demonstrated to cross the placenta and the blood-brain barrier (IPCS 1984).

Following either inhalation or ingestion, a large proportion of an absorbed dose is rapidly excreted unchanged via the lungs (IPCS 1984; USEPA 1985). Very little absorbed methylene chloride is deposited in adipose tissue (NRC 1980). Instead, the methylene chloride that is not excreted unchanged in expired air is rapidly metabolized in the liver to carbon monoxide and carbon dioxide. These two products are then excreted in expired air (NRC 1980). This process leads to the accumulation of carboxyhemoglobin in blood, the level of which parallels the level and duration of exposure to methylene chloride. For example, 8 hours exposure to either 100 ppm, 150 ppm or 200 ppm methylene chloride results in carboxyhemoglobin levels of 3.2%, 5.4% and 6.8% respectively (Divencenzo and Kaplan 1981), where normal levels range from 1-3%.

Health Effects

Acute Exposures

In humans, inhalation of high concentrations of methylene chloride (approximately 20,000 ppm) leads to central nervous system depression, narcosis and even death (IPCS 1984). Exposure to lower concentrations (around 500 ppm) leads to deficits in central nervous system function as evidenced by lethargy, short periods of sleep, reduced performance in eye-hand coordination tasks, and deficits in sensory detection thresholds. Exposure to concentrations greater than 868 ppm results in lightheadedness and difficulty with speech articulation (USEPA 1985). The use of paint removers has been associated with signs of central nervous system depression, narcosis, irritation of the eyes and respiratory tract, and lung edema. Corresponding increases in carboxyhemoglobin levels, indicative of methylene chloride metabolism, were also reported (IPCS 1984). Methylene chloride also has acute toxic effects on the heart as was shown in a report where exposure to this agent in a poorly ventilated room was associated with the occurrence of myocardial infarction (IPCS 1984). These effects, however, can be attributed to a byproduct of methylene chloride metabolism, carbon monoxide and the increased levels of carboxyhemoglobin in blood, and not a direct action of parent compound on cardiac tissue. The main concern upon exposure to methylene chloride would be those individuals with underlying heart disease, a population most likely affected by any compromise of cardiac function often associated with increases in blood carbon monoxide levels.

In laboratory animals, methylene chloride has a general depressive effect on behavior at exposures of about 500 ppm. The same central nervous system effects have been seen at oral doses as low as 0.001 ml/kg in the rat (Kimura et al. 1971). Slight narcosis occurs at exposures between 4,000 and 6,000 ppm in cats, with deep narcosis evident at 10,000 ppm (Lehman and Flury 1943 cited in ACGIH 1980). Oral LD₅₀ values for mice and rats are 1,987 mg/kg and 2,388-4,368 mg/kg respectively (Aviado et al. 1977; Ugazio et al. 1973; Kimura et al. 1971). The liver and kidney are target organs for nonlethal exposures to methylene chloride and there are numerous reports which describe the effects of this agent on hepatic and renal

function. Exposure of guinea pigs to 5,000-15,000 ppm of methylene chloride resulted in increased vacuolization and lipid droplets, and some centrilobular fatty degeneration of the liver (Morris et al. 1979 cited in IPCS 1984). Exposure of mice to 4,893 ppm for 24 hours resulted in increased liver weights and caused histopathological changes (Weinstein et al. 1972). Indications of renal damage, including proteinuria, were seen following intraperitoneal injection of mice with 1,995 mg/kg methylene chloride (Plaa and Larson 1965) and renal proximal tubular swelling in rats was reported following i.p. injection with 1,300 mg/kg (Kluwe et al. 1982).

Chronic Exposure

There is little available information on the effects of chronic exposure to methylene chloride in humans. Occupational exposures were reported to cause toxic encephalosis (Weiss 1967) and bilateral temporal lobe degeneration (Barrowcliff and Knell 1979). In both cases, however, methylene chloride was not the only chemical present in the work place.

Chronic exposure to methylene chloride in animals has little effect on the central nervous system at doses below 1000 ppm (USEPA 1985). Mice exposed to 5,000 ppm methylene chloride continuously for 7 days responded first with excitement and increased activity, followed by decreased activity and hunched posture, and by the 4th day showed adaptation to the agent by displaying normal behavior (Weinstein et al. 1972). Exposures of mice to 1,000 ppm continuously for 14 weeks was the only report which showed decreased activity levels following methylene chloride administration (Thomas et al. 1972).

In contrast to the effects of methylene chloride on the central nervous system, there are reports of significant effects by this agent on liver and kidney tissue. Inhalation exposure to methylene chloride levels as low as 100 ppm for 100 days resulted in slight cytoplasmic vacuolization in the liver with positive fat stains and tubular degeneration in the kidney of rats and mice (Haun et al. 1972). Similar

changes were seen in the livers of dogs and guinea pigs exposed to 10,000 ppm methylene chloride for 4 hours/day, 5 days/week for 8 weeks (Heppel et al. 1944). In a 2 year study by Dow Chemical Co. (Burek et al. 1980), rats and hamsters were exposed to 500, 1500 or 3500 ppm of methylene chloride for 6 hrs/day, 5 days/week. On necropsy, exposure at all levels in both rats and hamsters resulted in increased hepatic vacuolization and increased multinucleated hepatocytes.

Reproductive and Teratogenic Effects

There is no available information on the reproductive or teratogenic effects of methylene chloride in humans. In animals, exposure to methylene chloride has no adverse effects on reproductive parameters after either inhalation or oral administration (ATSDR 1988). Exposure of rats and mice to 1250 ppm methylene chloride for 7 hrs/day during days 6-15 of gestation resulted in an increased incidence of extra sternebrae among the pups (Schwetz et al. 1975). In another study, exposure of pregnant rats to 4,500 ppm methylene chloride 6 hrs/day, 7 days/week, throughout pregnancy, resulted in decreased body weights among the fetuses, a common sign of developmental toxicity (Hardin and Manson 1980).

Mutagenicity

Methylene chloride is considered to be a mutagen based upon studies in bacteria and in mammalian cells. It has been shown to increase the numbers of revertants of *S. typhimurium* TA98, TA100 and TA1535 from 3 to 7 fold (Nestmann et al. 1981). Metabolic activation by either induced rat liver S9 fraction, cytosol fraction, or microsomal fraction increases the mutagenicity. A dose-related increase in the frequency of mitotic gene conversions, recombinations and mutations occurs in cultures of *S. cerevisiae* exposed to methylene chloride in the absence of a metabolic activation system (Callen et al. 1980), and increases in chromosomal aberrations occur in cultured mammalian cells exposed to methylene chloride (Thilagen and

Kumaroo 1983). Additionally, exposure to methylene chloride has been shown to increase the incidence of sex-linked recessive lethal mutations in *Drosophila* (Gocke et al. 1981). This agent does not increase DNA synthesis in cultures of human fibroblasts or hamster cells, and no increase in cytogenic alterations of bone marrow are seen in rats exposed to 500, 1,500 or 3,500 ppm methylene chloride for a lifetime (Jongen et al. 1981; Burek et al. 1984).

Carcinogenicity

Based upon results in animal studies, methylene chloride has been classified in USEPA Group B2, a probable human carcinogen. A dose-related increase in the incidence of salivary gland region sarcomas was observed in male rats following 2 years of exposure to 1,500 ppm or 3,500 ppm methylene chloride for 6 hrs/day, 5 days/week (Burek et al. 1980). Male mice receiving about 235 mg/kg/day methylene chloride in drinking water for 24 months had a slight increase in the incidence of hepatocellular carcinomas and/or adenomas (National Coffee Association 1983, reported in Serota et al. 1984). In the same study, female rats showed a dose-related increase in the incidence of hepatocellular carcinomas and neoplastic nodules at doses of methylene chloride up to 250 mg/kg/day. In a National Toxicology Program sponsored study, rats and mice were exposed to methylene chloride at concentrations of 0-4000 ppm 6 hrs/day, 5 days/week for 2 years (NTP 1986). The incidence of mammary adenomas and fibroadenomas was significantly increased in male and female F344 rats in a dose-dependent manner, while mononuclear cell leukemias were only evident in female rats. In mice, the incidence of hepatocellular carcinomas and adenomas was significantly increased in both males and females at the highest dose, 4000 ppm methylene chloride.

There is no epidemiological evidence linking methylene chloride exposure to cancer in humans. Two cohort studies examined the mortality of workers occupationally exposed to methylene chloride, but neither study reported a significant increase in cancer-related deaths among the workers (Friedlander et al. 1978; Hearne

et al. 1987). It should be noted, however, that these results are not adequate evidence for ruling out any cancer risk associated with methylene chloride exposure.

Toxicity to Wildlife and Domestic Animals

The only available information on the toxicity of methylene chloride to wildlife and domestic animals was obtained in laboratory studies and may not be representative of environmental situations. Acute values for the freshwater species cladoceran (*Daphnia magna*), the fathead minnow (*Pimephales promelas*), and the bluegill (*Lepomis macrochirus*) were 224,000, 193,000 and 224,000 $\mu\text{g/liter}$ respectively under static conditions (USEPA 1980; Alexander et al. 1978). Acute values for the saltwater mysid shrimp and sheepshead minnow (*Cyprinodon variegatus*) were 256,000 and 331,000 $\mu\text{g/liter}$, respectively (USEPA 1980). No data concerning chronic toxicity are available. The 96-hour EC_{50} values for freshwater and saltwater algae were greater than the highest test concentration, 662,000 $\mu\text{g/liter}$ (USEPA 1980).

Regulations and Standards

The USEPA (1989) report an oral Reference Dose (RfD) for noncarcinogenic effects of methylene chloride as well as a carcinogenic assessment and drinking water health advisories. The RfD was derived based on a chronic drinking water study in rats and the appearance of histological changes in the liver. A NOAEL of 5.85 and 6.47 mg/kg/day methylene chloride for males and females respectively was reported, with a LOAEL of 52.58 and 58.32 mg/kg/day. From these values a RfD was estimated to be 6×10^{-2} mg/kg/day ($\text{UF} = 100$). The uncertainty factor (UF) of 100 was applied to account for intra- and interspecies variability in the toxicity of this agent.

Methylene chloride is classified as B2 based on sufficient chronic carcinogenicity data in rats and mice, as discussed previously, and the supporting

mutagenicity data. From these results, risk estimates were derived for both oral and inhalation exposures. An oral slope factor of 7.5×10^{-3} mg/kg/day and an oral unit cancer risk of 2.1×10^{-7} μ g/liter of drinking water have been estimated using a linearized multistage extrapolation procedure. Drinking water levels at specified risk levels were identified to be 500 μ g/liter (1 in 10,000), 50 μ g/liter (1 in 100,000), and 5 μ g/liter (1 in 1,000,000). From the same oral exposure data, inhalation risk estimates were also calculated. The inhalation slope factor is reported to be 1.4×10^{-2} mg/kg/day and the unit cancer risk is reported to be 4.1×10^{-6} / μ g/ m^3 . Air concentrations at specific risk levels are 20 μ g/ m^3 (1 in 10,000), 2 μ g/ m^3 (1 in 100,000), and 0.2 μ g/ m^3 (1 in 1,000,000)(USEPA 1989). The inhalation risk was calculated assuming 20 m^3 /day of air intake and almost total absorption of the methylene chloride vapor. As of December 1987, a revision of the cancer risk assessment is pending final approval. This revision contains a new inhalation potency based on the incorporation of information on pharmacokinetics and metabolism (USEPA 1989).

There are a number of regulations and guidelines for methylene chloride which are listed in Table 1.

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For carcinogens such as methylene chloride, the D_T value is based on the USEPA Cancer Assessment Group's cancer potency slopes. The cancer potency slopes have been estimated for oral exposure and for inhalation exposure for methylene chloride. The slopes are intended to be a plausible upper bound of the potency of a carcinogen in inducing cancer at low doses. Calculation of a D_T using a cancer potency slope requires selection of an acceptable cancer risk level. A range of risk levels from 10^{-4} to 10^{-6} will be considered for all carcinogens; therefore, a range

of D_T values is presented. Derivation of the D_T values for methylene chloride is as follows:

$$D_T = \frac{\text{Risk Level}}{\text{Potency Slope (mg/kg/day)}^{-1}}$$

$$= \frac{1 \times 10^{-4}}{1.4 \times 10^{-2} \text{ (mg/kg/day)}^{-1} \text{ [inhalation slope factor (USEPA 1989)]}}$$

$$= 7.1 \times 10^{-3} \text{ mg/kg/day}$$

$$D_T = \frac{1 \times 10^{-4}}{7.5 \times 10^{-3} \text{ (mg/kg/day)}^{-1} \text{ [oral slope factor (USEPA 1989)]}}$$

$$= 1.3 \times 10^{-2} \text{ mg/kg/day}$$

The range of D_T values for methylene chloride is presented below.

<u>Risk Level</u>	<u>Inhalation D_T</u>	<u>Oral D_T</u>
	<u>(mg/kg/day)</u>	<u>(mg/kg/day)</u>
10^{-4}	7.1×10^{-3}	1.3×10^{-2}
10^{-5}	7.1×10^{-4}	1.3×10^{-3}
10^{-6}	7.1×10^{-5}	1.3×10^{-4}

TABLE 1

<u>Agency</u>	<u>Description</u>	<u>Value</u>
OSHA	Permissible Exposure Limit	
	Time-weighted average	500 ppm
	Ceiling	1000 ppm
	Maximum peak	2000 ppm
USEPA (OERR)	Reportable quantity	1000 lb
FDA	Limit in decaffeinated coffee or soluble coffee extract	10 ppm
ACGIH	Threshold Limit Value	50 ppm
NIOSH	Recommended Exposure Limit	Low as feasible
	Immediately Dangerous to Life or Health	5000 ppm
USEPA (ODW)	Ambient water quality criteria for protection of human health ingesting water and organism organisms only	0.19 µg/L 15.7 µg/L
	Health advisories	
	one day (child)	13.3 mg/L
	ten day (child)	1.5 mg/L
	Lifetime Health advisory	None
	Drinking Water Equivalent Level	1.75 mg/L

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SUPONA

Summary

Supona is the trade name for an organophosphorus pesticide marketed by Shell that was introduced in 1963. More commonly known as chlorfenvinphos, this compound has been marketed worldwide as a soil insecticide, a foliar insecticide, and as a component of a variety of dermal animal health products. Chemically, this compound is a mixture of two isomers (cis and trans) that exist in liquid form. It is currently only approved for use in the U.S. as a miticide under the trade name Dermaton. Like other organophosphorus pesticides, the primary mode of toxicity is through irreversible inhibition of the enzyme acetylcholinesterase in mammalian systems. The effects of this agent in exposed animals and humans are the result of acetylcholinesterase inhibition, accumulation of acetylcholine, and enhanced acetylcholine activity. The symptoms of acute organophosphorus poisoning would include respiratory difficulty, gastrointestinal distress, bradycardia, hypotension, severe muscular weakness and paralysis, and a variety of central nervous system effects such as confusion, ataxia, generalized convulsions, coma, and respiratory paralysis. Chronic exposures to supona have been associated with significant depression in both animals and in man. Chronic exposure in rats has been associated with effects on gestation and weanling survival. Chlorfenvinphos is at best a weak mutagen. There are no available data on the carcinogenic potential of this compound.

CAS Number: 470-90-6

Chemical Formula: $C_{12}H_{14}PO_4Cl_3$

IUPAC Name: 2-chloro-1-(2,4-dichlorophenyl)vinyl diethyl phosphate

Important Synonyms and Trade Names: chlorfenvinphos, Supona, Birlane, Dermaton, Sapecron

Chemical and Physical Properties

Supona or chlorfenvinphos is an amber-colored liquid with a mild, pleasant odor. This compound exists as a mixture of two isomers, trans- and cis-2-chloro-1-(2,4-dichlorophenyl)vinyl diethyl phosphate. Typical samples of the technical grade product contain 83.8% trans-isomer of chlorfenvinphos (CAS No. 18708-86-6), 9.7% cis-isomer of chlorfenvinphos (CAS No. 18708-87-7), and 6.5% related compounds. It is slowly hydrolyzed by water or acid, with a half-life of greater than 700 hours at 38°C, pH 1.1 and greater than 400 hours at 38°C, pH 9.1.

Molecular Weight:	360 (Merck 1983)
Melting Point:	-19 to -23°C (TDB 1984)
Specific Gravity:	1.36 at 16°C (TDB 1984)
Solubility in Water:	145 mg/liter at 23°C (Merck 1983) 110 mg/liter at 20°C (Berg 1982)
Solubility in Organics:	miscible with acetone, ethanol, propylene glycol, hexane, kerosene, and xylene
Log Octanol/Water Partition Coefficient (K_{ow}):	3.11 (Briggs 1981)
Soil/Water Partition Coefficient (K_{oc}):	
1,172	Lyman et al. (1982) Eqn 4-8 ($\log K_{ow} = 3.11$)
763	Lyman and Loreti (1987) ($\log K_{ow} = 3.11$)

Bioconcentration Factor:

136	Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 3.11$)
111	Davies and Dobbs (1984) Eqn B ($\log K_{ow} = 3.11$)
65	Davies and Dobbs (1984) Eqn C ($\log K_{ow} = 3.11$)
40	Davies and Dobbs (1984) Eqn A ($S = 130$)

Vapor Pressure:

7.5×10^{-6} mm Hg at 25°C (Merck 1983)
1.7×10^{-7} mm Hg at 25°C (Edward 1973)
4×10^{-6} mm Hg at 20°C (TDB Peer Review Committee 1984)

Henry's Law Constant:

3.8×10^{-9} atm-m³/mole (calculated)

7.3×10^{-10} atm-m³/mole (calculated)

3.1×10^{-8} dimensionless

Transport and Fate

The low vapor pressure for supona suggests that losses through volatilization will not be a major transport process, and that there will be little chance of release of this agent into the atmosphere. Chlorfenvinphos is also very stable in water at ambient temperatures with a slow rate of hydrolysis except at very high pH values. For example, at a temperature of 38°C, the half-life estimate for this compound is greater than 400 hours at pH 9.1, greater than 9,200 hours at pH 3.0, and greater than 10,000 hours at pH 7.0 (Benyon et al. 1973). If the temperature of the water is raised to 85°C, then hydrolysis does occur with half-times of 46 hours at Ph 3, 72 hours at Ph 7, and 3 hours at Ph 10.5. There is one report on the degradation and fate of chlorfenvinphos in a pond when it was sprayed at an exaggerated level of 74 kg/ha (Benyon et al. 1971). Residues of this agent decreased from 6.1 to 20 ppm in 5 hours, and to 0.12 ppm within one month. The agent was also detected in the mud at the bottom of the pond within 5 hours of treatment to reach a maximum value of 0.32 ppm 115 hours after treatment.

In unspecified soil types, the TDB Peer Review Committee (1984) reports an expected loss of 50% in a "few weeks". There are laboratory studies which have explored the degradation of ¹⁴C-chlorfenvinphos in soils. The degradation for this agent is reported to be fastest in sand and slowest in peat, a result that is linked to the degree of adsorption of the pesticide to the soil (Benyon and Wright 1967). A number of breakdown products were identified in the soil and it was suggested that microbiological reactions were responsible for the majority of the reactions. In field studies, chlorfenvinphos has shown similar properties, with half-lives in the range of 4 to 30 weeks, and a little residue accumulation from season to season (Benyon et al. 1973). Chlorfenvinphos has also been shown to leach very little from soil in both

laboratory and field studies. The breakdown products of this agent are more persistent in the soil than the parent compound but do not exert the same toxic actions (Benyon et al. 1973). The range of estimated soil/water partition coefficients reported above as well as laboratory data indicated that sorption of supona to soils and sediments will occur. The combined water solubility and moderate organic partitioning data for supona suggest that this compound will exhibit some degree of environmental mobility.

Once this compound is applied to soil or to plants, there is some degree of uptake and degradation. Half-lives of chlorfenvinphos residues on the foliage of potatoes and cabbage, for example, have been reported to be in the range of 2-3 days, with faster rates of depletion in the presence of rain (Benyon et al. 1973). There are also reports of metabolism of this agent on foliage. Residues of chlorfenvinphos in plants grown in treated soil have been reported. In a laboratory study, residues in the outer leaves and heart of cabbage plants were low (0.06 ppm), with no detectable breakdown products (Benyon and Wright 1967). However, dead ground leaves and stumps had much higher residues (0.15-0.26 ppm), with only small amounts of breakdown products detectable (less than 10% of the total recovered radioactivity). In field studies, residues are generally much lower. There are reports of uptake of supona in carrots after treatment of the soil (Suett et al. 1971 as cited in Benyon et al. 1973). A residue of 0.12 ppm was detected in carrots 18 weeks after application of 30 mg/ft² chlorfenvinphos; soil concentration was 2.2 ppm (Benyon et al. 1973).

A range of estimated bioconcentration factors (BCF's) for supona is also reported above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the concentration factors suggests that appreciable bioconcentration or biomagnification of supona residues is not likely to occur.

Health Effects

Human Data

Inhibition of plasma acetylcholinesterase has been the marker studied after exposure to supona in humans, and there are reports of inhibition after both oral and dermal exposures. In a volunteer study to examine the hazard of occupational exposure (dermal toxicity), 9 men had varying formulations of chlorfenvinphos applied to the left forearm for up to 4 hours (Hunter 1969). The men showed no outward signs such as disturbances to cardiovascular or renal function; however, there were significant decreases in plasma cholinesterase activity even 24 hours after the exposure. In another study, a volunteer given a single oral dose of 1 mg/kg supona exhibited temporary glycosuria (Shell Chemical Company 1967). Erythrocyte acetylcholinesterase was depressed 44% after six hours. Twenty-six days following the initial exposure, plasma cholinesterase of the volunteer was inhibited by 41%. Erythrocyte cholinesterase recovered to within 94% of the pre-exposure level after 54 days, while plasma cholinesterase returned to 100% of initial levels during the same period. Reports of accidental poisonings with chlorfenvinphos are also available for assessment of the oral toxicity of this agent in humans. Symptoms have included abdominal cramps, nausea, vomiting, weakness, muscle twitching, hypothermia, hypoglycemia, disorientation, hallucinations, and even death. In all cases, ingestion of chlorfenvinphos significantly depressed plasma cholinesterase to as much as 10% of normal.

Animal Data

Like humans, inhibition of plasma acetylcholinesterase is the marker of chlorfenvinphos exposure in animals and has been seen after all routes of exposure (oral, intraperitoneal, intravenous, dermal, subcutaneous, inhalation, and intracerebral). There is an unusual amount of species variation associated with the acute toxicity of chlorfenvinphos. LD₅₀ values show a wide range. Oral toxicity is reported to be 10-39 mg/kg in rats, greater than 5000 mg/kg (LD₅₀) in dogs (Hutson and Hathaway 1967), 125-250 mg/kg in guinea pigs, 150-200 mg/kg in mice, and

500-1000 mg/kg in rabbits. Intravenous LD₅₀ values also vary from 6.6 mg/kg in rats, to 50.4 mg/kg in dogs, to 61.9 mg/kg in mice. Intraperitoneal LD₅₀ values have been reported for rats (8.5 mg/kg) and mice (37 mg/kg). Subcutaneous LD₅₀ values also vary widely but are most affected by the degree of absorption by this route and range from 31-108 mg/kg in rats and 400-4700 mg/kg in rabbits. In one study, an attempt was made to determine an intracerebral LD₅₀ in mice; however, even at the highest dose tested (2.1 mg/kg), there were no effects (Natoff 1970). It was seen that the dog was especially tolerant to the toxic actions of chlorfenvinphos and in a study by Hutson and Hathaway (1967) it was found that this difference in sensitivity could be explained by differences in the rates of absorption and metabolism, the availability of the compound in blood, the rate of brain uptake of the compound, and the sensitivity of brain acetylcholinesterase in dogs towards the insecticide.

Plasma acetylcholinesterase in male and female rats was significantly depressed at all treatment levels after one week when supona was consumed at concentrations of 0, 10, 30, 100, or 300 ppm for up to 103 weeks (Shell Chemical Company 1967). Cholinesterase depression remained constant except in males at 10 ppm which exhibited normal levels during the second year. During the first three months of exposure, erythrocyte cholinesterase was inhibited only in the 300 ppm dose group. Thereafter, depression was observed at all levels but recovered in males during the second year of exposure. Females in the two high dose groups exhibited a tendency for lesser weight gains. In another 2 year study, male and female dogs were fed supona for two years at concentrations of 0, 30, 200, or 1000 ppm (0, 0.75, 5, or 25 mg/kg/day). Significant depression of plasma acetylcholinesterase activity occurred during the first nine months of exposure at all treatment levels; however, the health of the dogs was not affected (Shell Chemical Company 1967). Levels of acetylcholinesterase activity returned to within control levels for the rest of the study, months 9 to 24. Erythrocyte cholinesterase function was depressed only at the 1000 ppm level, but hematology remained normal. A subchronic oral toxicity study in beagle dogs utilized dose levels of 0, 0.5, 1, or 3 ppm chlorfenvinphos (0, 0.0125, 0.025, or 0.075 mg/kg/day) and determined a no-observed-effect-level (NOEL) of 3

ppm (Shell Chemical Company 1967). It is important to note, however, that this NOEL was determined in the dog, the species that has been shown to be the least sensitive to chlorfenvinphos, and thus may not be a good estimate of the NOEL in humans.

In a three generation reproduction study, albino rats fed concentrations of supona of 0, 30, 100, or 300 ppm (0, 0.75, 2.5, or 7.5 mg/kg/day) exhibited effects on certain reproductive parameters (Shell Chemical Company 1967). At the two high dose levels, interference with gestation (and possibly lactation) occurred. Effects on weanling survival rates were also observed. Only nine of 20 second generation females at 30 ppm cast litters compared with 18 of 20 control females. Twenty females at 30 ppm supona in the second and third generations also experienced a reduction in the number of litters cast (6 of 20) compared with controls (14 of 20). There are only a few reports on the mutagenic potential of chlorfenvinphos. In one study using a bacterial test system (*S. typhimurium*) with metabolic activation, chlorfenvinphos did not significantly alter the mutation rate above the level seen in control (Szarapinska-Kwaszewska et al. 1984). Therefore, the compound was identified as nonmutagenic in the assay system. In another study using a bacterial test system (*S. typhimurium* TA100 and TA1535), chlorfenvinphos was found to be a weak mutagen in the TA100 strain (Shirasu et al. 1984). There are no reports on the carcinogenicity of chlorfenvinphos in available literature.

Pharmacokinetics and Metabolism

There are no specific data on the pharmacokinetics or metabolism of supona in man. In animals, there is a species variation in the absorption and metabolism of this compound. Chlorfenvinphos is not readily absorbed when administered subcutaneously or orally as evidenced by its lowered toxicity as compared to intravenous or intraperitoneal injection (Natoff 1967). In both dogs and rats, chlorfenvinphos is distributed throughout the body and into the brain, the site of action for life-threatening effects. A study by Hutson et al. (1967) examined the metabolism of chlorfenvinphos in rats and dogs. Within 4 days of administration of a

single oral dose of ^{14}C -vinyl chlorfenvinphos in rats, 87% of the label was excreted in the urine, 11% in the feces, and 1% in expired air. During the first day, total label excretion was 67.5%. In dogs, 94% of the label was excreted in urine and feces within 4 days, with 86% in the urine and 4% in the feces on day one. Chlorfenvinphos was shown to be completely metabolized in both dogs and rats, with no evidence of unchanged compound present in urine or carcass after 4 days (complete elimination). The main metabolites of chlorfenvinphos were shown to be desethyl chlorfenvinphos, [1-(2',4'-dichlorophenyl)ethyl- β -D-glucopyranosid] uronic acid, 2,4-dichloromandelic acid, 2,4-dichlorophenylethanediol glucuronide, and 2,4-dichlorohippuric acid. There were some differences in the proportion of the metabolites produced between the two species. None of these metabolites are toxic; therefore, metabolism of chlorfenvinphos represents a detoxication mechanism.

Toxicity to Wildlife and Domestic Animals

There are only a few reports available in the English translated literature on the aquatic toxicity of chlorfenvinphos. It has been identified as a class I chemical with respect to toxicity to aquatic life, making this pesticide one of the most toxic (Lakota et al. 1982). Like other organophosphate insecticides, chlorfenvinphos is particularly toxic to crustaceans with an LC_{50} value for *Daphnia magna* in a 24-hour test of 0.38 $\mu\text{g/liter}$ (Kaminski 1975 as cited in Lakota et al. 1982). In a 14-day exposure test in rainbow trout (*Salmo gairdneri*), chlorfenvinphos inhibited acetylcholinesterase at a concentration of 0.1 mg/liter (Groba and Trzcinska 1979 as cited in Lakota et al. 1982). In a species of carp (*Cyprinus carpio*), a 96-hour near LC_{50} value of 0.25 mg/liter was reported for chlorfenvinphos as well as a near threshold for nonlethal effects of 0.025 mg/liter (Lakota et al. 1982). In this study, the fish that did not die due to contact with the agent macroscopically showed darkening of the skin, increased secretion of mucus in the skin and gills, and hyperemia of the kidneys, heart and hepatopancreas. Microscopically there was congestion in the vasculature of the gill lamellae, edema in the gill lamellae, desquamation of epithelial cells, a loss of the vacuolization seen in cytoplasm of

hepatocytes, and focal regressive changes in kidney tubules. The threshold dose of 0.025 mg/l was reported, for at this dose only slight microscopic changes were seen in gills, kidneys and the hepatopancreas of exposed fish, with no effects on their appearance or behavior. There is also one report available on the effects of chlorfenvinphos (in the formulation Birlane) on the ovaries of a freshwater teleost, *Mystus vittatus* (Haider and Upadhyaya 1985). Two aspects of reproductive capacity were examined: 1) the histology and histochemistry of the midvitellogenic ovary and 2) the activity of steroidogenic enzymes in the ovary. Vitellogenesis, or yolk accumulation by the oocyte, begins in stage I oocytes and results in the appearance of stage II and III oocytes. Birlane was shown to significantly reduce the number of stage II and III oocytes in the fish ovary. Further, this agent reduced steroidogenesis as evidenced by the decreased activity of Δ^5 -3 β -hydroxysteroid dehydrogenase.

In addition to this data in aquatic species, there are acute toxicity values available for avian species such as the mallard duck (*Anas platyrhynchos*). The LD₅₀ values for these species are 85, 80-160, and 63.5 mg/kg, respectively (Hudson et al. 1984). There are also acute oral toxicities (LD₅₀) of supona reported for goats (71.25 mg/kg) and cattle (20 mg/kg).

Regulations and Standards

Chlorfenvinphos is currently only marketed in the U.S. as an ingredient in the miticide Dermaton. It is a restricted use pesticide for domestic and nondomestic uses due to its acute dermal toxicity (USEPA FR Doc. 79-23613 filed 7/31/79). There are no other regulations or standards available for this agent.

D_T Values

D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For supona, the D_T value is based on a subchronic (120 day) oral feeding study in beagle dogs (Shell Chemical Company 1967). Groups of dogs were fed

dietary concentrations of 0.5, 1.0, and 3.0 ppm supona (0.025, 0.05 and 0.15 mg/kg/day). No effects on cholinesterase were observed. Liver function tests were normal at the conclusion of the feeding period and autopsy failed to show any gross or histological abnormalities. The no-observed-effects-level (NOEL) was identified as 0.3 ppm (0.15 mg/kg/day) (Shell Chemical Company 1967). An uncertainty factor (UF) of 1,000 is included in the derivation of the D_T to address extrapolation of the results to humans (10), intraspecies variability (sensitive subgroups) (10), and to account for using a subchronic rather than a chronic exposure duration (10). Derivation of the D_T for supona is as follows:

$$\begin{aligned} D_T &= \frac{\text{NOEL (mg/kg/day)}}{\text{UF}} \\ &= \frac{0.15}{1000} \\ &= 0.00015 \text{ mg/kg/day} \end{aligned}$$

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1,1,2,2-TETRACHLOROETHANE

Summary

1,1,2,2-Tetrachloroethane has been used widely in the past as a precursor in the production of other chemicals and as an industrial solvent. Current use is thought to be limited, although information on production and uses is unavailable (ATSDR 1989).

In humans, acute exposures to 1,1,2,2-tetrachloroethane have been associated with general neurological effects such as tremors, dizziness, and at high concentrations, unconsciousness, and with gastrointestinal effects such as stomach ache, nausea, and vomiting. Chronic systemic effects in humans are evident in the liver. Deaths have been reported in humans following the ingestion of greater than 3 mls. Acute and chronic exposures to experimental animals have resulted in adverse effects on the liver and central nervous system. An increased incidence of malformations effect, were reported after intraperitoneal administration to pregnant mice, although no effects on fetal weight, number of resorptions, or number of pregnancies were seen.

1,1,2,2-Tetrachloroethane has been demonstrated to induce liver tumors in mice of both sexes upon administration in corn oil by gavage in one chronic study (NCI 1978). It was shown to be mutagenic in three out of seven microbial short-term assays, but positive for only one out of eight assays in mammalian cells. Due to the limited evidence of carcinogenicity, the EPA has classified, 1,1,2,2-tetrachloroethane as Group C, "possible human carcinogen" and IARC has classified it as Group 3, "not classifiable as to carcinogenicity in humans" (ATSDR 1989).

Environmentally-released 1,1,2,2-tetrachloroethane can migrate into the atmosphere and groundwater. 1,1,2,2-Tetrachloroethane has been detected in indoor and outdoor air. In the urban environment, of the few percent of air samples in which 1,1,2,2-

tetrachloroethane is present, the typical average concentration is 5 ppt, but may reach 57 ppb (ATSDR 1989). Concentrations in homes averaged 1.8 ppb in one study, the source likely being products used inside the home (ATSDR 1989). A study in an industrialized state in the late 1970s found that 6% of groundwater and 11% of surface waters contained 1,1,2,2-tetrachloroethane in concentrations as high as 2.7 and 3.0 ppb, respectively (ATSDR 1989). Human exposure 1,1,2,2-tetrachloroethane through drinking water is very infrequent. 1,1,2,2-Tetrachloroethane has not been detected in food or soil and is not expected to accumulate in the food chain.

This compound has been detected in 25 of 951 NPL hazardous waste sites (ATSDR 1989). No release of the chemical in the form of a gas from these sites has been reported. In landfills and groundwater, 1,1,2,2-tetrachloroethane may be converted into chemicals such as trichloroethylene.

Occupational exposures result from the inhalation of or dermal contact with 1,1,2,2-tetrachloroethane either through normal operations or accidents, more often when the chemical is used as a solvent than when used as a starting chemical in closed or automated systems. With declines in the use of 1,1,2,2-tetrachloroethane, a decline in the number of workers exposed has occurred; fewer than 4,145 workers are exposed (1981-1983 figure (ATSDR 1989)).

CAS Number:	79-34-5
Chemical Formula:	$C_2H_2Cl_4$
IUPAC Name:	1,1,2,2-Tetrachloroethane

Important Synonyms and Trade Names:	sym-tetrachloroethane acetylene tetrachloride, dichloro-2,2-dichloroethane
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Chemical and Physical Properties

Molecular Weight:	167.85 (Weast 1981)
Boiling Point	146.2°C (Weast 1981)
Melting Point:	-36°C (Weast 1981)
Specific Gravity:	1.5953 at 20°C
Solubility in Water:	2,900 mg/L at 20°C
Solubility in Organics:	Soluble in alcohol, ether, acetone, benzene, petroleum ether, carbon tetrachloride, chloroform, carbon disulfide, dimethylformamide, and oils.
Log Octanol/Water Partition Coefficient:	2.56
Vapor Pressure:	5 mm Hg at 20°C
Vapor Density:	5.79
Soil/Water Partition Coefficient (K_{oc}):	118 (Mabey et. al. 1982, USEPA 1986)
Bioconcentration Factor:	8 (USEPA 1980)
Henry's Law Constant:	3.8×10^{-4} (Mabey et. al. 1982, USEPA 1986)

Transportation and Fate

Relatively little information is available pertaining specifically to the atmospheric fate of 1,1,2,2-tetrachloroethane. Based on analogy with 1,1,1-trichloroethane, tropospheric photooxidation via reaction with hydroxy radicals, and stratospheric photodissociation by high energy ultraviolet light, are likely to be relatively important processes in the atmosphere. Degradation is sufficiently slow, allowing wide dispersion. The estimated half-life is 53 days for photooxidation by hydroxy radicals (ATSDR 1989). Diffusion to the stratosphere is slow. The tropospheric to stratospheric turnover half-life is estimated to be 30 years. Thus only 1% is expected to reach the stratosphere where chlorine radicals resulting from photolysis may react with and destroy the stratospheric ozone layer (ATSDR 1989). Removal of

1,1,2,2-tetrachloroethane from the atmosphere may also occur through washout by precipitation, although revolatilization is possible.

In aquatic systems, photolysis and oxidation do not appear to be significant fate processes for 1,1,2,2-tetrachloroethane. No information related specifically to hydrolysis of 1,1,2,2-tetrachloroethane in the environment is available; but hydrolysis studies using 1,1,1-trichloroethane have indicated an experimental half-life of six months. This decomposition was attributed almost exclusively to hydrolysis (Versar 1979). This would suggest that hydrolysis of 1,1,2,2-tetrachloroethane may also occur slowly with a half-life ranging from several months to years (Versar 1979). Data on the volatilization of 1,1,2,2-tetrachloroethane indicates that rapid and extensive transport from surface waters to air may occur, the half-life being 6.8 hours in a model river (ATSDR 1989).

Releases to soil or lagoons volatilize or leach into subsurface and groundwaters. In groundwater, 1,1,2,2-tetrachloroethane is likely to break down by anaerobic biodegradation and chemical hydrolysis. The mechanism of biodegradation is dehydrodehalogenation. End products include 1,1,2-trichloroethane, trichloroethylene, dichloroethylene, and vinyl chloride. Chemical hydrolysis, which is more rapid with basic or neutral pH, yields a half-life of 29 to 102 days at neutral pH, with shorter half-lives under ionic environmental conditions (ATSDR 1989). The primary product of hydrolysis is trichloroethylene.

The adsorption coefficient (K_{oc}) for 1,1,2,2-tetrachloroethane in silt loam soil is 46 and the partition to low organic carbon soil is 0.05 (ATSDR 1989). These factors indicate that adsorption to soil, suspended solids, and sediment is minimal. Significant sorption to high clay content-dry soils is possible. The compound is likely to leach from soil surfaces into subsurface soil and groundwater.

Based on theory and experimentation, adsorption to sediment and bioconcentration in fish is not thought to be significant. A bioconcentration factor of 8 was found in a two week study in bluegill fish, which is not considered to be significant (bioconcentration in fish is significant only when the value is greater than 500-1000) (ATSDR 1989). The half life of 1,1,2,2-tetrachloroethane in fish tissue is less than one day (ATSDR 1989).

Health Effects

Humans can be exposed to 1,1,2,2-tetrachloroethane through the inhalation dermal, and oral routes. Death in humans has resulted from the ingestion of greater than 3 mL 1,1,2,2-tetrachloroethane in a single dose (ATSDR 1989). The oral LD₅₀ in rats is 250 mg/kg (NIOSH 1984). The dermal LD₅₀ in rabbits is 6.38 g/kg (ATSDR 1989).

Systemic effects in humans are evident in the liver (jaundice and enlarged liver) and gastrointestinal tract (stomach ache, nausea, vomiting) following administration by inhalation at ambient levels of 116 ppm for 10 minutes for gastrointestinal effects and 1.5 to 36 ppm for months for liver effects (ATSDR 1989). Mice and rats have exhibited fatty degeneration of the liver after inhalation of 1,1,2,2-tetrachloroethane in concentrations of 600 ppm for hours to weeks (ATSDR 1989). Rabbits have exhibited changes in blood levels of acetylcholine, indicative of hepatocellular and nervous system damage when chronically exposed to 14 and 69 ppm of 1,1,2,2-tetrachloroethane (ATSDR 1989). Only minor effects on the respiratory, cardiovascular, hematological, musculoskeletal, and renal systems have been noted in humans. No data on human studies and little data on animal studies are available to evaluate immunological effects. Exposure to 1,1,2,2-tetrachloroethane causes general neurological effects such as hand tremors, dizziness, and unconsciousness at high levels (inhalation or ingestion) in humans and impaired motor activity or leaning in rats (intraperitoneally administered).

No studies were found reporting on reproductive effects in humans. In a study in rats, exposure to 2 ppm for four days resulted in histological changes in the testes of male rats. No effect on the ability of male rat to sire offspring was seen when rats were exposed for 10 days to 38 weeks to an ambient concentration of 2 ppm, thus making the aforementioned pathologic results suspect (ATSDR 1989). No studies on the developmental effects of 1,1,2,2-tetrachloroethane were found for the inhalation or dermal routes in either humans or animals. Intraperitoneal administration of 1,1,2,2-tetrachloroethane to mice during gestation at 700 mg/kg/day for 9 days had moderate effects on skeletal development (ATSDR 1989). Even at this high dose no effects were seen on fetal weight, number of resorptions, or number of pregnancies. No effects were seen at 300 mg/kg/day.

An epidemiologic study found a weak association between exposure to 1,1,2,2-tetrachloroethane and development of genital tumors and leukemia; however, many confounders were uncontrolled in the study. A second human study found no association between exposure and liver tumors or cirrhosis of the liver.

Cancer induction by 1,1,2,2-tetrachloroethane was assessed in three chronic assays. Mice and rats were administered 1,1,2,2-tetrachloroethane in corn oil by gavage for 78 weeks, with an additional 132 weeks of observation at high and low doses (NCI 1978). These doses, expressed as time-weighted averages, were 108 and 62 mg/kg/day for male rats 76 and 43 mg/kg/day for female rats, and 284 and 142 mg/kg/day for mice. A significantly increased, dose-related incidence of hepatocellular carcinoma was noted in mice. No significant increase of neoplasms was detected in rats of either sex. In a third study, Strain A mice were administered 400 mg/kg/day of 1,1,2,2-tetrachloroethane intraperitoneally for eight weeks (ATSDR 1989). No statistically significant increase in tumors was detected.

Overall, genotoxicity tests in mammalian cells yielded mostly negative results (7/8, 1 positive assay for sister chromatic exchange in Chinese Hamster Ovary cells)

(ATSDR 1989), while those in bacteria, yeast or insects yielded mixed results (4/7 negative; 2 positive assays in bacterial strains *S. typhimurium* and *E. coli* and 1 positive in yeast) (ATSDR 1989, USEPA 1984).

Due to the limited evidence of carcinogenicity, the EPA has classified 1,1,2,2-tetrachloroethane as Group C, "possible human carcinogen" and IARC has classified it as Group 3, "not classifiable as to carcinogenicity in humans" (ATSDR 1989).

In a rat liver foci assay, the mechanism of liver tumor induction in rats was examined and found to be suggestive of a promotion mechanism (ATSDR 1989).

Toxicity to Wildlife and Domestic Animals

Acute values for freshwater species range from 9,320 ug/L for an invertebrate species to approximately 20,000 ug/L for two species of fish. An embryo-larval test conducted with the fathead minnow yielded a chronic value of 2,400 ug/L and an acute-chronic ratio of 8.5 for this species. Among saltwater species, acute values of 9,020 ug/liter for the mysid shrimp and 12,300 ug/L for the sheepshead minnow are reported. Exposure to 1,1,2,2-tetrachloroethane affects chlorophyll and cell numbers of freshwater and marine algae exposed to approximately 141,000 ug/L and 6,300 ug/L, respectively.

Regulation and Standards

Ambient Water Quality Criteria (USEPA 1980a and b):

Aquatic Life

The available data are not adequate for establishing criteria.

Human Health

Estimates of the carcinogenic risks with lifetime exposure to various concentration of 1,1,2,2-tetrachloroethane in water are (USEPA 1989):

<u>Risk</u>	<u>Concentration</u>
10 ⁻⁴	20 ug/L
10 ⁻⁵	2.0 ug/L
10 ⁻⁶	0.2 ug/L

NIOSH Recommended Standard: 7 mg/m³ TWA (NIOSH 1976)

OSHA Standard: 35 mg/m³

CAG Potency Slope for Oral Exposures (USEPA 1989):

2.0 x 10⁻¹ (mg/kg/day)⁻¹

CAG Potency Slope for Inhalation Exposures (USEPA 1989): 2.0 x 10⁻¹
(mg/kg/day)⁻¹

EPA-OWRS (water) 1.7 ug/mL (ATSDR 1989)

EPA-OERR (other) 100 lbs reportable quantity (ATSDR 1989)

State Regulations

Acceptable ambient limits of toxic air pollutants in Kentucky: 0.7 mg/m³ 8 hr. TWA
(ATSDR 1989)

Acceptable ambient air concentrations: from 1.2 ug/m³ 24 hr. average to 168.7 ug/m³
yearly average (ATSDR 1989)

Drinking water quality guidelines: 0.5-10 ug/L (ATSDR 1989)

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than predetermined risk level.

For carcinogens such as 1,1,2,2-tetrachloroethane, the D_T value was derived using USEPA Cancer Assessment Group's cancer potency slopes. Cancer potency slopes have been estimated for 1,1,2,2-tetrachloroethane for both oral and inhalation exposure routes. A cancer potency slope of 2×10^{-1} (mg/kg/day)⁻¹ was derived for both oral and inhalation exposures based on an observed dose-response increase in liver cancers in mice treated with 1,1,2,2-tetrachloroethane at doses up to 174 mg/kg/day (NCI 1978; USEPA 1989). Using the cancer potency slopes, the D_T value was derived as follows:

$$D_T = \frac{\text{Risk Level}}{\text{Potency Slope (mg/kg/day)}^{-1}}$$

$$\text{Potency Slope (mg/kg/day)}^{-1}$$

$$= \frac{1 \times 10^{-4}}{2.0 \times 10^{-1} \text{ (mg/kg/day)}^{-1}}$$

$$5.0 \times 10^{-4} \text{ (mg/kg/day)}$$

The range of oral and inhalation D_T values for 1,1,2,2-tetrachloroethane are present below:

	D_T Oral Exposure	D_T Inhalation Exposure
<u>Risk level</u>	<u>(mg/kg/day)</u>	<u>(mg/kg/day)</u>
10^{-4}	5.0×10^{-4}	5.0×10^{-4}
10^{-5}	5.0×10^{-5}	5.0×10^{-5}
10^{-6}	5.0×10^{-6}	5.0×10^{-6}

Although cancer potency slopes and contaminant intake rates at predetermined risk levels have been calculated for 1,1,2,2-tetrachloroethane, it should be emphasized that the evidence available for determination of carcinogenicity in humans is limited. It may be more appropriate to derive and use an oral RfD based on non-cancer effects for this chemical.

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TETRACHLOROETHYLENE

Summary

Tetrachloroethylene is a chlorinated hydrocarbon solvent important in metal degreasing and in the dry cleaning and textile processing industries. While early bioassays for carcinogenicity in rats have been interpreted as negative, NTP (1989) finds there is clear evidence for carcinogenicity in male rats and some evidence in female rats based on a 1986 bioassay. Tetrachloroethylene (PCE) induced liver tumors following oral and inhalation administration to mice. As a result, tetrachloroethylene has been classified as a "C" chemical (possible human carcinogen, based on limited animal evidence; USEPA, 1985), as a "B2" carcinogen (probable human carcinogen, based on adequate evidence in animals; USEPA, 1989) and as an IARC Class 3 chemical (unable to classify as to human carcinogenicity (USEPA, 1985). Many mutagenicity tests were negative for tetrachloroethylene. The mammalian tests performed to date do not indicate any significant teratogenic potential in the species tested (USEPA 1985). Developmental toxicity was observed in pregnant rats and mice following exposure to high concentrations of tetrachloroethylene. Effects were attributable to delayed development and were generally reversible. The significance of these effects for the teratogenic potential of tetrachloroethylene in humans is unknown (USEPA 1985). Animals exposed via inhalation exhibited liver, kidney, and central nervous system damage. In humans, central nervous system depression and liver toxicity are also the principal effects exhibited following high and moderate tetrachloroethylene exposure, respectively. Although there are no known natural sources of tetrachloroethylene emissions, it has been detected in ambient air and surface and groundwater. The global average background level is estimated at 25 parts per trillion (ppt) (USEPA, 1985).

CAS Number: 127-18-4

Chemical Formula: C_2Cl_4

IUPAC Name: Tetrachloroethene

Important Synonyms and Trade Names: Perchloroethylene, PCE

Chemical and Physical Properties

Molecular Weight: 165.83

Boiling Point: 121°C

Melting Point: -22.7°C

Flash point: None; non-flammable

Specific Gravity:

1.63

Solubility in Water:

150 - 200 mg/liter at 20°C

Solubility in Organics:

Soluble in alcohol, ether, chloroform, hexane and benzene

Log Octanol/Water Partition Coefficient (K_{ow}):

2.60 (Hansch and Leo 1979)

2.53 (Veith *et al.* 1983)

Soil/Water Partition Coefficient (K_{sw}):

270, 306	Lyman and Loreti (1987) ($\log K_{sw} = 2.53; 2.60$)
360	Chiou <i>et al.</i> (1979) (experimental)
567, 619	Lyman <i>et al.</i> (1982) Eqn 4-8 ($\log K_{sw} = 2.53, 2.6$)
364	USEPA (1986a)

Bioconcentration Factor:

49	Davies and Dobbs Table 2 (experimental)
38-19	Davies and Dobbs (1984) Eqn A ($S = 140-500$)
30.6	ECAO 1980
55.7	Lyman <i>et al.</i> (1982) Eqn 5-2 ($\log K_{sw} = 2.6$)
49.3	Lyman <i>et al.</i> (1982) Eqn 5-2 ($\log K_{sw} = 2.53$)
26.9	Davies and Dobbs (1984) Eqn C ($\log K_{sw} = 2.55$)
51.3	Davies and Dobbs (1984) Eqn B ($\log K_{sw} = 2.55$)
51.1	Lyman <i>et al.</i> (1982) Eqn 5-2 ($\log K_{sw} = 2.55$)

Vapor Pressure:

14 mm Hg at 20°C

17.8 mm Hg (USEPA 1986a)

Henry's Law constant:

1.4×10^{-2} atm-m³/mole (calculated)

2.59×10^{-2} atm-m³/mole (USEPA 1985)

1.09 Dimensionless

Transport and Fate

Tetrachloroethylene volatilizes rapidly into the atmosphere where it reacts with hydroxyl radicals to produce HCl, CO, CO₂ and carboxylic acid. This is probably the most important transport and fate process for tetrachloroethylene in the environment. The half-life of PCE in air is approximately 47 days (USEPA 1984). The half-life of PCE in water may range from 1-30 days (USEPA 1986a).

About 85% of the tetrachloroethylene used annually in the U.S. is lost to the atmosphere. In 1974, this amount was estimated to be 550 million pounds. Numerous studies have found tetrachloroethylene in the air in the U.S. at concentrations ranging from 30 ppt in rural areas to 4.5 ppb in metropolitan or industrial areas. Tetrachloroethylene may be formed in small quantities during chlorination of water. It has also been detected in rainwater, sea water, rivers and groundwater, and in commercial deionized charcoal-filtered water. Tetrachloroethylene has been found in foods, such as dairy produce, meats, oils and fats, beverages, fruits and vegetables, and fresh bread, and in the tissues of marine fish, shellfish, mammals, and algae (IARC V.20, 1979, and ATSDR, 1987, as cited in NTP, 1989).

A range of experimental and estimated soil-water partition coefficients (K_{oc}) is reported above and indicates that sorption of tetrachloroethylene to soils/sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of volatile organic compounds will range from low to moderate. The combined water solubility and organic partitioning data indicate that tetrachloroethylene will exhibit some degree of environmental mobility. It is uncertain if organically bound tetrachloroethylene can be efficiently degraded by microorganisms.

A range of experimental and estimated bioconcentration factors (BCFs) for tetrachloroethylene is also reported above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for

causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the concentration factors suggest that appreciable bioconcentration or biomagnification of tetrachloroethylene residues is not likely to occur.

Pharmacokinetics

Tetrachloroethylene is readily absorbed following inhalation exposure. Absorption following ingestion is also rapid and nearly complete. Absorption through the skin is poor. Physiologically based pharmacokinetic models predict that a large percentage of an absorbed dose will be distributed to the fat tissue. Concentrations in the fat of experimental animals may be 60 times those in the blood. Tetrachloroethylene readily crosses the blood-brain and placental barriers. Metabolism appears to differ among mammalian species, which has implications for extrapolation from experimental animals to humans. It is primarily metabolized in the liver, although other tissues may metabolize it as well. Metabolism is rate-limited and saturated at fairly low exposure levels. Treatment by P-450 inducers increases metabolism of tetrachloroethylene. Urinary metabolites in humans are primarily trichloroacetic acid and trichloroethanol; in experimental rats but not mice, oxalic acid is also an important if not the primary metabolite in addition to the first two. The metabolic pathways are not known for this compound at the present, but carcinogenic effects are probably mediated by a reactive metabolite. Most tetrachloroethylene is excreted unmetabolized through exhalation; only a small percentage of an absorbed dose is metabolized and excreted as urinary metabolites (ATSDR, 1987 and EPA, 1985).

Health Effects

Acute effects

Sufficient quantities of tetrachloroethylene can cause central nervous system depression, but have only limited abilities to cause organ damage.

Tetrachloroethylene is one of the least hepatotoxic and nephrotoxic of a series of alkyl halides when administered as a single dose by intraperitoneal injection to several

species of animals, and near-lethal doses are usually required to produce significant tissue injury (NAS, 1980). Acute oral LD₅₀s reported are: dogs, 4,000 mg/kg; rabbits, 5,000 mg/kg; rat, 8850 mg/kg (Sax and Lewis, 1989); rat, 3000 mg/kg (ATSDR, 1987). Acute inhalation doses reported are: LC₅₀, mouse, 4 hour: 5,200 ppm; LC_{low}, rat, 4 hour: 4,000 ppm. Ingestion of 60 to 86 mg/kg doses of tetrachloroethylene by humans for anthelmintic medication was reported to be nonlethal (ATSDR, 1987).

Acute inhalation exposure to high levels of tetrachloroethylene includes eye and upper respiratory irritation, headache, dizziness, and drowsiness. Human and animal data indicate that a threshold for central nervous system effects is likely and appears to be in the range of 100 to 200 ppm for humans (ATSDR, 1987).

Chronic effects

Health effects in humans following chronic exposure to high levels of tetrachloroethylene include respiratory tract irritation, nausea, headache, sleeplessness, abdominal pains, constipation, liver cirrhosis, hepatitis, and nephritis (USEPA 1984). Central nervous system depression and liver toxicity are the principal systemic effects exhibited following tetrachloroethylene exposure.

Renal toxicity and hepatotoxicity were exhibited by rats following chronic inhalation exposure at levels of 1,356 mg/m³ tetrachloroethylene. During the first 2 weeks of a subchronic inhalation study, exposure to concentrations of 1,622 ppm (10,867 mg/m³) of tetrachloroethylene produced signs of central nervous system depression and cholinergic stimulation in rabbits, monkeys, rats, and guinea pigs.

Buben and O'Flaherty (1985) exposed Swiss-Cox mice to tetrachloroethylene in corn oil by gavage at doses of 0, 20, 100, 200, 500, 1500, and 2000 mg/kg, 5 days/ week for 6 weeks. Liver toxicity was evaluated by several parameters including liver weight/body weight ratio, hepatic triglyceride concentration, DNA content, histopath-

ological evaluation, and serum enzyme levels. Increased liver triglycerides were first observed in mice treated with 100 mg/kg. Liver weight/body weight ratios were significantly higher than controls for animals treated with 100 mg/kg. At higher doses, hepatotoxic effects included decreased DNA content, increased SGPT, decreased levels of G6P and hepatocellular necrosis, degeneration and polyploidy. A similar NOEL of 14 mg/kg/day was established in a second study (Hayes *et al.*, 1986, cited in EPA, 1990). Groups of 20 Sprague-Dawley rats of both sexes were administered doses of 14, 400, or 1400 mg/kg/day in drinking water. Males in the high-dose group and females in the two highest groups exhibited depressed body weights. Equivocal evidence of hepatotoxicity (increased liver and kidney weight/body weight ratios) were also observed at the higher doses (EPA, 1990).

Mutagenicity

Tetrachloroethylene was not mutagenic in several Salmonella typhimurium strains either with or without metabolic activation (NTP 1986). It was not mutagenic in mouse lymphoma cells with or without metabolic activation and did not induce sex-linked recessive lethal mutations in Drosophila melanogaster (NTP 1986).

Tetrachloroethylene did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells with or without metabolic activation. Results of a mutagenicity test using L5178Y mouse lymphoma cells were positive for tetrachloroethylene (NTP, 1987).

Carcinogenicity

In male and female mice, tetrachloroethylene was found to produce liver cancer when orally administered by gavage (NCI 1977). The National Toxicology Program (NTP) recently completed a chronic (103 week) inhalation study with PCE in rats and mice (NTP 1986). The exposure concentrations were 0, 200, or 400 ppm for rats and 0, 100, or 200 ppm for mice. Survival of male rats was affected at the high dose and survival of male mice was affected at both doses. Survival of female mice was reduced at 200 ppm. Both concentrations of PCE were associated with mononuclear

cell leukemia in male and female rats. PCE caused renal tubular cell hyperplasia in male rats, renal tubular cell adenomas or adenocarcinomas in male rats (not statistically significant), and renal tubular cell karyomegaly in male and female rats. One low dose male rat had a kidney lipoma and another had a nephroblastoma. In male and female mice, PCE caused increased incidences of hepatocellular neoplasms. High dose males had increased incidences of hepatocellular adenomas while an increased incidence of hepatocellular carcinomas occurred at both concentrations in males and females. The authors conclude that there was clear evidence of carcinogenicity for male rats, some evidence for female rats, and clear evidence for mice of both sexes.

In a 1977 National Toxicology Program bioassay, Osborne-Mendel rats and B6C3F₁ mice were exposed by gavage to tetrachloroethylene in corn oil 5 days/week for 70 weeks, followed by observation for 32 weeks (rats) and 12 weeks (mice). No increases in tumor incidences were observed for rats, but mice of both sexes showed significant increases in hepatocellular carcinomas (ATSDR, 1987). An earlier inhalation bioassay (Rampy *et al.*, 1978, cited in EPA, 1985) of large groups (96 per sex per dose) to higher levels of tetrachloroethylene (300 or 600 ppm) 6 hours/day, 5 days/week was negative, but the study was only 12 months long.

Epidemiological evidence for carcinogenicity of tetrachloroethylene in humans is insufficient to show either that it is carcinogenic in humans or that it is not. Blair *et al.* (1979) observed an excess of lung, cervical, and skin cancers and slight increases in leukemia and liver cancer in a study of deceased laundry and dry-cleaning workers with known exposures to PCE, carbon tetrachloride, and trichloroethylene. Brown and Kaplan (1987) conducted a retrospective cohort mortality study of 1,690 workers in the dry cleaning industry. Observed mortality was less than expected (493 deaths observed versus 575.5 expected), but mortality from all cancers was greater than expected (142 observed versus 122.9 expected). Potential exposure to petroleum solvents occurred, which is a confounding factor. These two studies and others are

limited by failure to consider confounding factors such as exposure to other chemicals, smoking, and socioeconomic status and are thus considered inconclusive (ATSDR, 1987).

Tetrachloroethylene has been classified according to EPA's Guidelines for Carcinogenic Risk Assessment in EPA's Group B2 (probable human carcinogen) based on sufficient evidence in animals and inadequate evidence in humans (USEPA 1986b). Previously (EPA, 1985) EPA classified it as a C chemical (possible human carcinogen based on "limited" evidence). At this writing, EPA's evaluation of PCE has been withdrawn from IRIS pending further evaluation of the weight of evidence.

Reproductive and developmental effects

No information regarding potential reproductive or developmental effects following oral exposure to tetrachloroethylene could be located. Exposure via inhalation of pregnant mice and rats to concentrations of 300 ppm (about 2,000 mg/m³) for 7 hours per day on days 6 through 15 of gestation produced no apparent substantial fetal toxicity or teratogenicity (Schwetz *et al.*, 1975, cited in Shepard, 1986). In the Schwetz study, however, there were some modest but statistically significant deviations from controls, including increased maternal body weight, decreased mouse fetal body weight, increased rat fetal resorptions, and increased incidence of split sternbrae, subcutaneous edema, and delayed ossification of skull bones in mouse fetuses (NAS, 1980). Nelson *et al.* (1980) (also cited in Shepard, 1986) exposed rats by inhalation to 100 ppm for 7 hours per day on days 14 to 20 of gestation and found no differences between control and treated pups on behavioral tests, but at 900 ppm under the same exposure regimen, the maternal animals gained less weight, and the offspring did not perform as well on neuromotor tests and had lower levels of brain acetylcholine and dopamine.

Toxicity to Wildlife and Domestic Animals

Tetrachloroethylene is the most toxic of the chloroethylenes to aquatic organisms. Limited acute toxicity data are available for PCE; however, these data appear to indicate that the LC_{50} values for saltwater and freshwater species are similar--approximately 10,000 ug/liter. The trout was the most sensitive species evaluated (LC_{50} = 4,800 ug/liter). Chronic values were 840 and 450 ug/liter for freshwater and saltwater species, respectively. An acute-chronic ratio of 19 has been computed for tetrachloroethylene.

Tetrachloroethylene was extensively used as an intestinal anthelmintic in ruminants until it was largely replaced in recent years by drugs with fewer toxic side effects.

No information on the toxicity of tetrachloroethylene to terrestrial wildlife was available in the literature reviewed.

Regulations and Standards

Ambient Water Quality Criteria (USEPA 1986c):

The available data are not adequate for establishing criteria. However, EPA does report the lowest values known to be toxic to aquatic organisms.

Aquatic Life (Freshwater)

Acute toxicity: 5,280 ug/liter

Chronic toxicity: 840 ug/liter

Aquatic Life (Saltwater)

Acute toxicity: 10,200 ug/liter

Chronic toxicity: 450 ug/liter

Human Health

Due to the potential carcinogenicity of tetrachloroethylene, the ambient water criterion is set at zero. However, estimates of the upper bound on the carcinogenic risks associated with lifetime exposure from ingestion of contaminated water and contaminated aquatic organisms are:

Risk	<u>Concentration</u>
10 ⁻⁴	80 ug/liter
10 ⁻⁵	8.0 ug/liter
10 ⁻⁶	0.8 ug/liter

The following CAG Potency Slope values have been withdrawn while they undergo further review by EPA's CRAVE group:

CAG Potency Slope for oral exposure (USEPA 1986b):

$$5.1 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$$

CAG Potency Slope for inhalation exposure (USEPA 1989):

$$3.3 \times 10^{-3} \text{ (mg/kg/day)}^{-1}$$

NIOSH Recommended Standards (air):

TWA¹ = 335 mg/m³

Ceiling Level = 670 mg/m³ (15 min.)

OSHA Standards (air):

TWA = 670 mg/m³

Ceiling Level = 1,340 mg/m³

Peak Level = 2,010 mg/m³ (5 min. every 3 hr.)

Drinking Water Health Advisory: (USEPA 1989)

Ten-day HA -- 2E+0 mg/L (protective for a child)

Longer-term (Child) HA -- 1.4E+0 mg/L

The ten-day health advisory is based on the NOEL from Buben and O'Flaherty, 1985. An uncertainty factor of 100 was applied, and the NOEL was not modified to reflect the dosing schedule. The longer-term health advisory is based on the same study, but the NOEL was modified to account for the weekdays-only dosing schedule.

Chronic RfD (Reference Dose) from IRIS (USEPA, 1989):

RfD = 1E-02 mg/kg/day

This reference dose is based on a NOEL of 14 mg/kg/day identified in a 6 week gavage study in rats and mice (Buben and O'Flaherty, 1985) that resulted in hepatotoxicity. An uncertainty factor of 1,000 was applied.

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

¹ TWA: Time-Weighted Average

For potential carcinogens such as tetrachloroethylene, the D_T value is based on the USEPA Cancer Assessment Group's cancer potency slopes. The values given here have been withdrawn for further evaluation by the EPA and are thus presented as interim values. The cancer potency slopes have been estimated for oral exposure routes and for inhalation exposure for tetrachloroethylene. The slopes are intended to be a plausible upper bound of the potency of a carcinogen in inducing cancer at low doses. Calculation of a D_T using a cancer potency slope requires selection of an acceptable cancer risk level. A range of risk levels from 10^{-4} to 10^{-6} is considered for all carcinogens; therefore, a range of D_T values is presented. Derivation of the D_T values for tetrachloroethylene is as follows:

$$\begin{aligned}
 D_T &= \frac{\text{Risk Level}}{\text{Potency Slope (}/\text{mg}/\text{kg}/\text{day)}} \\
 &= \frac{1 \times 10^{-4}}{5.1 \times 10^{-2}} \\
 &= 1.9 \times 10^{-3} \text{ mg}/\text{kg}/\text{day}
 \end{aligned}$$

The range of D_T values for tetrachloroethylene is presented below:

<u>Risk Level</u>	<u>D_T Oral Exposure (mg/kg/day)</u>	<u>D_T Inhalation Exposure (mg/kg/day)</u>
10^{-4}	1.9×10^{-3}	3.0×10^{-2}
10^{-5}	1.9×10^{-4}	3.0×10^{-3}
10^{-6}	1.9×10^{-5}	3.0×10^{-4}

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1,1,2-TRICHLOROETHANE

Summary

1,1,2-Trichloroethane is predominantly used where 1,1-dichloroethene (vinylidene chloride) is manufactured but is also used as a solvent and may be found in some consumer products. However, the nature of these products has not been identified (ATSDR 1989).

Approximately 1/4 to 1/2 of the urban population may be exposed through contaminated ambient air with median levels of exposure being 22 parts per trillion. Results from a nationwide study of groundwater has shown that exposure to 1,1,2-trichloroethane from contaminated drinking water is uncommon (Westrick et al. 1984 in ATSDR 1989).

Only trace amounts of 1,1,2-trichloroethane were found in personal air samples, drinking water samples, breath samples, and food samples from 12 volunteers in New Jersey and North Carolina (Wallace et al. 1984 in ATSDR 1989). A study done in the Ruhr region of Germany from 1976-78 found an average level in drinking water samples from 100 German cities of 5.8 $\mu\text{g/l}$ 1,1,2-trichloroethane; air concentrations were rarely greater than 1 $\mu\text{g/m}^3$ (Bauer 1981a, b in ATSDR 1989). 1,1,2-Trichloroethane was not detected in the foods or cosmetic products from the region. However, small amounts were found in the tissues of 15 people exposed primarily via the air: 6 $\mu\text{g/kg}$ in adrenal capsule adipose tissue, 14 $\mu\text{g/kg}$ in subdermal adipose tissue, 2 $\mu\text{g/kg}$ in the lungs, 3 $\mu\text{g/kg}$ in the liver, and 17 $\mu\text{g/kg}$ in muscle tissue.

Acute toxicity studies of 1,1,2-trichloroethane by oral administration and inhalation exposure have resulted in liver and kidney damage, adverse neurological effects, and death in various species of animals (ATSDR 1989). Dermal studies have shown skin irritation in humans and animals and death in animals. 1,1,2-Trichloroethane was found to cause cancer in mice but not rats in a 78-week oral bioassay performed by the National Cancer Institute (NCI). This study has been

criticized since the 78-week dosing period is not adequate for rats; it does not represent the major portion of the rat's lifetime (ATSDR 1989). However, EPA classifies 1,1,2-trichloroethane as a group C carcinogen (possible human carcinogen) on the basis of this study (U.S. EPA 1989). Available genotoxicity studies have shown that 1,1,2-trichloroethane is not mutagenic in bacteria, but may interact with mammalian DNA in vivo. No adverse reproductive effects have been found in animal studies examining this endpoint; teratology studies are not available. Human epidemiologic studies relating exposure to health effects do not exist.

CAS Number: 79-00-5

Chemical Formula: $\text{CH}_2\text{ClCHCl}_2$ or
 $\text{C}_2\text{H}_3\text{Cl}_3$ (CAS 1988 in ATSDR 1989)

IUPAC Name: 1,1,2-Trichloroethane

Important Synonyms and Trade Names:

Vinyl trichloride, ethane trichloride; B-Trichloroethane, 1,2,2-Trichloroethane; B-T, Cement T-339 (CAS 1988, SANSS 1988 in ATSDR 1989)

Chemical and Physical Properties

Molecular Weight: 133.41

Boiling Point: 133.8°C
114°C (TDB Peer Review Committee, 1984)

Melting Point: -36.5°C

Specific Gravity: 1.4397 at 20°C

Solubility in Water: 4,500 mg/liter at 20°C (USEPA 1986a)

Solubility in Organics: Soluble in alcohol, ether, esters and ketones
(Hawley 1981 in ATSDR 1989)

Log Octanol/Water Partition Coefficient (K_{ow}): 2.47 (USEPA 1986a)

Soil/Water Partition Coefficient (K_{oc}):

526	Lyman et al. (1982) Eqn 4-8 ($\log K_{ow} = 2.47$)
242	Lyman and Loreti (1987) ($\log K_{ow} = 2.47$)
56	USEPA (1986a)

Bioconcentration Factor:

22.0	Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 2.07$)
5.4	Davies and Dobbs (1984) Eqn A ($S = 4,400$)
16	Davies and Dobbs (1984) Eqn C ($\log K_{ow} = 2$)
24	Davies and Dobbs (1984) Eqn B ($\log K_{ow} = 2$)
15.3	Davies and Dobbs (1984) Eqn C ($\log K_{ow} = 2.07$)
26.5	Davies and Dobbs (1984) Eqn B ($\log K_{ow} = 2.07$)

Vapor Pressure: 19 mm Hg at 20°C
20 mm Hg at 21.6°C (Perry and Chilton, 1973)
23.5 mm Hg at 25°C (Estimated: Lyman et al., 1982)
30 mm Hg (USEPA 1986a)

Vapor Density: 4.63

Henry's Law Constant: 9×10^{-4} atm-m³/mole (calculated)
 1.17×10^{-3} atm-m³/mole (USEPA 1986a)
 4.92×10^{-2} Dimensionless

Transport and Fate

Volatilization and subsequent photooxidation in the troposphere are probably the primary transport and fate processes for 1,1,2-trichloroethane in aqueous media. A range of estimated soil-water partition coefficient (K_{oc}) is reported above and indicates that some sorption of 1,1,2-trichloroethane to soils/sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of volatile organic compounds will range from low to moderate. Due to its moderately high vapor pressure and low adsorptivity to soil, 1,1,2-trichloroethane is expected to volatilize rapidly from soil surfaces (ATSDR 1989). The combined water solubility and low

organic partitioning suggests that 1,1,2-trichloroethane will exhibit a high degree of environmental mobility.

A range of estimated bioconcentration factors (BCFs) for 1,1,2-trichloroethane is also reported above. ASTM (1985) indicated that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chain. The magnitude of the concentration factors suggest that appreciable bioconcentration or biomagnification of 1,1,2-trichloroethane residues is not likely to occur.

1,1,2-Trichloroethane may also be formed in landfills when 1,1,2,2-tetrachloroethane is broken down. When it is released into the environment, it ends up in the atmosphere or groundwater where it reacts very slowly. In the air, the half-life is about 49 days while in water, limited studies have suggested that it may persist for years (ATSDR 1989). It has not been reported in food or soil.

Health Effects

1,1,2-Trichloroethane can produce temporary stinging and burning pain in humans when applied to the skin for 5 minutes at 698 mg/cm²/day (Wahlberg 1984a in ATSDR 1989). There is no other information available regarding human health effects.

Many acute inhalation experiments have been done on mice and rats (ATSDR 1989). The lowest levels at which fatalities were found are 416 ppm after 6 hours exposure (Gradiski et al. 1978 in ATSDR 1989) and 500 ppm after 8 hours exposure (Smith et al. 1969 in ATSDR 1989), respectively, in mice and rats. However, another study identified a NOAEL of 890 ppm for rats exposed for 2 hours (Carlson 1973 in ATSDR 1989); at higher levels (2080 ppm) increased SGPT was noted. Chronic inhalation exposure to 15 ppm of 1,1,2-trichloroethane for 6 months did not increase mortality in rats, guinea pigs, or rabbits (Torkelson and Rowe 1981 in ATSDR 1989).

Increased SGPT levels were also observed in two studies in mice although the results were very inconsistent; the LOAEL's were 800 ppm with 3 hours of inhalation exposure (Takahara 1986a in ATSDR 1989) and 3750 ppm with 15 hours of inhalation exposure (Gehring 1968 in ATSDR 1989). Loss of reflex control occurred at 2749 ppm and lying down on side at 1833 ppm for 2 hours in mice exposed through inhalation (Lazarew 1929 in ATSDR 1989). Rats exposed in air to 1654 ppm for 6 hours experienced somnolence (Bonnet et al. 1980 in ATSDR 1989).

Mortality occurred after acute oral exposure to 1,1,2-trichloroethane administered by gavage to male mice at 378 mg/kg and females at 491 mg/kg (LD_{50} s) (White et al. 1985 in ATSDR 1989) or once per day for seven days at 300 mg/kg/day (7/7 dead) (Kallman et al. 1983 in ATSDR 1989). The latter study identified a NOAEL of 100 mg/kg. The rat LD_{50} was 837 mg/kg after a one time dose by gavage (Smyth et al. 1969 in ATSDR 1989). A dog experiment did not show any effect at 433 mg/kg, while 722 mg/kg was lethal (Wright and Schaffer 1932 in ATSDR 1989).

It is interesting to note that systemic effects in rats occurred after one time oral dosing by gavage of 1080 mg/kg 1,1,2-trichloroethane which is greater than the LD_{50} of 837 mg/kg; these effects included biochemical changes in the liver (Moody and Smuckler 1986, Moody et al. 1981 in ATSDR 1989). Levels as low as 60 mg/kg/day increased SGOT and SGPT levels in the liver of rats receiving one dose by gavage (Tyson et al. 1983 in ATSDR 1989). Body weight changes were noted in rats exposed by gavage 5 days/week for 7 weeks to 69 mg/kg/day (Story et al. 1986 in ATSDR 1989).

A NOAEL of 38 mg/kg/day was observed for systemic (White et al. 1985 in ATSDR 1989) and immunological (Sanders et al. 1985 in ATSDR 1989) effects in mice receiving one dose by gavage for 14 days. Neurological effects occurred after one dose by gavage to 450 mg/kg/day (sedation) (White et al. 1985 in ATSDR 1989) or 128 mg/kg/day (motor impairment) (Borzelleca 1983 in ATSDR 1989).

Dogs receiving a one-time dose of 144 mg/kg experienced mild adverse effects on their gastrointestinal, hepatic, and renal systems, while 433 mg/kg caused hemorrhage in the gastric system and necrosis of the liver; 289 mg/kg caused

drowsiness and 144 mg/kg was the NOAEL in this study (Wright and Schaffer 1932 in ATSDR 1989).

A developmental study done on mice exposed by gavage from days 8-12 of gestation to 350 mg/kg/day did not show any adverse effect (Seidenberg et al. 1986 in ATSDR 1989). Another study examined various systemic effects including reproductive effects and found that male mice exposed to 46 mg/kg had significantly increased testis weight after 90 days exposure in their drinking water; adverse liver effects at 46 mg/kg/day and body weight changes at 305 mg/kg/day also occurred in both sexes (White et al. 1985 in ATSDR 1989). NOAELs were identified for hematopoietic (305 mg/kg/day), hepatic (4.4 mg/kg/day), renal (305 mg/kg/day), and body weight changes (46 mg/kg/day) (White et al. 1985 in ATSDR 1989). A similarly designed study found immune effects at 44 mg/kg/day (Sanders et al. 1985 in ATSDR 1989).

Chronic studies investigating lethality, systemic effects and carcinogenicity in rats and mice administered 1,1,2 trichloroethane 5 days/week for 78 weeks by gavage were conducted by the National Cancer Institute (NCI 1978 in ATSDR 1989). Increased mortality and cancer of the liver and adrenals was observed in mice given 195 mg/kg/day. A NOAEL of 92 mg/kg/day was observed for lethality and systemic effects in rats and a NOAEL of 390 mg/kg/day was observed for systemic effects in mice.

Guinea pigs dermally exposed for 12 hours experienced skin damage at 465 mg/cm²/day (LOAEL) (Kronevi et al. 1977 in ATSDR 1989); exposure to a single application of 116 mg/cm²/day which was allowed to remain on the skin for 5-7 days caused death in 5/20 animals within 28 days (Wahlberg 1976 in ATSDR 1989).

In vitro mutagenicity assays were negative in *Salmonella typhimurium* (Simmon et al. 1977, Rannug et al. 1978, Barber and Donish 1982, Mitoma et al. 1984, Zeiger et al. 1988 all reported in ATSDR 1989) and positive in *Saccharomyces cerevisiae* (Bronzetti et al. 1987 in ATSDR 1989). Mammalian cell transformation and DNA repair tests were negative using mouse BALB/C-3T3 cells and mouse hepatocytes (Tu et al. 1985, Williams 1983 in ATSDR 1989); however, DNA repair tests using rat

hepatocytes were positive, as were DNA adduct formation tests using calf thymus, mouse liver, and rat liver (Williams 1983, DiRenzo et al. 1982, Mazzullo et al. 1986 in ATSDR 1989). An in vitro test examining the inhibition of DNA synthesis using mouse testis was also positive (Borzelleca 1983 in ATSDR 1989).

Toxicity to Wildlife and Domestic Animals

The acute LC₅₀ values for 1,1,2-trichloroethane for freshwater aquatic organisms ranged from 18,000 to 81,700 µg/liter. One chronic test indicated that the acute-chronic ratio for 1,1,2-trichloroethane was approximately 8.7. No information on the toxicity of 1,1,2-trichloroethane to saltwater species, terrestrial wildlife, or domestic animals was available in the literature reviewed.

Regulations and Standards

Ambient Water Quality Criteria (ATSDR 1989): 0.6 µg/l

EPA does report the lowest values known to be toxic in aquatic organisms (USEPA 1986b):

Aquatic Life (Freshwater)

Acute toxicity: 18,000 µg/liter (1,1,1 and 1,1,2 - TCA)

Chronic toxicity: 9,400 µg/liter

Aquatic Life (Saltwater)

Acute toxicity: No available data

Chronic toxicity: No available data

Human Health

Due to the carcinogenicity of 1,1,2-trichloroethane the ambient water criterion is set at zero. However, estimates of the carcinogenic risks associated with

lifetime exposure from ingestion of contaminated water and aquatic organisms are:

<u>Risk</u>	<u>Concentration</u>
10^{-3}	6.0 $\mu\text{g/liter}$
10^{-4}	0.6 $\mu\text{g/liter}$

CAG Potency Slope for oral exposure (USEPA 1989): $5.7 \times 10^{-2} (\text{mg/kg/day})^{-1}$

CAG Potency Slope for inhalation exposure (USEPA 1989): $5.7 \times 10^{-2} (\text{mg/kg/day})^{-1}$

OSHA PEL (OSHA 1985 in ATSDR 1989): 10 ppm in air

ACGIH TWA (ACGIH 1988 in ATSDR 1989): 10 ppm in skin

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level. EPA classifies 1,1,2-trichloroethane as group C, a possible human carcinogen based on the NCI study (NCI 1978 in USEPA 1989).

For carcinogens such as 1,1,2-trichloroethane, the oral and inhalation D_T values are based on the USEPA Cancer Assessment Group's cancer potency slope. The cancer potency slopes have been estimated for oral exposure routes and for inhalation exposure for some chemicals. The slopes are intended to be a plausible upper bound of the potency of a carcinogen in inducing cancer at low doses. Calculation of a D_T using a cancer potency slope requires selection of an acceptable cancer risk level. A range of risk levels from 10^{-4} to 10^{-6} is considered for all carcinogens, therefore a range of D_T values is presented. Derivation of the oral and inhalation D_T values for 1,1,2-trichloroethane is as follows:

$$\begin{aligned}
 D_T &= \frac{\text{Risk Level}}{\text{Potency Slope (mg/kg/day)}^{-1}} \\
 &= \frac{1 \times 10^{-4}}{5.7 \times 10^{-2} \text{ (mg/kg/day)}^{-1}} \\
 &= 1.7 \times 10^{-3} \text{ mg/kg/day}
 \end{aligned}$$

The range of D_T values for 1,1,2-trichloroethane is presented below:

<u>Risk Level</u>	<u>D_T Oral Exposure (mg/kg/day)</u>	<u>D_T Inhalation Exposure (mg/kg/day)</u>
10^{-4}	1.7×10^{-3}	1.7×10^{-3}
10^{-5}	1.7×10^{-4}	1.7×10^{-4}
10^{-6}	1.7×10^{-5}	1.7×10^{-5}

EPA has calculated a reference dose (RfD) of 0.004 mg/kg/day based on a NOAEL of 20 mg/l (4 mg/kg/day), a LOAEL of 200 mg/l (40 mg/kg/day), and an uncertainty factor of 1,000 (10 for interspecies variation x 10 for human variability x 10 for extrapolation to lifetime exposure) (USEPA 1989). These figures are based on studies by White et al. (1985 in USEPA 1989) and Sanders et al. (1985 in USEPA 1989) because they are adequate studies in which mice of both sexes were exposed to 1,1,2-trichloroethane in drinking water for 90 days. Doses of 0, 20, 200, or 2,000 mg/l were given. Adverse liver effects occurred at 2,000 mg/l and depressed immune status occurred at greater than 200 mg/l. This RfD has a medium confidence rating because of the lack of appropriate toxicologic data.

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TRICHLOROETHYLENE

Summary

Trichloroethylene (TCE) is an organic, synthetically produced volatile liquid that is poorly soluble in water. TCE is primarily used as a solvent in the degreasing of metal components and in the dry-cleaning industry. At one time, it was used as a general anesthetic for various surgical procedures. Because of its widespread use, TCE has become a ubiquitous environmental contaminant. TCE has been detected in soil, precipitation, and sources of drinking water (ATSDR 1988). Numerous in vivo and in vitro studies with laboratory animals indicate that TCE is carcinogenic. Currently, data are inadequate to assess the carcinogenicity of TCE in humans. But given the data provided by animal studies, the EPA currently considers TCE a probable human carcinogen (Group B2). The current USEPA recommended water quality criteria are 270 µg/liter, 27 µg/liter, and 2.7 µg/liter, corresponding to a 10^{-4} , 10^{-5} , and 10^{-6} incremental increase in cancer over a lifetime (USEPA 1987). The carcinogen assessment summary of TCE has been withdrawn pending further review.

CAS Number:	79-01-6
Chemical Formula:	C_2HCl_3
IUPAC Name:	Trichloroethylene

Chemical and Physical Properties

Important Synonyms and Trade Names:	Trichloroethylene, TCE, and ethylene trichloride
Molecular Weight:	131.5
Boiling Point:	87°C
Melting Point:	-73°C
Specific Gravity:	1.4642 at 20°C

Solubility in Water:	1,100 mg/liter (Rogers et al. 1980) Table IV) 825 mg/liter (Valvani et al., 1980)
Solubility in Organics:	Soluble in alcohol, ether, acetone, and chloroform
Log Octanol/Water Partition Coefficient (K_{ow}):	2.29 (Hansch and Leo 1979) 2.29 (Rogers et al., 1980) 2.42 (Veith et al., 1983) 2.53 (Tewari et al., 1982) 3.24 (Geyer et al., 1984) 3.3 (Valvani et al., 1980) 3.3 (Davies and Dobbs 1984) 2.38 (USEPA 1986a)
Soil/Water Partition Coefficient (K_{ow}):	
188	Rogers et al. (1980) Table V (experimental)
420; 1,487	Lyman et al. (1982) Eqn 4-8 ($\log K_{ow} = 2.29; 3.30$)
175; 1,073	Lyman and Loreti (1987) ($\log K_{ow} = 2.29; 3.30$)
Bioconcentration Factor:	
95	Davies and Dobbs (1984) Eqn B ($\log K_{ow} = 3$)
17	Kenaga (1980) Table 3 (experimental)
17	Davies and Dobbs Table 2 (experimental)
31.8	Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 2.28$)
32.4	Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 2.29$)
40.7	Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 2.42$)
189.7	Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 3.3$)
14	Davies and Dobbs (1984) Eqn A ($S = 825$)
27.5	Davies and Dobbs (1984) Eqn C ($\log K_{ow} = 2.57$)
52.8	Davies and Dobbs (1984) Eqn B ($\log K_{ow} = 2.57$)
52.9	Lyman et al. (1982) Eqn 5-2 ($\log K_{ow} = 2.57$)
Vapor Pressure:	60 mm Hg at 20°C
	57.9 mm Hg at 25°C (USEPA 1986a)
Vapor Density:	4.53
Henry's Law	

Constant: 1.3×10^{-2} atm-m³/mole (calculated)
 9.1×10^{-3} atm-m³/mole (USEPA 1985a)
 3.82×10^{-1} Dimensionless

Transport and Fate

Trichloroethylene (TCE) rapidly volatilizes into the atmosphere from surface waters and soil surfaces where it reacts with hydroxyl radicals to produce hydrochloric acid, carbon monoxide, carbon dioxide, and carboxylic acid. The atmospheric lifetime of TCE estimated on the basis of reactions with hydroxyl radicals is 54 hours (USEPA 1985a).

A range of experimental and estimated soil-water partition coefficients (K_{oc}) is reported above and indicates that some sorption of trichloroethylene to soils/sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of volatile organic compounds will range from low to moderate. The combined water solubility and organic partitioning of trichloroethylene suggests that this compound will exhibit some degree of environmental mobility. There is evidence that microorganisms can metabolize TCE; however, it is unclear whether trichloroethylene bound to organic materials can be transformed directly or whether it must be disturbed in order to be degraded.

A range of experimental and estimated bioconcentration factors (BCFs) for trichloroethylene is also reported above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the concentration factors suggests that appreciable bioconcentration or biomagnification of trichloroethylene residues is not likely to occur. This may not be true for subsurface environments (e.g., groundwater leaching), where anaerobic conditions prevail and where volatilization is probably reduced.

Health Effects

A number of chronic bioassays employing several strains of rats and mice have been conducted by both inhalation and oral routes of exposure. Henschler et al. (1980) exposed NMRI mice, Wistar rats, and Syrian hamsters to TCE (purified) at 0, 100, or 500 ppm, 6 hours/day, 5 days/week for 18 months. The only statistically significant effect was an increased incidence and rate of development of malignant lymphomas in female mice (ATSDR 1988). It is theorized that lymphoma susceptibility may have been enhanced by a virus and immunosuppression (EPA 1987a).

Fukuda et al. (1983) exposed ICR mice and Sprague-Dawley rats to TCE at 0, 50, 150, or 450 ppm, 7 hours/day, 5 days/week for 104 weeks. A statistically significant increase in the frequency of lung adenocarcinomas was observed in mice but not rats exposed to TCE (ATSDR 1988).

Maltoni et al. (1986) exposed Sprague-Dawley rats to TCE at 0, 100, 300, or 600 ppm, 7 hours/day, 5 days/week for 104 weeks and observed a significant dose-related increase in testicular Leydig cell tumors at concentrations ≥ 100 ppm, as well as slight increases in renal adenocarcinomas at 600 ppm (males only). Tumor incidences were not increased among female rats. In further studies, Maltoni et al. (1986) exposed Swiss mice, B6C3F₁ (NCI) mice and B6C3F₁ (CRL) mice to TCE at similar concentrations and dosage regimens for 78 weeks. Increased incidences of hepatomas and lung tumors (adenomas) occurred in male Swiss mice at concentrations ≥ 300 ppm (lung) or 600 ppm (liver). Although liver and lung tumors were not significantly increased in female Swiss mice, the incidence data for lung tumors were used in the derivation of a carcinogenic potency estimate (EPA 1987a). In the study employing B6C3F₁ (NCI) mice, the only statistically significant increase in tumor incidence was pulmonary tumors (adenomas) in the high-dose female group (600 ppm) only. The increase in total number of malignant tumors in females was statistically significant at all exposure levels. The study in male B6C3F₁ (CRL) mice was conducted because survival of male B6C3F₁ (NCI) mice was reduced due to fighting.

This subsequent study revealed no increase in tumor incidences at any exposure level when compared to controls (ATSDR 1988).

Several studies have been conducted employing the oral route of exposure. NCI (1976) treated male and female B6C3F₁ mice and Osborne-Mendel rats with TCE in corn oil by gavage, 5 days/week for 78 weeks. The TCE was 99% pure, but contained epoxide stabilizers, including 0.09% epichlorohydrin (a strong alkylating agent and currently classified as a probable human carcinogen (Group B2)). TWA doses were calculated for the study, as dose levels were changed during the course of the study. TWA doses were 0, 1169, or 2339 mg/kg/day for male mice; 0, 869, or 1739 mg/kg/day for female mice; and 0, 549, or 1097 mg/kg/day for male and female rats. No compound-related carcinogenic effects were noted in rats, but poor survival within all groups of rats limits the usefulness of the conclusions. A statistically significant increase in the incidence of hepatocellular carcinomas was observed in male mice at both dose levels (1169 and 2339 mg/kg/day) but only at the high dose level (1739 mg/kg/day) in female mice (ATSDR 1988).

NTP (1982, 1986a) conducted a cancer bioassay employing Fischer 344 rats (F-344). The TCE used had a purity > 99.9%, and levels of epichlorohydrin were not detected, in contrast to the NCI bioassay (1976). Male and female rats received 0, 500, or 1,000 mg of TCE/kg/day, 5 days/week for 103 weeks. Survival of male rats was poor. High-dose (1,000 mg/kg/day) males displayed a significant increase in renal tubular adenocarcinomas when compared to controls. No other treatment-related increases in tumor incidence were observed in male or female rats. Nevertheless, NTP has concluded that this study is inadequate for judging the carcinogenicity of TCE, as the high dose employed in this study appears to have exceeded the maximally tolerated dose as defined by NCI, and indicated by the poor survival in male rats (ATSDR 1988). NTP (1982, 1986a) also conducted a cancer bioassay employing B6C3F₁ mice. Male and female mice received 0 or 1,000 mg of TCE/kg/day, 5 days/week, for 103 weeks. This study also employed pure TCE (no detectable levels of epichlorohydrin). A statistically significant increase in the incidence of hepatocellular carcinoma was observed in both male and female TCE-

treated mice. These results confirm those of the NCI (1976) study, which also reported an increased incidence of hepatocellular carcinoma in male and female B6C3F₁ mice given TCE stabilized with epichlorohydrin and other epoxides. The NTP results suggest that epoxides were not a requisite factor in the carcinogenic response observed (ATSDR 1988).

In a further study by NTP (1987), male and female ACI, August, Marshall, or Osborne-Mendel rats were administered epichlorohydrin-free TCE by gavage at doses of 0, 500, or 1,000 mg/kg/day, 5 days/week for 103 to 104 weeks. The only treatment-related increases in tumor incidences observed were renal tubular cell adenomas in the low-dose (500 mg/kg) male Osborne-Mendel rats only and interstitial cell tumors of the testis in high-dose (1,000 mg/kg) male Marshall rats only. However, NTP (1987) concluded that these bioassays were inadequate for assessing either the presence or absence of carcinogenicity because of chemically induced toxicity, reduced survival, and deficiencies in the conduct of the studies as revealed by data audits (ATSDR 1988). Based on consideration of these findings, the EPA currently classifies TCE as a probable human carcinogen (Group B2) according to the Agency's Proposed Guidelines for Carcinogen Risk Assessment (USEPA 1989, cited in ATSDR 1988). However, NTP (1989) has not included TCE on its list of probable human carcinogens.

TCE appears to be weakly mutagenic in the presence of a metabolic activating system, based on results from various in vitro mutagenicity assays. In vivo and in vitro genotoxicity assays of trichloroethylene in nonhuman systems are suggestive of a genotoxic effect, with both positive and negative results reported. However, the in vitro assays for gene mutation in bacteria were weakly positive only in the presence of an activating system, providing evidence that a metabolite rather than TCE may be the mutagen.

Developmental toxicity studies with TCE indicate that it is fetotoxic but not teratogenic to rodents. Effects related to TCE exposure include delayed ossification of the skeleton, increases in resorptions and decreases in the fetal body weights of rats (ATSDR 1988). Embryo toxicity occurred in rats exposed via inhalation to TCE at

1,800 ppm for 2 weeks prior to mating and during days 1-20 of gestation. Inhalation of TCE for 3 weeks prior to mating and during gestation days 1-18 (rat) and during gestation days 1-21 (rabbit) also resulted in embryo toxicity (ATSDR 1988).

Treatment-related effects on the male reproductive tracts of mice and rats have been reported. These effects were restricted to changes in the testes/epididymis weight ratio, and decreases in sperm motility. Since fertility, reproductive performance, and reproductive system histology were normal, these effects on males were not considered adverse (ATSDR 1988).

Both humans and rodents extensively metabolize absorbed doses of TCE. Most absorbed TCE undergoes urinary excretion as trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid in both humans and rodents. Minor metabolites include chloral hydrate, monochloroacetic acid, and N-hydroxyacetyl aminoethanol. Rodents also seem to produce minor metabolites, such as glutathione conjugates of TCE, that are not found in humans (ATSDR 1988). Glutathione conjugates of TCE may be important in the manifestation of TCE's chronic toxicity.

TCE has been shown to cause renal toxicity, hepatotoxicity, neurotoxicity, and dermatological reactions in animals following chronic exposure to levels greater than 2,000 mg/m³ for 6 months (USEPA 1985a). The acute oral LD₅₀ value of trichloroethylene in the rat is 4,920 and 2,404 mg/kg in the mouse.

In humans, chronic exposure to TCE is characterized by dizziness, nausea, headache, ataxia, decreased appetite, and sleep disturbances (USEPA 1985a). Effects of short-term exposure include mild eye irritation, nausea, vertigo, headache and confusion. Unconsciousness and death may occur following exposure to excessive concentrations (USEPA 1985a). NIOSH (ATSDR 1988) reported a lowest observed concentration for lethality in humans as 2,900 ppm TCE after acute inhalation exposure.

Toxicity to Wildlife and Domestic Animals

Only limited data were available on the toxicity of trichloroethylene to aquatic organisms. The acute toxicity to freshwater species was similar in the three species tested, with LC_{50} values of about 50 mg/liter (USEPA 1980). No LC_{50} values were available for saltwater species (USEPA 1980). However, 2 mg/liter caused erratic swimming and loss of equilibrium in the grass shrimp. No chronic toxicity tests were reported.

No information on the toxicity of trichloroethylene to domestic animals or terrestrial wildlife was available in the literature reviewed.

Regulations and Standards

Ambient Water Quality Criteria (USEPA 1986b):

The available data are not adequate for establishing criteria. However, EPA does report the lowest values known to be toxic in aquatic organisms.

Aquatic Life (Freshwater)

Acute toxicity: 45 mg/liter

Chronic toxicity: 21.9 mg/liter

Aquatic Life (Saltwater)

Acute toxicity: 2 mg/liter

Chronic toxicity: No available data

Human Health

Due to the carcinogenicity of trichloroethylene the ambient water criterion is set at zero. Estimates of the carcinogenic risks associated

with lifetime exposure from ingestion of contaminated water and contaminated aquatic organisms are:

<u>Risk</u>	<u>Concentration</u>
10^{-4}	270 mg/liter
10^{-5}	27 mg/liter
10^{-6}	2.7 mg/liter

National Primary Drinking Water Standard: 5 μ g/liter. This value becomes effective January 9, 1989 (ATSDR 1988).

CAG Potency Slope for Oral Exposure (USEPA 1989): 1.1×10^{-2}
(mg/kg/day)⁻¹

CAG Potency Slope for Inhalation Exposure (USEPA 1989): 1.3×10^{-2}
(mg/kg/day)⁻¹

The inhalation risk estimate has been revised to 1.7×10^{-2} (mg/kg/day)⁻¹ and is based on the lung tumor incidence data from inhalation bioassays with mice. The EPA is currently reviewing this revised risk estimate (USEPA 1989); therefore, the range of D_T values for Trichloroethylene presented on the following page employs the CAG potency slope factor of 1.3×10^{-2} (mg/kg/day)⁻¹.

NIOSH Recommended Standards (air): TWA¹ = 540 mg/m³
Ceiling Level = 760 mg/m³ 10-min

OSHA Standards (air):
TWA = 540 mg/m³
Ceiling Level = 1,075 mg/m³/15-min

¹ Time Weighted Average.

Peak Concentration = 1,620 mg/m³ for 5 min every 3 hour,

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For potential human carcinogens such as trichloroethylene, the D_T value is based on the USEPA Cancer Assessment Group's cancer potency slopes. The cancer potency slopes for oral and inhalation exposure have been estimated, although they have been withdrawn by the EPA. The slopes are intended to be a plausible upper bound of the potency of a carcinogen in inducing cancer at low doses. Calculation of a D_T using a cancer potency slope requires selection of an acceptable cancer risk level. A range of risk levels from 10⁻⁴ to 10⁻⁶ will be considered for all carcinogens; therefore, a range of D_T values is presented. Derivation of the D_T values for trichloroethylene is as follows:

$$\begin{aligned} D_T &= \frac{\text{Risk Level}}{\text{Potency Slope (mg/kg/day)}^{-1}} \\ &= \frac{1 \times 10^{-4}}{1.1 \times 10^{-2} \text{ (mg/kg/day)}^{-1}} \\ &= 9.1 \times 10^{-3} \text{ mg/kg/day} \end{aligned}$$

The range of D_T values for trichloroethylene is presented below.

<u>Risk Level</u>	<u>Oral D_T</u> <u>(mg/kg/day)</u>	<u>Inhalation D_T</u> <u>(mg/kg/day)</u>
10 ⁻⁴	9.1 x 10 ⁻³	7.7 x 10 ⁻³
10 ⁻⁵	9.1 x 10 ⁻⁴	7.7 x 10 ⁻⁴
10 ⁻⁶	9.1 x 10 ⁻⁵	7.7 x 10 ⁻⁵

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